

Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and management

J Malcolm O Arnold MD FRCPC (Chair)¹, Peter Liu MD FRCPC (Co-Chair)², Catherine Demers MD FRCPC³, Paul Dorian MD FRCPC⁴, Nadia Giannetti MD FRCPC⁵, Haissam Haddad MD FRCPC⁶, George A Heckman MD FRCPC³, Jonathan G Howlett MD FRCPC⁷, Andrew Ignaszewski MD FRCPC⁸, David E Johnstone MD FRCPC⁷, Philip Jong MD FRCPC², Robert S McKelvie MD FRCPC³, Gordon W Moe MD FRCPC⁴, John D Parker MD FRCPC⁹, Vivek Rao MD FRCSC², Heather J Ross MD FRCPC¹⁰, Errol J Sequeira MD FCFP¹¹, Anna M Svendsen RN MS⁷, Koon Teo MBBCh FRCPC³, Ross T Tsuyuki PharmD FCSHP¹², Michel White MD FRCPC¹³

JMO Arnold, P Liu, C Demers, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and management. *Can J Cardiol* 2006;22(1):23-45.

Heart failure remains a common diagnosis, especially in older individuals. It continues to be associated with significant morbidity and mortality, but major advances in both diagnosis and management have occurred and will continue to improve symptoms and other outcomes in patients. The Canadian Cardiovascular Society published its first consensus conference recommendations on the diagnosis and management of heart failure in 1994, followed by two brief updates, and reconvened this consensus conference to provide a comprehensive review of current knowledge and management strategies.

New clinical trial evidence and meta-analyses were critically reviewed by a multidisciplinary primary panel who developed both recommendations and practical tips, which were reviewed by a secondary panel. The resulting document is intended to provide practical advice for specialists, family physicians, nurses, pharmacists and others who are involved in the care of heart failure patients.

Management of heart failure begins with an accurate diagnosis, and requires rational combination drug therapy, individualization of care for each patient (based on their symptoms, clinical presentation and disease severity), appropriate mechanical interventions including revascularization and devices, collaborative efforts among health care professionals, and education and cooperation of the patient and their immediate caregivers. The goal is to translate best evidence-based therapies into clinical practice with a measurable impact on the health of heart failure patients in Canada.

Key Words: *Consensus statement; Disease management; Drug therapy; Guidelines; Heart failure; Heart failure clinics*

HEART FAILURE

Many definitions of heart failure have been used, reflecting the existing understanding of the pathophysiological condition at that time. Heart failure is a complex syndrome in which abnormal heart function results in, or increases the subsequent risk of, clinical symptoms and signs of low cardiac output and/or

Recommandations de la Conférence consensuelle de la Société canadienne de cardiologie 2006 sur l'insuffisance cardiaque : Diagnostic et prise en charge

L'insuffisance cardiaque demeure un diagnostic répandu, surtout chez les sujets âgés. Elle continue d'être associée à une morbidité et à une mortalité importantes, mais de grands progrès ont été accomplis sur les plans du diagnostic et de la prise en charge de la maladie et ils amélioreront encore les symptômes et le pronostic des patients. C'est en 1994 que la Société canadienne de cardiologie a publié son premier rapport consensuel sur le diagnostic et la prise en charge de l'insuffisance cardiaque, suivi de brèves mises à jour; et elle a choisi de répéter l'exercice afin de faire le point de manière globale sur les connaissances et les stratégies thérapeutiques actuelles.

Les conclusions et méta-analyses d'essais cliniques récents ont été analysées par un comité principal pluridisciplinaire qui a formulé ses recommandations et ses conseils pratiques avant de les soumettre à un second comité. Le document qui en résulte vise à guider de manière concrète les spécialistes, médecins de famille, infirmières, pharmaciens et autres intervenants appelés à soigner les insuffisants cardiaques.

La prise en charge de l'insuffisance cardiaque commence par un diagnostic juste et repose sur l'administration de traitements pharmacologiques associatifs, sur une individualisation de l'approche thérapeutique (selon les symptômes, le tableau clinique et la gravité de chaque cas), sur des interventions de type mécanique appropriées, telles que l'angioplastie ou d'autres dispositifs, sur une approche pluridisciplinaire concertée et sur l'enseignement au patient et à ses aidants naturels, pour une meilleure coopération. L'objectif est de transposer dans la pratique clinique les meilleurs traitements issus de la recherche, éprouvés et susceptibles d'exercer un impact véritable sur la santé des insuffisants cardiaques au Canada.

pulmonary or systemic congestion. Because most evidence-based recommendations are based on clinical trials where significant left ventricular systolic dysfunction is present, the term 'heart failure' is used in this document to refer to predominant left ventricular systolic dysfunction unless otherwise stated. Diastolic heart failure (or heart failure with preserved

¹University of Western Ontario, London, Ontario; ²University of Toronto, Toronto, Ontario; ³McMaster University, Hamilton, Ontario; ⁴St Michael's Hospital, Toronto, Ontario; ⁵McGill University, Montreal, Quebec; ⁶Ottawa Heart Institute, Ottawa, Ontario; ⁷Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; ⁸St Paul's Hospital, Vancouver, British Columbia; ⁹Mount Sinai Hospital, Toronto, Ontario;

¹⁰Toronto General Hospital, Toronto, Ontario; ¹¹Credit Valley Hospital, Mississauga, Ontario; ¹²University of Alberta, Edmonton, Alberta;

¹³Institut de Cardiologie de Montreal, Montreal, Quebec

Correspondence: Dr J Malcolm O Arnold, Room C6 – 124D, University Hospital, London Health Sciences Centre, 339 Windermere Road, London, Ontario N6A 5A5. Telephone 519-663-3496, fax 519-663-3497, e-mail malcolm.arnold@lhsc.on.ca

Received for publication November 23, 2005. Accepted November 30, 2005

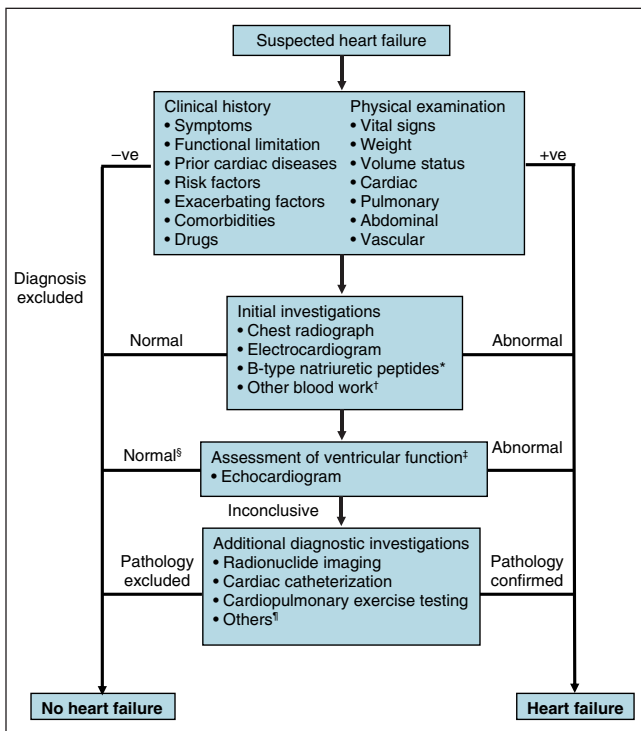


Figure 1) Algorithm for diagnosis of heart failure. *Useful in selected care settings (eg, emergency room); †Some laboratory tests are recommended at the time of initial evaluation if diagnostic suspicion is high (complete blood count, electrolytes, renal function, urinalysis, glucose, lipids, liver enzymes and function, and thyroid function) and others are recommended when clinically indicated (eg, ferritin, antinuclear antibody, rheumatoid factor, metanephrines or HIV); ‡Includes both systolic and diastolic parameters (eg, ejection fraction, transmitral and pulmonary venous flow patterns, or mitral annulus velocities); §Heart failure with preserved systolic function may not be identified on a routine echocardiogram and clinical judgment is required if other indicators point strongly to heart failure as a diagnosis; ¶Magnetic resonance imaging, multislice computed tomography or endomyocardial biopsy

systolic function [PSF]), right heart failure, left or right ventricular failure, biventricular heart failure, congestive heart failure (CHF), acute or chronic heart failure, cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, ischemic cardiomyopathy and nonischemic cardiomyopathy are examples of other terms often used in clinical practice and research to describe specific presentations and underlying pathologies.

Heart failure is common, especially in older patients, and its incidence is predicted to increase (1). It reduces quality of life, exercise tolerance and survival. Depending on the severity of symptoms, heart dysfunction, age and other factors, heart failure can be associated with an annual mortality of 5% to 50%. A better understanding of the underlying pathophysiological mechanisms, combined with many new treatments developed over the past 20 years, has greatly improved the prognosis; many patients can now hope for long periods of stable, improved symptoms and improved heart function. Nonetheless, an inexorable course can also occur, and many new approaches to treatment continue to be developed.

This consensus conference was convened by the Canadian Cardiovascular Society (CCS) to review new evidence and update previous consensus conferences (2-4) to provide a set of evidence-informed recommendations that would provide clinicians, and other health care professionals involved in the

management of heart failure patients, with clear directions and options to optimize care of individual patients. Furthermore, a concurrent plan for knowledge translation was developed. Through increased use of these evidence-based proven therapies and other recommendations based on the consensus of heart failure experts where adequate clinical trial evidence was not available, the purpose is to improve health outcomes and quality of life across the broad spectrum of heart failure patients in Canada and to measure that impact. Specific patient subgroups are identified in individual recommendations when appropriate. The present document does not repeat the reviews of data presented in the previous consensus conferences, but aims to highlight new data while updating previous recommendations where appropriate. Readers are referred to the previous publications for additional background information and rationale. New or expanded sections cover diagnosis and investigation, acute heart failure (AHF), multidisciplinary care and heart failure clinics, polypharmacy, device therapy, surgical approaches, heart failure in the elderly and issues related to end-of-life care. Following a review of the literature and a critical appraisal of the evidence, recommendations were arrived at by informed consensus through face-to-face meetings, conference calls, e-mail correspondence, and final review by all members of both the primary and the secondary panel. The primary panelists were principally responsible for the document, but the secondary panelists reviewed the recommendations and provided feedback, and some were involved in section working groups.

The class of recommendation and the grade of evidence were determined as follows:

Class I: Evidence or general agreement that a given procedure or treatment is beneficial, useful and effective.

Class II: Conflicting evidence or a divergence of opinion about the usefulness or efficacy of the procedure or treatment.

Class IIa: Weight of evidence is in favour of usefulness or efficacy.

Class IIb: Usefulness or efficacy is less well established by evidence or opinion.

Class III: Evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful.

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B: Data derived from a single randomized clinical trial or nonrandomized studies.

Level of Evidence C: Consensus of opinion of experts and/or small studies.

DIAGNOSIS AND INVESTIGATION

Recommendations

- Clinical history, physical examination and laboratory testing should be performed on all patients with suspected heart failure to establish the diagnosis and identify modifiable factors that may affect the development or progression of heart failure (class I, level C) (Figure 1).
- Transthoracic echocardiography should be performed in all patients with suspected heart failure to assess ventricular size and function, as well as valvular and other abnormalities. To assess ventricular size and function, gated radionuclide ventriculography should be substituted when echocardiography is unavailable or inadequate (class I, level C).

TABLE 1
Clinical presentations of heart failure

Common	Uncommon
Dyspnea	Cognitive impairment*
Orthopnea	Altered mentation or delirium*
Paroxysmal nocturnal dyspnea	Nausea
Fatigue	Abdominal discomfort
Weakness	Oliguria
Exercise intolerance	Anorexia
Dependent edema	Cyanosis
Cough	
Weight gain	
Abdominal distension	
Nocturia	
Cool extremities	

*May be a more common presentation in elderly patients

- Coronary angiography should be considered for patients who are suspected or known to have coronary artery disease as the underlying or contributing cause of heart failure (class I, level C).
- A validated measure of functional capacity, such as the New York Heart Association (NYHA) classification, should be used to document functional capacity in all patients with heart failure (class I, level C).
- Measurement of plasma B-type or brain natriuretic peptides (BNPs) should be considered, where available, in patients with suspected heart failure when clinical uncertainty exists (class IIa, level A).

The diagnosis of clinical heart failure is made when symptoms and signs of impaired cardiac output and/or volume overload are documented in the setting of abnormal systolic and/or diastolic cardiac function. The cardinal triad of edema, fatigue and dyspnea is neither a sensitive nor a specific manifestation of heart failure, and atypical presentations of heart failure should be recognized (Table 1), particularly when evaluating women, obese patients and the elderly. A relevant clinical history and physical examination should be performed in all patients, and initial investigations should be targeted to confirm or exclude heart failure as the diagnosis and to identify systemic disorders (eg, thyroid dysfunction) that may affect its development or progression (Figure 1). Measurement of plasma natriuretic peptides, such as BNP, is likely to become more widely available and is helpful because low concentrations are useful in excluding heart failure and high concentrations can confirm heart failure in patients presenting with dyspnea when the clinical diagnosis remains uncertain (5).

Two-dimensional and Doppler transthoracic echocardiography are the initial imaging modalities of choice in patients suspected to have heart failure because they assess systolic and diastolic ventricular function, wall thickness, chamber sizes, valvular function and pericardial disease. Radionuclide angiography is useful in patients where echocardiographic images are poor (eg, obese patients and patients with emphysema). Cardiac catheterization with hemodynamic measurements and contrast ventriculography, or magnetic resonance imaging when available, may be used in specific cases in which initial noninvasive tests are inconclusive.

TABLE 2
New York Heart Association functional classification

Class	Definition
I	No symptoms
II	Symptoms with ordinary activity
III	Symptoms with less than ordinary activity
IV	Symptoms at rest or with any minimal activity

Once heart failure is diagnosed, functional capacity should be assessed to document the degree of physical limitations, and the NYHA functional classification (6) is recommended as a simple, validated measure of heart failure clinical severity (Table 2). A six-minute walk test may help assess exercise limitations and prognosis. Cardiopulmonary exercise testing is infrequently necessary but may be used to determine the extent to which heart failure contributes to exercise intolerance, particularly in patients in whom there is disparity between the reported symptoms and the clinical assessment. When coronary artery disease is suspected, noninvasive testing, such as radionuclide perfusion imaging or stress echocardiography, is useful to ascertain the presence or extent of myocardial infarction, ischemia or viability that may warrant further evaluation. Coronary angiography should also be considered, especially in those who have angina or positive noninvasive tests and are candidates for revascularization. Endomyocardial biopsy is not recommended in the routine evaluation of heart failure; it has limited diagnostic value except in suspected rare disorders, such as infiltrative or inflammatory myocardial diseases.

Practical tips

- Patients may have heart failure even without a history or current evidence of volume overload. Thus, the term 'heart failure' is generally preferred over 'congestive heart failure' as the clinical diagnosis.
- A normal ejection fraction does not exclude heart failure as a diagnosis (eg, heart failure with PSF).
- Screening for diseases that can cause heart failure should be determined by clinical suspicion in individual patients: hemochromatosis, sarcoidosis, amyloidosis, HIV infection, neuroendocrinopathies (eg, pheochromocytoma, hypothyroidism), rheumatological diseases (eg, collagen vascular diseases), nutritional deficiencies (eg, thiamine) and sleep apnea.

NONPHARMACOLOGICAL MANAGEMENT

Exercise training

Recommendations

- Regular physical activity is recommended for all patients with stable heart failure symptoms and impaired left ventricular systolic function (class IIa, level B).
- Exercise training three to five times a week for 30 min to 45 min per session (to include warm-up and cool-down) should be considered for stable NYHA class II to III heart failure patients with left ventricular ejection fraction (LVEF) less than 40% (class IIa, level B).
- Before starting an exercise program, all patients should have a graded exercise stress test to assess functional capacity,

identify angina or ischemia, and determine an optimal target heart rate for training (class IIa, level B).

- Training for both aerobic activity and resistance training should be at a moderate intensity (class IIa, level B).
- Individualized exercise training may initially be performed in a supervised setting with trained personnel and external defibrillators when resources are available and accessible (class IIb, level C).

The role of exercise training in the management of heart failure was last reviewed in the 2001 CCS consensus guideline update for the management and prevention of heart failure (3). Exercise intolerance is recognized as a hallmark of heart failure. Until the late 1980s, heart failure patients were advised to avoid physical activity in the hope that it might minimize symptoms and protect the already damaged heart. It is now understood that exercise intolerance in heart failure has a multifactorial etiology and that parameters such as intracardiac filling pressures and LVEF may not be reliable predictors of exercise capacity. Changes in the periphery and left ventricular function are both important determinants of exercise capacity. Exercise training programs in selected patients have been shown to be safe, but they also can reverse many of these peripheral abnormalities that are believed to play a role in exercise intolerance and improve overall exercise capacity (7,8). As a result, there has been a gradual move from reluctance to consider exercise programs for patients with heart failure and left ventricular dysfunction toward referral of selected patients.

Numerous clinical and mechanistic studies and some randomized studies have shown that regular exercise performed by either interval training (eg, biking and treadmill training) or steady state exercise can safely increase physical capacity by 15% to 25% and improve symptoms and quality of life in patients with NYHA II to III heart failure (7,8). However, the studies have been small and have used mainly physiological end points. The Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH) Collaborative (9) addressed the question of whether exercise training reduces morbidity and mortality in heart failure patients by using individual patient data from nine relatively small studies published since 1990 involving a total of 801 patients. The ExTraMATCH review provided further support for the safety of exercise training in stabilized NYHA I to III heart failure patients, and reported relative risk reductions of 32% for death and 23% for the combined end point (death or hospital admission) for exercise training versus usual care. Several detailed discussions are available on exercise and CHF (10-13).

The data stimulate continued enthusiasm for ongoing research into how exercise training may affect outcomes and for conducting a more definitive trial – recognizing the difficulties of performing such a trial in this patient population. A 3000-patient, multicentre trial, Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), sponsored by the National Heart, Lung, and Blood Institute is ongoing in the United States, Canada and Europe.

Practical tips

- To prevent muscle deconditioning, heart failure patients should be encouraged to carry out regular daily physical and

leisure activities that do not induce symptoms. Unsupervised strenuous or isometric exercises should be avoided.

- Referral to a cardiac rehabilitation program should be considered for all stable NYHA I to III heart failure patients based on the available data.
- Patients should be considered for exercise training when their symptoms have stabilized and they are euvolemic.
- Exercise training may be most successful when the mode of exercise is chosen to match the patient's preference (eg, walking, biking, treadmill or swimming)
- It is important to individualize the exercise program for each patient, with the more deconditioned patients starting at a lower training intensity and with shorter sessions.
- For stable NYHA I to III heart failure patients, exercise training should be moderate (60% to 80% of peak heart rate, Borg rate of perceived exertion of 4 [scale 1 to 10] or 60% to 80% of peak oxygen consumption).
- Stable heart failure patients who incorporate resistance training into their program should exercise two times per week at an intensity of 50% to 60% of their 'one repetition maximum', and 10 to 15 repetitions should be included in a 'set'.

Salt and fluid restriction and weight management

Recommendations

- All patients with symptomatic heart failure should restrict their dietary salt intake to a no-added-salt diet (2 g/day to 3 g/day). Patients with more advanced heart failure and fluid retention may be advised to restrict salt intake further to 1 g/day to 2 g/day (low-salt diet). Other causes of fluid retention should also be looked for and corrected (class I, level C).
- Daily morning weight should be monitored in heart failure patients with fluid retention or congestion that is not easily controlled with diuretics, or in patients with significant renal dysfunction (class I, level C).
- Concomitant restriction of daily fluid intake to between 1.5 L/day to 2 L/day should be considered for all patients with fluid retention or congestion that is not easily controlled with diuretics, or in patients with significant renal dysfunction or hyponatremia (class I, level C).

Forced fluid intake beyond normal requirements to prevent thirst is not recommended (class III, level C).

Supplements and other alternative therapies

Recommendations

- Coenzyme Q10, vitamin and herbal supplements are not recommended as heart failure therapy (class III, level C).
- Chelation therapy should not be used as heart failure therapy (class III, level C).

Multidisciplinary outpatient heart failure management and disease management programs

Recommendations

- Specialized hospital-based clinics or disease management programs staffed by physicians, nurses, pharmacists and other health care professionals with expertise in heart failure

management should be developed and used for assessment and management of higher risk patients with heart failure (class I, level A).

- The optimal care model should reflect local circumstances, present resources and available health care personnel (class I, level C).
- Multidisciplinary care should include close clinical follow-up, patient and caregiver education, telemanagement or telemonitoring, and home visits by specialized heart failure health care professionals where resources are available (class I, level A).
- Patients with recurrent heart failure hospitalizations should be referred by family physicians, internists and cardiologists for follow-up within four weeks of hospital discharge, or sooner when feasible (14) (class I, level A).
- Practical resources to aid in heart failure diagnosis and management should be made available across the continuum of community health care delivery (class I, level C).

Despite the clear survival benefits supporting the use of pharmacological therapies in the management of heart failure patients, prognosis associated with recurrent and prolonged hospitalizations remains poor. In recent years, many small, randomized clinical trials evaluating different multidisciplinary strategies have shown benefits on recurrent hospitalizations and duration of hospital stay. In these studies, many of the interventions were similar, including patient education, telemanagement, and home and hospital-based clinic visits with health care professionals specialized in heart failure care. Based on these trials, systematic reviews and meta-analyses have been published evaluating the effectiveness of multidisciplinary heart failure management programs (15-17). Strategies incorporating postdischarge follow-up by a multidisciplinary team of specially trained staff and/or access to specialized heart failure clinics reduced mortality and all-cause hospitalizations. Although there were conflicting results between earlier systematic overviews on the survival benefit of these interventions, a recent review (15) found a significant reduction in all-cause mortality.

Patients with recent or recurrent hospital admissions for heart failure appear to benefit the most from multidisciplinary heart failure or function clinics. Despite an improvement in short-term clinical outcomes, the persistence of long-term benefits and cost-effectiveness of these strategies remain to be determined after patients have stabilized. Heart failure or function clinics characterized by specialized multidisciplinary care can provide evidence-based medical therapy and referral to appropriate electrophysiological and surgical interventions. Patient education is a common key principle to improve patients' recognition of early warning symptoms and signs and to provide the patient with strategies they can use to intervene early and prevent further acute deterioration.

Practical tips

- Telephone calls by experienced nurses to patients with heart failure appear to be a key intervention in preventing recurrent heart failure hospitalizations.
- Teaching patients to weigh themselves daily and to recognize symptoms of worsening heart failure, and providing

an algorithm to adjust their diuretics are key strategies to clinical stability in patients with recurrent fluid retention.

- Heart failure or function clinics may also provide opportunities for exploration of a full range of treatment options, including pharmacological, interventional, electrophysiological and surgical therapeutic options.
- In Canada, suggestions on how to set up a multidisciplinary heart failure or function clinic are available at <www.cchfc.org>, the Web site of the Canadian Congestive Heart Failure Clinics Network.

When to refer

Recommendations

- Patients with new-onset heart failure, a recent heart failure hospitalization, heart failure associated with ischemia, hypertension, valvular disease, syncope, renal dysfunction, other multiple comorbidities, heart failure of unknown etiology, intolerance to recommended drug therapies or poor compliance with the treatment regimen should be referred for specialist consultation (class I, level C).
- First-degree family members should be screened if the index heart failure patient has a family history of cardiomyopathy or sudden death (class I, level C).

Immunization, continuous positive airway pressure and enhanced external counterpulsation

Recommendations

- Physicians should immunize heart failure patients against influenza (annually) and pneumococcal pneumonia (if not received in last six years) to reduce the risk of respiratory infections that may seriously aggravate heart failure (class I, level C)
- Continuous positive airway pressure should not be used for the treatment of central sleep apnea in heart failure patients due to lack of evidence for benefit (18) (class III, level B).
- Enhanced external counterpulsation should not be used for the treatment of heart failure due to lack of evidence for benefit (class III, level C).

DRUG THERAPY

General recommendations

- Specific contraindications to individual drugs should be identified in each patient (class I, level C) and this is assumed in all of the following recommendations.
- Cardiovascular risk factors should be aggressively managed with appropriate drugs and lifestyle modifications to targets identified in other disease-specific national guidelines (class I, level A).
- A simplified algorithm of recommended heart failure management including drug therapy is shown in Figure 2.
- Contraindications to the use of a drug in an individual patient should be carefully evaluated before prescribing, and emergent new signs or symptoms should be assessed to determine whether they could be side effects related to the drug (class I, level C).
- All patients with heart failure and an LVEF less than 40% should be treated with an angiotensin-converting enzyme

TABLE 3
Evidence-based drugs and oral doses as shown in large clinical trials

Drug	Start dose	Target dose
ACE inhibitor		
Captopril	6.25 mg to 12.5 mg tid	25 mg to 50 mg tid
Enalapril	1.25 mg to 2.5 mg bid	10 mg bid
Ramipril	1.25 mg to 2.5 mg bid	5 mg bid*
Lisinopril	2.5 mg to 5 mg od	20 mg to 35 mg od
Beta-blocker		
Carvedilol	3.125 mg bid	25 mg bid
Bisoprolol	1.25 mg od	10 mg od
Metoprolol CR/XL†	12.5 mg to 25 mg od	200 mg od
ARB		
Candesartan	4 mg od	32 mg od
Valsartan	40 mg bid	160 mg bid
Aldosterone antagonist		
Spironolactone	12.5 mg od	50 mg od
Eplerenone†	25 mg od	50 mg od
Vasodilator		
Isosorbide dinitrate	20 mg tid	40 mg tid
Hydralazine	37.5 mg tid	75 mg tid

*The Healing and Early Afterload Reducing Therapy (HEART) trial (165) showed that 10 mg once a day (od) was effective for attenuating left ventricular remodelling; †Not available in Canada. ACE Angiotensin-converting enzyme; ARB Angiotensin receptor blocker; bid Twice a day; CR/XL Controlled release/extended release; tid Three times a day

(ACE) inhibitor in combination with a beta-blocker unless a specific contraindication exists (class I, level A).

- Drugs that have proved to be beneficial in large-scale clinical trials are recommended because the effective target doses are known (Table 3) (class I, level A).
- The target drug dose should be either the dose used in large-scale clinical trials or a lesser but maximum dose that is tolerated by the patient (class I, level A).
- If a drug with proven mortality or morbidity benefits does not appear to be tolerated by the patient (eg, low blood pressure, low heart rate or renal dysfunction), other concomitant drugs with less proven benefit should be carefully re-evaluated to determine whether their dose can be reduced or the drug discontinued to allow better tolerance of the proven drug (class I, level B).

There have been many landmark clinical trials and meta-analyses of the use of ACE inhibitors (19-25) and beta-blockers (26-29) in heart failure, as well as other meta-analyses (30-32), such that ACE inhibitors and beta-blockers have become standard therapy and should be considered in all patients diagnosed with heart failure. The timing of introduction should be individualized to maximize tolerability and long-term persistence with therapy. In general, acute symptoms should be relieved, but an ACE inhibitor or a beta-blocker should be introduced as early as the patient's condition allows. Heart rate and blood pressure abnormalities may dictate which drug class should be used first or preferentially uptitrated. Because most of the clinical trials studied ACE inhibitors first, most physicians would start with an ACE inhibitor and add a beta-blocker but not necessarily delay introduction until the target ACE inhibitor dose was reached. The Cardiac Insufficiency Bisoprolol Study

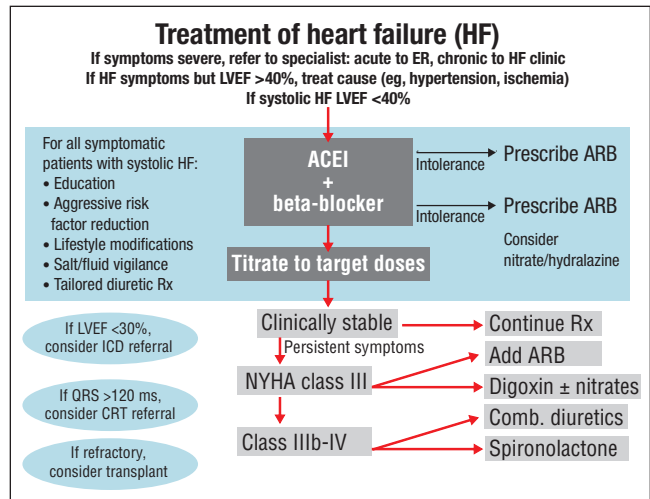


Figure 2 A simplified algorithm of heart failure management including drug and device therapy (see text for full recommendations). ACEI Angiotensin-converting enzyme inhibitor; ARB Angiotensin receptor blocker; Comb. Combination; CRT Cardiac resynchronization therapy; ER Emergency room; ICD Implantable cardioverter defibrillator; LVEF Left ventricular ejection fraction; NYHA New York Heart Association; Rx Treatment

(CIBIS) III (33), a recent open-label trial of 1010 patients with mild to moderate heart failure and an LVEF of 35% or less, showed that both strategies of ACE inhibitor or beta-blocker for the first six months, followed by the combination for six to 24 months, were similar, with some small, nonsignificant differences in tolerability and outcome. Heart rate, blood pressure and comorbidities may dictate which drug class should be used first or preferentially uptitrated. If an ACE inhibitor is not tolerated, there is good evidence that an angiotensin receptor blocker (ARB) can be substituted (34,35), and this may also apply if a beta-blocker is not tolerated, although those data are not as strong. In patients who are already on combination ACE inhibitor plus beta-blocker, but continue to have heart failure symptoms or hospitalizations, an ARB should be added (36-38). Aldosterone antagonists (spironolactone is the only agent available in Canada) are effective in patients with severe heart failure postmyocardial infarction or in chronic follow-up, especially if recently hospitalized for heart failure (39,40). Symptoms, blood pressure sitting and standing, heart rate, renal function and electrolytes should be followed closely when combinations of drugs affecting the renin-angiotensin-aldosterone system are used. A previous study (22) compared an ACE inhibitor with isosorbide dinitrate and hydralazine combination and found that the ACE inhibitor enalapril reduced mortality at two years. The recent African-American Heart Failure Trial (A-HeFT) (41) of self-identified African-American patients with systolic heart failure showed that adding a fixed-dose combination of isosorbide dinitrate plus hydralazine to standard therapy reduced mortality as well as first hospitalization for heart failure and improved quality of life.

ACE inhibition, angiotensin receptor blockade and aldosterone antagonism

Recommendations

- ACE inhibitors should be used in all patients as soon as safely possible after acute myocardial infarction, and should be continued indefinitely if LVEF is less than 40% or if AHF complicated the myocardial infarction (class I, level A).

- ACE inhibitors should be used in all asymptomatic patients with an LVEF less than 35% (class I, level A).
- ACE inhibitors should be used in all patients with symptoms of heart failure and an LVEF less than 40% (class I, level A).
- ARBs should be used in patients who cannot tolerate ACE inhibition, although renal dysfunction and hyperkalemia may recur (class I, level A).
- ARBs should be added to an ACE inhibitor for patients with persistent heart failure symptoms who are assessed to be at increased risk of heart failure hospitalization, despite optimal treatment with other recommended drugs (class I, level A).
- ARBs may be considered instead of an ACE inhibitor for patients with acute myocardial infarction with AHF or an LVEF less than 40% (class I, level B).
- ARBs may also be considered as adjunctive therapy to ACE inhibitors when beta-blockers are either contraindicated or not tolerated after careful attempts at initiation (class IIa, level B).
- Aldosterone antagonism with spironolactone should be considered for patients with an LVEF less than 30% and severe symptomatic chronic heart failure despite optimization of other recommended treatments (class I, level B), or AHF with an LVEF less than 30% following acute myocardial infarction (class IIa, level B), if serum creatinine is less than 200 µmol/L and potassium is less than 5.2 mmol/L.

Practical tips

- Blood pressure may fall when an ACE inhibitor or ARB is introduced, especially if at too high a dose. Check blood pressure supine and erect to detect whether symptomatic hypotension is present, requiring slower uptitration.
- If symptomatic hypotension persists with ACE inhibitor or ARB use, consider separating the administration of the dose from the timing of other medications that could also lower blood pressure.
- 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 nitrates, if no longer clinically needed.
- An increase in serum creatinine of up to 30% is not unexpected in many patients with heart failure when an ACE inhibitor or ARB is introduced; if the increase stabilizes at less than 30%, there is not a need to stop the drug, but closer long-term monitoring may be required.
- Spironolactone can increase serum potassium, especially during an acute dehydrating illness where renal dysfunction can worsen, and close monitoring of serum creatinine and potassium is required.
- Because combining an ACE inhibitor, ARB and spironolactone together could increase the risk of hyperkalemia, this combination is discouraged unless followed closely in a specialist heart failure clinic.

Beta-adrenoceptor blockade

Recommendations

- All heart failure patients with an LVEF equal to or less than 40% should receive a beta-blocker proven to be beneficial in large-scale clinical trials (see Table 3) (class I, level A).

- Patients with NYHA class IV symptoms should be stabilized before initiation of a beta-blocker (class I, level C).
- Therapy should be initiated at a low dose and titrated to the target dose used in large-scale clinical trials or the maximum tolerated dose if less than the target dose (see Table 3) (class I, level B).
- Beta-blockers should not normally be introduced in patients with symptomatic hypotension despite adjustment of other therapies, severe reactive airways disease, symptomatic bradycardia or significant atrioventricular (AV) block without a permanent pacemaker. Stable chronic obstructive pulmonary disease is not a contraindication (class I, level B).

Practical tips

- Patients in NYHA class I or II can be safely initiated and titrated with a beta-blocker by nonspecialist physicians.
- Patients in NYHA class III or IV should have their beta-blocker therapy initiated by a specialist experienced in heart failure management and titrated in the setting of close follow-up, such as can be provided in a specialized clinic, if available.
- The dose of beta-blocker should be increased slowly (eg, double the dose every two to four weeks).
- Objective improvement in cardiac function may not be apparent for six to 12 months.
- If concomitant reactive airways disease is present, consider using more selective beta-1 blockade (eg, bisoprolol).
- Major reduction of beta-blocker dose or abrupt withdrawal should generally be avoided.
- If the patient is hypotensive, consider reducing the dose of other medications or change the timing of medications before reducing the beta-blocker dosage.
- In acute decompensated heart failure (AdHF), beta-blocker therapy down-titration may be required, including for those patients on positive inotropic support with a beta-agonist, but not necessarily discontinued unless the patient is in cardiogenic shock.
- If AV block is present, consider decreasing other AV blocking drugs, such as digoxin or amiodarone (where appropriate).
- Beta blockade should be considered in patient groups where it has often been underutilized (eg, the elderly and those with asymptomatic left ventricular dysfunction).

Vasodilation

Recommendation

- The combination of isosorbide dinitrate and hydralazine should be considered in addition to standard therapy for African-Americans with systolic dysfunction (class IIa, level A), and may be considered for other heart failure patients unable to tolerate other recommended standard therapy (class IIb, level B).

Practical tips

- Nitrates alone can also be useful to relieve orthopnea, paroxysmal nocturnal dyspnea, exercise-induced dyspnea or angina in patients when used as tablet, spray or transdermal

patch, but continuous use should generally be avoided because most patients will develop tolerance.

- Other vasodilators, such as calcium channel blockers or alpha-blockers, are not used as a primary therapy for heart failure but may have other specific indications for selected patients.

Diuresis

Recommendations

- A loop diuretic, such as furosemide, is recommended for most patients with heart failure and congestive symptoms. Once acute congestion is cleared, the lowest minimal dose should be used that is compatible with stable signs and symptoms (class I, level C).
- For patients with persistent volume overload despite optimal other medical therapy and increases in loop diuretics, cautious addition of a second diuretic (eg, a thiazide or low-dose metolazone) may be considered as long as it is possible to closely monitor morning daily weight, renal function and serum potassium (class IIb, level B).

Practical tips

- Before and after introduction of a diuretic, or a significant increase in dose, blood work should be checked for electrolytes and renal function.
- Serum potassium should be maintained at 4 mmol/L or greater, and serum magnesium and calcium should be checked if ventricular arrhythmias or muscle cramps occur.
- In significant renal dysfunction, higher doses or combination diuretics may be needed, but blood work needs to be closely followed.
- Some patients with recurrent fluid retention who are able to closely follow instructions can be taught how to adjust their diuretic dose based on symptoms and changes in body weight.

Digoxin

Recommendations

- In patients in sinus rhythm who continue to have moderate to severe persistent symptoms despite optimized heart failure medical therapy, digoxin is recommended to relieve symptoms and reduce hospitalizations (class I, level A).
- In patients with chronic atrial fibrillation and poor control of ventricular rate despite beta-blocker therapy, or when beta-blockers cannot be used, digoxin should be considered (class IIa, level B).
- In patients receiving digoxin, serum potassium and creatinine should be measured with increases in digoxin or diuretic dose, or during a dehydrating illness, to reduce the risk of digoxin toxicity (class IIa, level C).

Practical tip

- Trough (8 h to 12 h postdose) serum digoxin concentration can be lower than previously thought at approximately 1 ng/mL to achieve optimal benefit on heart failure with a reduced risk of side effects.

Platelet inhibition and anticoagulation

Recommendations

- Acetylsalicylic acid (ASA) should be considered in heart failure patients if there is a clear indication for secondary prevention of atherosclerotic disease (class I, level C).
- The dose of ASA used should be between 81 mg and 325 mg; the lower dose appears to be associated with a lower risk of gastrointestinal symptoms (class I, level B).
- Anticoagulant therapy (international normalized ratio of 2 to 3) should be given to all patients with heart failure and associated atrial fibrillation (class I, level A).
- In patients requiring anticoagulant therapy who are at high risk of complications from that therapy, antiplatelet therapy may be considered (class IIb, level C).
- Anticoagulation is not recommended routinely for patients with sinus rhythm, but it should be considered for patients with demonstrated intracardiac thrombus, spontaneous echocardiographic contrast or severe reduction in left ventricular systolic function when intraventricular thrombus cannot be excluded (class IIa, level C).
- Combination of antiplatelet and anticoagulant therapy should not be used routinely (class III, level A), except if indicated in other concomitant conditions, such as acute coronary syndromes.

Practical tips

- ASA is not required for patients with an idiopathic dilated cardiomyopathy and no other indication for ASA.
- High doses of ASA may share the same risks as nonsteroidal anti-inflammatory drugs (NSAIDs) and may aggravate heart failure, especially in unstable patients.

POLYPHARMACY

Recommendations

- Evidence-based combination drug therapy is recommended for most patients with heart failure (class I, level A).
- Members of the health care team must be aware of known drug-drug interactions and should be alert for unexpected drug-drug interactions (Figure 3) (class I, level C).
- Common drugs that should be used with caution by heart failure patients include NSAIDs, cyclooxygenase-2 inhibitors, thiazolidinediones (glitazones), negative inotropic calcium channel blockers and antiarrhythmics (class I, level B).

General principles

Patients with heart failure are generally elderly and have multiple comorbidities; therefore, the addition of multidrug therapy for heart failure adds to an already complex pharmacological regimen. As such, drug interactions, additive adverse effects (such as hypotension) and poor medication adherence occur commonly (Table 4).

Drugs to be used with caution or avoided

Patients with heart failure are clinically fragile (42,43) and are especially susceptible to drugs that worsen heart failure symptoms (either by reducing contractility or by causing fluid retention). Drug-induced heart failure has been recently reviewed (44,45). Medications implicated in exacerbation of heart

	ACEIs/ ARBs	Amiodarone	β-blockers	Digoxin	Loop diuretics	Potassium	Spirolactone
Amiodarone							
β-blockers	[↓BP]*	↑ effect of β-blocker					
Digoxin		↑ serum digoxin levels ~twofold	[↓HR, ↓AV conduction], carvedilol may ↑ digoxin levels ~25%				
Loop diuretics	[↓BP]*		[↓BP]*	hypokalemia, ↑ digoxin effect			
Potassium	↑K ⁺						
Spirolactone	[↓BP]*, ↑K ⁺		[↓BP]*	may ↑ digoxin levels	[↓BP, dehydration]*	↑K ⁺	
Warfarin		↑ warfarin effect					

Figure 3) Drug interactions with commonly used medications for congestive heart failure. Possible drug interactions with moderate to major impact are listed. Individual patient responses may vary. *Additive pharmacological effect (eg, additive hypotensive effects [↓ blood pressure (BP)]). ↑ Increase; ↓ Decrease; ACEIs Angiotensin-converting enzyme inhibitors; ARBs Angiotensin receptor blockers; AV Atrioventricular; HR Heart rate. Adapted from reference 170

failure include calcium channel blockers (nifedipine, diltiazem and verapamil), thiazolidinediones (pioglitazone, rosiglitazone), antiarrhythmic agents, doxorubicin, NSAIDs, celecoxib and beta-blockers (Table 4). Isolated reports (46) also implicate corticosteroids, tricyclic antidepressants, penicillins, clozapine, venlafaxine, zidovudine, licorice-containing products and anti-cancer agents. Because patients may receive these agents from various health care providers, good communication is necessary to avoid iatrogenic heart failure exacerbations.

Practical tips

- Dihydropyridine calcium channel blockers and glitazones can cause fluid retention, mimicking worsening heart failure and occasionally exacerbating heart failure.
- For patients prescribed many medications, consider asking the pharmacy to ‘blister pack’ medications to reduce medication errors, especially for elderly or confused patients.
- When intercurrent medications or tests require an unstable heart failure patient to drink excessive amounts of liquid (eg, antibiotics for urinary tract infections or pelvic ultrasounds), consider temporary increases in diuretic dose to avoid decompensation.

HEART FAILURE WITH PSF

Recommendations

- Systolic and diastolic hypertension should be controlled in accordance with the published hypertension guidelines (47) (class I, level A).
- The ventricular rate should be controlled in patients with atrial fibrillation at rest and during exercise (class I, level C).
- Restoration and maintenance of sinus rhythm in patients with atrial fibrillation may be considered to improve symptoms (class IIb, level C).
- Diuretics should be used to control pulmonary congestion and peripheral edema (class I, level C).
- ACE inhibitors and beta-blockers should be considered for most patients (class IIa, level B).

TABLE 4
Drug interactions and additive adverse effects of common medications

Drug	Effect
Calcium channel blockers (nifedipine, verapamil, diltiazem)	Negative inotropic effect
Thiazolidinediones (glitazones)	Cause fluid retention
Antiarrhythmic agents (especially flecainide, propafenone, disopyramide and calcium channel blockers, and less so for amiodarone, dofetilide and ibutilide)	Negative inotropic effect
Doxorubicin	Direct cardiotoxic effect
Nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors (celecoxib)	Cause fluid retention
Beta-blockers	Negative inotropic effect initially

- ARBs may be considered to reduce heart failure hospitalizations (class IIa, level B).
- Coronary artery bypass graft surgery may be considered for patients in whom symptomatic or demonstrable ischemia is judged to have an adverse affect on cardiac function (class IIa, level C).
- Beta-blockers, ACE inhibitors, calcium channel blockers and digoxin may be considered to minimize symptoms of heart failure (class IIb, level C).

Heart failure with PSF (LVEF greater than 40%) is also known as diastolic heart failure, but because the commonly available measurement techniques are imperfect in detecting diastolic dysfunction even if it is present, we use the former as the preferred term in the present recommendations. Although it has been recognized for a number of years that patients can have heart failure with PSF, only more recently has there been a greater appreciation of the prevalence of this condition (48,49). Depending on the study examined, approximately 40% to 50% of patients with clinical heart failure have PSF (50). Clinically, it is difficult to distinguish this condition from heart failure with

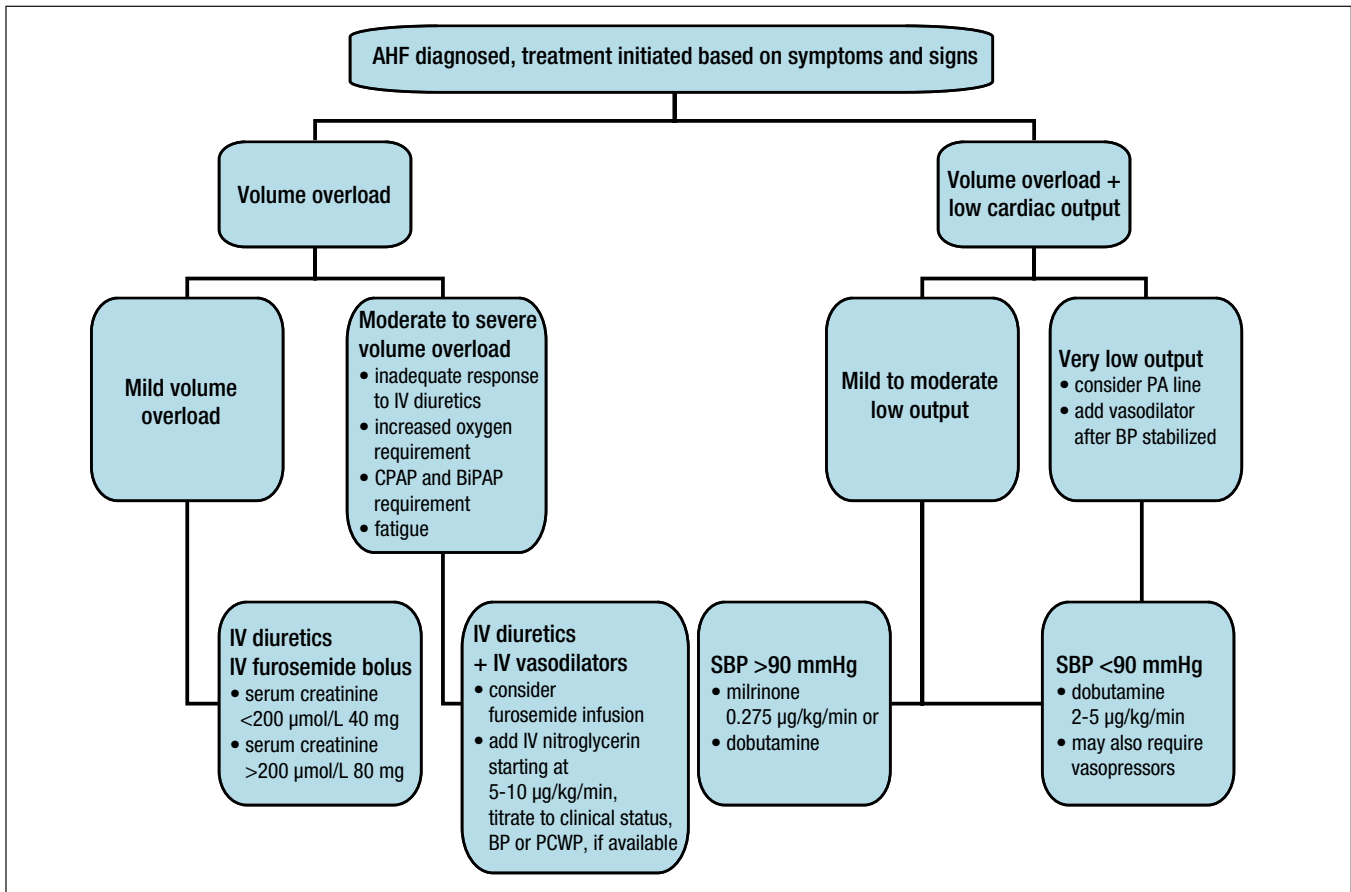


Figure 4) Treatment algorithm for acute heart failure (AHF). BiPAP Bilevel positive airway pressure; BP Blood pressure; CPAP Continuous positive airway pressure; IV Intravenous; PA Pulmonary artery; PCWP Pulmonary capillary wedge pressure; SBP Systolic blood pressure

a reduced LVEF (less than 40%). However, heart failure with PSF is more prevalent in the elderly, in women and in patients with a history of hypertension or, less often, ischemic heart disease. In practice, the diagnosis is generally based on the finding of typical symptoms and signs of heart failure in a patient who is shown to have a normal LVEF and no valvular abnormalities on echocardiography (51). The mortality associated with this condition may be somewhat better than that found with heart failure with a reduced LVEF, although some studies have suggested it may be the same. However, studies have generally shown that morbidity, especially heart failure hospitalizations, is similar to that found with heart failure and a reduced LVEF. Recommendations for treatment of this condition remain speculative because of the limited data available on various therapies (52). The treatment is based on control of physiological factors known to exert important effects on ventricular diastolic function. ACE inhibitors may improve relaxation and cardiac distensibility directly. Diuretics are useful to treat fluid overload but should be used cautiously to avoid producing a significant reduction in preload that could adversely affect cardiac filling. Beta-blockers may be useful to improve symptoms by decreasing heart rate and increasing diastolic filling time. Calcium channel blockers, such as verapamil, may also be useful for improving symptoms by decreasing heart rate and increasing diastolic filling time. A recent study (53) showed that ARBs may be useful for reducing heart failure hospitalizations.

Practical tips

- It is very important to control the comorbidities, such as hypertension and diabetes mellitus, that are often associated with heart failure and PSF.
- These patients should not use diuretics excessively because this can easily lead to decreases in cardiac output and compromise of renal function.

ATRIAL FIBRILLATION

Recommendations

- In patients with persistent (nonself-terminating) atrial fibrillation, electrical cardioversion may be considered, although its success rate may depend on the duration of atrial fibrillation and the left atrial size (class IIa, level B).
- In patients with atrial fibrillation and clinical heart failure or a reduced LVEF, the use of antiarrhythmic therapy to achieve and maintain sinus rhythm should be restricted to amiodarone (class I, level C).
- In patients who are asymptomatic with an LVEF less than 40%, beta-blocker, digoxin or a combination may be considered for control of the ventricular rate (class I, level B).
- In patients who are symptomatic with systolic dysfunction, digoxin is the first choice, and beta-blocker may be added when the patient has stabilized (class IIa, level C).

- In heart failure patients with PSF, rate-limiting calcium channel blockers may be considered (class IIa, level C).
- In patients with chronic atrial fibrillation, anticoagulation should always be considered and used unless contraindicated (class I, level C).

Atrial fibrillation is a relatively common problem for heart failure patients. The presence of atrial fibrillation can potentially cause an adverse effect in several different ways (54-57). Loss of atrial enhancement of ventricular filling may compromise cardiac output. The increase in ventricular rate in those who are not controlled may increase myocardial oxygen demand and, because of a decrease in diastolic time, produce a decrease in coronary perfusion. Also, a poorly controlled ventricular rate may cause impairment of both cardiac contraction and cardiac relaxation. Atrial fibrillation may also cause atrial thrombosis with the increased risk of embolization from the atria. Interestingly, there are no current data to support that aggressive rhythm control improves mortality or morbidity, although a large clinical trial, Atrial Fibrillation and Congestive Heart Failure (58), is in progress. However, there are data to support that a rate-control strategy is associated with fewer hospitalizations and fewer side effects from drug therapy. Thus, the treatment for these patients should be individualized.

AHF

Recommendations

- The diagnosis of AHF should be established in less than 2 h of the initial contact in the emergency department (class IIa, level C).
- Treatment for AHF should be initiated as soon as possible after diagnosis. Response to initial therapy and the need for additional therapy should be assessed less than 2 h after treatment initiation. Plans for patient disposition should be determined less than 8 h after the first medical contact (class IIb, level C).
- Clinical, radiographic and biochemical evaluation should assess the presence of volume overload, presence or absence of low cardiac output, and poor tissue perfusion for risk stratification and choice of appropriate therapy (class I, level B).
- If available, blood BNP or N-terminal proBNP (NT-proBNP) level should be measured if the diagnosis is in doubt despite a careful clinical evaluation (class I, level A).
- Patients with predominant volume overload should be given intravenous (IV) bolus(es) of furosemide. If the response is inadequate, combined IV boluses or infusion diuretics plus vasodilator therapy (IV nitroglycerin infusion started at 5 µg/min to 10 µg/min) should be given (class I, level B).
- Patients with low cardiac output and a systolic blood pressure (SBP) less than 90 mmHg should be given a positive inotrope (eg, dobutamine 2 µg/kg/min to 5 µg/kg/min or milrinone 0.275 µg/kg/min). Depending on the hemodynamic profile, treatment should include combined IV diuretics and inotropes. Once SBP is improved by inotropes, vasodilator therapy can be added to further lower filling pressures (class I, level B).
- With evidence of very low cardiac output and poor tissue perfusion, an arterial line with or without pulmonary artery catheterization is recommended (class I, level B).
- Patients with impending respiratory failure from pulmonary edema require rapid initiation of supported ventilation. Judicious use of noninvasive ventilation, including continuous positive airway pressure and bilevel positive airway pressure, may reduce the need for endotracheal intubation (class IIa, level B).

AHF can best be defined as the rapid onset of symptoms and signs secondary to any abnormalities in cardiac function that may be life threatening and require urgent treatment. AHF can present de novo in a patient with no known cardiac dysfunction, but more commonly it presents as an acute worsening of chronic heart failure, sometimes referred to as AdHF. AHF has emerged as a major public health problem leading to an increase in hospitalizations (59,60). Early readmission for heart failure is common (61,62) and, based on 1996/97 Canadian data (63), once a hospitalized patient is discharged with heart failure, the readmission rate for heart failure is 16% in one month and 53% in one year. This underscores potential gaps in care and a need to develop and implement consensus guidelines for the management of AHF. Current heart failure guidelines have focused exclusively on chronic heart failure (64,65), at least in part because there are very few large randomized controlled trials in AHF. At present, there is only one national or international consensus guideline for the management of AHF (66).

An accurate and rapid diagnosis of AHF is important to the timely institution of appropriate therapy and to improve clinical outcomes (67-69), and is based on a careful evaluation of symptoms and clinical findings, supported by appropriate investigations such as electrocardiography, chest radiography and, if available, echocardiography and biomarkers. It is important to classify patients based on the presence or absence of congestion and signs of low cardiac output and impaired tissue perfusion to administer the appropriate therapy (70,71). Detailed information on demographics and common clinical presentations of AdHF have been reported from the Acute Decompensated Heart Failure National Registry (ADHERE) (72). Clinical parameters that are predictive of high risk include impaired renal function, low SBP, high respiratory rate, low serum sodium and the presence of comorbid conditions (73,74). Several trials have now clearly established the utility of BNP and NT-proBNP as diagnostic and prognostic biomarkers in patients with AHF (75-77). These assays are most useful in patients in whom the diagnosis is not clinically obvious. They should not, however, replace a careful clinical evaluation. A BNP concentration less than 100 pg/mL or an NT-proBNP concentration less than 300 pg/mL indicates low probability for AdHF. Conversely, a BNP concentration greater than 500 pg/mL or an NT-proBNP concentration greater than 1800 pg/mL indicates a very high probability of AHF.

Among the allied health care professionals who are involved with the management of patients with AHF, nurses probably play the most important role. In addition to assessment of patients, nursing actions that are crucial to AHF patients' outcomes are administration of medications, evaluation of treatment effectiveness, and education and ongoing communications with patients, patients' families and the health care team (78).

A proposed treatment algorithm is illustrated in Figure 4.

Diuretics

Diuretics provide symptomatic relief and should be the first-line treatment for patients with pulmonary or systemic congestion, but there is no trial evidence that diuretics improve outcomes after the acute presentation. Diuretics may cause neurohormonal activation and aggravate systemic vasoconstriction. Consequently, hemodynamic improvements with diuretics may be attenuated and relief of symptoms may be incomplete (diuretic resistance), increasing the subsequent risk of rehospitalization. Although diuretic resistance can be overcome by continuous IV infusion, or combining a loop and thiazide diuretic (79), patients with AHF may derive incremental benefit from the addition of IV vasoactive therapy (vasodilator or inotrope) (80).

Vasodilators

Vasodilators can rapidly reduce ventricular filling pressures and myocardial oxygen consumption. They can also decrease systemic vascular resistance, decrease ventricular workload, increase stroke volume and improve cardiac output (81). Nitroglycerin is a vasodilator commonly used to relieve pulmonary congestion in patients with AHF. While it is an effective vasodilator, frequent dose titration of IV nitroglycerin is often necessary to produce the desired hemodynamic effects and symptom relief. Doses greater than 140 µg/min to 160 µg/min may be necessary to sufficiently decrease filling pressures and alleviate symptoms (82). Because IV nitroglycerin requires frequent dose titration and may cause dose-dependent hypotension, patients with AHF treated with IV nitroglycerin should be monitored in an intensive care unit and may require invasive hemodynamic monitoring while being treated. Nesiritide, a peptide identical to human BNP, has been studied in clinical trials but is not available in Canada. Emerging data suggest that early initiation of IV vasoactive therapy reduces the subsequent length of hospital stay (67,68).

Positive inotropes

Historically, positive inotropes have been the mainstay for adjuvant therapy for AHF because they improve cardiac output. However, large-scale clinical trials evaluating dobutamine and milrinone for AHF are lacking. The use of dobutamine is supported by small studies documenting improved hemodynamics in AHF patients (83). However, evidence from outcome-driven trials (84) indicates a lack of efficacy in many AHF patients and has revealed safety concerns. Given the lack of compelling evidence supporting the use of positive inotropes and the increased incidence of adverse effects, positive inotropic support for patients with AHF should be reserved for patients with signs of low or very low cardiac output.

Assisted ventilation

Patients with impending respiratory failure from pulmonary edema require rapid initiation of supported ventilation. Endotracheal intubation is often required. However, recent data (85,86) suggest that judicious use of noninvasive ventilation, including continuous positive airway pressure and bilevel positive airway pressure, may obviate the need for intubations in up to 75% of cases.

Practical tips

- Patients with AHF are frequently readmitted; therefore, it is important to determine the cause of the exacerbation because many exacerbations are precipitated by avoidable factors, such as excessive sodium intake or poor adherence to medications (87).

- Patient education and reinforcement regarding heart failure and self-care should be provided to all patients with AHF.
- In patients with very low SBP (less than 90 mmHg), dobutamine may be preferred over milrinone.
- The cardiorenal syndrome (significant worsening of renal dysfunction with severe heart failure) is a serious complication associated with worse outcomes, and it requires consultation with a nephrologist and close monitoring.

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR AND CARDIAC RESYNCHRONIZATION THERAPY

Recommendations

- The decision to implant a device in a heart failure patient should be made with assessment and discussion between the heart failure and arrhythmia specialists (class I, level C).
- An implantable cardioverter defibrillator (ICD) should be considered in patients with ischemic heart disease with or without mild to moderate heart failure symptoms and an LVEF less than or equal to 30%, measured at least one month postmyocardial infarction and at least three months postcoronary revascularization procedure (class I, level A).
- An ICD may be considered in patients with nonischemic cardiomyopathy present for at least nine months, NYHA functional class II to III heart failure, and an LVEF less than or equal to 30% (class IIa, level B) or an LVEF of 31% to 35% (class IIb, level C).
- An ICD may be considered in patients with ischemic heart disease, prior myocardial infarction, three months postcoronary revascularization, left ventricular dysfunction (LVEF 31% to 35%), and with inducible ventricular fibrillation/sustained ventricular tachycardia at electrophysiology study (class IIa, level B), or with either no inducible ventricular fibrillation/sustained ventricular tachycardia at electrophysiology study or without an electrophysiology study (class IIb, level C).
- An ICD should not be implanted in patients with NYHA class IV heart failure who are not expected to improve with any further therapy and who are not candidates for cardiac transplantation (class III, level C).
- Antiarrhythmic drug therapy is discouraged in heart failure patients unless symptomatic arrhythmias persist despite optimal medical therapy with ACE inhibitor plus beta-blocker and correction of any ischemia or electrolyte and metabolic abnormalities (class I, level B).

The CCS and the Heart Rhythm Society recently published a position paper on ICD use (88). Given that no new, relevant randomized controlled trials have been published since then, the recommendations for ICD implantation in heart failure patients in the present document are similar.

Indications for ICDs in patients with heart failure and a previous occurrence of sustained ventricular arrhythmia (secondary prevention)

Three large randomized studies (89-91) (and a subsequent meta-analysis [92]) have compared the use of an ICD with

antiarrhythmic drug therapy (primarily amiodarone) in patients with a history of life-threatening ventricular arrhythmias. Most of the patients in these three trials had left ventricular dysfunction, and many had symptomatic heart failure. Although heart failure per se was not a specific inclusion criterion in any of the trials, the majority of patients had coronary artery disease with prior myocardial infarction or noncoronary congestive cardiomyopathy, with mean ejection fractions in the range of 30% to 35%. As a primary end point, all-cause mortality was reduced in all studies in the defibrillator-treated patients compared with in the antiarrhythmic drug-treated patients (significantly lower in the Antiarrhythmics Versus Implantable Defibrillators [AVID] study [90] and in the meta-analysis [92]); in the secondary analyses of the studies and the meta-analysis, patients with lower ejection fractions (less than 35%), higher NYHA class (classes III or IV) and older age had a higher risk of death and received greater relative and absolute benefits from ICD therapy than did patients without these risk factors. ICDs are the therapy of choice for the prevention of sudden death and all-cause mortality in patients with a history of sustained ventricular tachycardia or ventricular fibrillation, cardiac arrest or unexplained syncope in the presence of left ventricular dysfunction. Patients with symptomatic heart failure, especially with ejection fractions less than 35%, are at particularly high risk of death and stand to receive at least as much benefit as patients not meeting these clinical criteria.

Evidence for ICD benefit in patients with heart failure without a history of sustained ventricular arrhythmia (primary prevention)

All of the 'primary prevention' multicentre trials, which assessed the usefulness of implanted defibrillators to reduce all-cause mortality, selected patients with low LVEF; the most common LVEF cut-off was 35%, although a large study, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II [93]), had a cut-off of 30%. Most studies did not specifically select patients with symptomatic CHF, although the largest study, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT [94]), did select patients with current symptoms, NYHA class II or III, and a history of heart failure for more than three months.

When considering the risk of sudden death and potential benefit from an ICD, the contribution of systolic dysfunction per se versus heart failure symptoms has not been fully defined. Secondary analyses of most studies have indicated that the absolute risk of sudden death, as well as the relative and absolute mortality benefits of an ICD, was greater for patients with lower LVEFs (eg, MADIT II suggested that the majority of the benefit was found in the patients with LVEFs below the median of 27%). In the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study (95), which comprised patients with nonischemic cardiomyopathy, mortality was significantly reduced in patients in NYHA class III with an LVEF less than 30% compared with patients with an LVEF of 30% to 35%. In SCD-HeFT, all-cause mortality was greater in the subgroup with LVEFs less than 30%, and the relative benefit from the ICD was greater (albeit not statistically significantly) than in those patients with LVEFs between 30% and 35%.

It is important to note that in one randomized clinical trial, the Defibrillator in Acute Myocardial Infarction Trial

(DINAMIT [96]), which specifically selected patients soon (less than 40 days) after a myocardial infarction, with an average LVEF of 28% and 52% of the patients having had symptomatic heart failure, there was no significant benefit from the ICD compared with control therapy. Therefore, ICDs are not recommended within the first month after myocardial infarction, and the data suggest that some time needs to elapse after a myocardial infarction before patients are sufficiently stable to derive benefit from prophylactic ICDs. There are fewer data for patients with nonischemic cardiomyopathy than for patients with coronary artery disease, and the absolute mortality for patients with nonischemic cardiomyopathy, at any given LVEF, is less than for patients with coronary artery disease and ischemic cardiomyopathy.

The contribution of heart failure symptoms (as distinct from LVEF) to the absolute and relative benefit of an ICD is less clear. In MADIT II, in which patients with NYHA class I, II or III could be enrolled, patients with greater symptoms of heart failure appeared to derive relatively greater benefit from an ICD. On the other hand, patients in SCD-HeFT with class III heart failure appeared to derive less benefit (smaller relative risk reduction) than those with NYHA class II symptoms. It is plausible to assume that heart failure patients with class III symptoms have higher all-cause mortality than patients with class II symptoms but that they may receive less absolute benefit from an ICD if nonarrhythmic death rates are increased in class III patients or, conversely, that certain patient subsets may receive more absolute benefit if the relative benefit is similar but absolute death rates are increased. Given the uncertainties in the secondary analyses from the clinical trials, there is no clear evidence that NYHA functional class within I to III should be used as a selection criterion for the implantation of an ICD.

CARDIAC RESYNCHRONIZATION THERAPY

Recommendations

- Patients with symptomatic (NYHA III to IV) heart failure despite optimal medical therapy who are in normal sinus rhythm with a QRS duration of 120 ms or longer and an LVEF of 35% or less should be considered for cardiac resynchronization therapy (CRT) (class I, level A).
- The addition of ICD therapy should be considered for patients being referred for CRT who meet the requirements for ICD (class IIa, level B).

Despite patient education, lifestyle modification and improved pharmacological therapy available for heart failure, many patients have persistent severe symptoms. Commonly, these patients have intra- and interventricular conduction delays that are associated with cardiac mechanical dyssynchrony. This compromises ventricular function and is frequently associated with severe symptoms and poor prognosis. CRT uses biventricular pacing to attempt to synchronize the activation of the septum and left ventricular free wall, and to improve the overall left ventricular function. The left ventricular free wall can be paced percutaneously through the coronary sinus in the majority of patients. Failing that, a minithoracotomy can be performed, with the placement of an epicardial lead on the left ventricle.

Since the last CCS heart failure consensus conference, two major studies (97,98) and many smaller studies have been published on CRT in heart failure patients. The large-scale

Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study (97) assessed the role of CRT, with or without ICD, in patients with NYHA III to IV symptoms on optimal medical therapy, a QRS duration greater than or equal to 120 ms, and an LVEF of 35% or less. Patients were randomly assigned to medical therapy alone or to medical therapy in combination with CRT or CRT/ICD therapy. At 12 months, compared with medical therapy alone, CRT significantly reduced the rate of death or hospitalization from any cause. CRT therapy alone nonsignificantly reduced the risk of death from any cause by 24% compared with medical therapy alone ($P=0.059$). Of interest, in the group treated with CRT/ICD, the risk of death was reduced significantly by 36% ($P=0.003$). Finally, the NYHA class, six-minute walked distance and quality of life scores were significantly better in the CRT group than in the medical therapy-only group.

The second large-scale study, Cardiac Resynchronization in Heart Failure (CARE-HF [98]), assessed patients with a history of heart failure of at least six weeks who were in NYHA class III or IV despite optimal medical therapy, and who had an LVEF of 35% or less and a QRS interval of at least 120 ms on an electrocardiogram. Patients with a QRS interval of 120 ms to 149 ms were required to meet two of three additional criteria for dyssynchrony: an aortic pre-ejection delay of more than 140 ms, an interventricular mechanical delay of more than 40 ms or delayed activation of the posterolateral left ventricular wall. Patients were randomly assigned to CRT plus optimal medical therapy or optimal medical therapy alone. The CRT group, compared with the medical therapy-only group, had significantly fewer deaths from any cause and fewer unplanned hospitalizations for a major cardiovascular event. The CRT group also had significantly fewer deaths from any cause than the medical therapy group. As well, the CRT group had better improvement in ejection fraction, overall symptoms and quality of life scores than the medical therapy-only group.

In the past three years, two CRT meta-analysis have been published (99,100). The first meta-analysis (99) showed that CRT reduced the number of deaths from progressive CHF by 51% and heart failure hospitalizations by 29%. In this meta-analysis, CRT was not associated with a significant reduction in all-cause mortality. The second meta-analysis (100) combined data from nine clinical trials to look at the efficacy of CRT. It showed that CRT reduced heart failure hospitalizations but its benefit was seen mainly in patients with NYHA III to IV symptoms. This meta-analysis did not examine the effect of CRT alone in improving survival. With respect to safety issues, the second meta-analysis pooled data from 18 trials to show that CRT was associated with a 0.4% death rate (associated with implantation) and had a 90% implantation success rate.

Unanswered questions remain about exactly who benefits from CRT therapy. Why do all severely symptomatic patients with a wide QRS not benefit from this form of therapy? Does the QRS duration itself matter as much as the finding of cardiac dyssynchrony on echocardiography? What is the best way to evaluate cardiac dyssynchrony? What is the role of CRT in patients with chronic atrial fibrillation? What about patients with right bundle branch block? Should CRT be used in less symptomatic patients to prevent the progression of symptoms? Is there a better way to optimize CRT function by using certain echocardiographic parameters? Several smaller studies have attempted to answer these questions, but the results are not conclusive.

Practical tips

- The decision to implant an ICD in any given patient should be individualized because subgroup analyses of clinical trials have suggested that some patients may not benefit from an ICD.
- Patients with significant comorbidities may not benefit from an ICD. Additional risk stratifiers, such as QRS duration and T wave alternans, are under investigation.
- Subgroup analyses of the primary prevention trials have suggested that the relative and absolute benefits in patients with an LVEF in the 31% to 35% range may be smaller. An electrophysiological study may help to select higher risk patients in this group.
- The LVEF in most patients in the trials, including patients with dilated cardiomyopathy, was very low (average 21% to 25%); therefore, patients with higher LVEF measurements were under-represented in the trials showing benefit.
- A CRT/ICD in highly selected patients with heart failure believed to be 'end stage' may be, in some cases, considered to be appropriate on the grounds that CRT/ICD may in itself improve the prognosis.
- Patients being considered for ICD should have a reasonable quality of life and a life expectancy greater than one year.
- Echocardiography may become used more often to help identify patients and predict clinical response to CRT.

SURGICAL CONSIDERATIONS IN HEART FAILURE PATIENTS

Recommendations

- Heart failure patients with severe refractory symptoms despite optimal medical therapy, and an otherwise good life expectancy, should be considered for heart transplantation (class I, level A).
- Heart failure patients with persistent symptomatic ischemia or large areas of viability should be evaluated for revascularization, either percutaneous or surgical (class I, level C).
- Coronary artery bypass surgery should be offered to patients with appropriate coronary anatomy and mild to moderate left ventricular dysfunction if their predominant symptom is angina (class I, level A).
- Surgical revascularization may be considered in heart failure patients with appropriate anatomy and demonstrable areas of reversible ischemia or viability (class IIb, level C).
- Coronary artery bypass surgery in patients with severe left ventricular dysfunction should be considered only by surgical teams with extensive experience in this group of patients (class I, level B).
- In patients deemed to be favourable surgical candidates who meet the criteria for coronary revascularization, concomitant ventricular reconstruction can be considered by surgical teams experienced with this technique (class IIb, level C).
- Patients requiring surgical coronary revascularization who have evidence of at least moderate mitral insufficiency may be considered for concomitant mitral valve repair or replacement (class IIb, level C).

- Mechanical circulatory support may be offered to selected individuals with end-stage heart failure who are inotrope-dependent and do not meet the traditional criteria for cardiac transplantation (class IIb, level B).

Heart failure remains a disease primarily addressed with medical therapy, and surgical therapy has traditionally been limited to a small minority of patients. Cardiac transplantation remains the preferred treatment for the fortunate few who are eligible and receive a suitable donor organ. Unfortunately for the vast majority of patients, orthotopic heart transplantation is not an option, and they must rely on alternative forms of medical and/or surgical therapy for their debilitating disease.

Because ischemia can depress myocardial function and may progress to further myocardial damage, heart failure patients with coronary artery disease should have all atherosclerotic risk factors aggressively treated; should be investigated for evidence of ischemia or viability; and should be evaluated for revascularization in the presence of persistent angina or documented large areas of ischemia or viability when appropriate. Percutaneous revascularization can generally be performed safely on most heart failure patients with a suitable coronary anatomy. To date, no trial has prospectively evaluated surgical revascularization as a therapy for heart failure. The 'deemed' indications for revascularization in patients with triple-vessel disease and impaired left ventricular function (derived from the Coronary Artery Surgery Study [CASS] [101] results) do not apply in patients with heart failure symptoms. The Surgical Therapy for Ischemic Congestive Heart Failure (STICH) trial is a large, National Institutes of Health-sponsored, multinational trial evaluating surgical therapy, including revascularization, for ischemic cardiomyopathy (102). Similarly, no prospective study has ever shown that left ventricular reconstructive surgery for anterior hypokinesia or akinesia results in either prognostic or symptomatic benefit (103,104). The second primary objective of STICH is to define the role of left ventricular reconstruction in patients undergoing coronary revascularization. The trial has three arms, which are medical therapy, conventional revascularization and revascularization with left ventricular remodelling. Highly symptomatic patients who require surgical revascularization are still candidates for this trial if they meet the minimum criteria for remodelling surgery. In addition, the predictive role of 'viability' assessments will be evaluated in long-term follow-up. The trial has not yet completed enrolment or follow-up.

Recent interest has focused on mitral valve repair for both ischemic and dilated forms of cardiomyopathy. Bolling et al (105), Wu et al (106) and Badhwar et al (107) have shown that the mitral valve can be repaired with an undersized annuloplasty ring in selected patients with reasonable morbidity and mortality. However, two-year survival following surgery is estimated at 70%, and a recent retrospective analysis determined no survival benefit of mitral valve repair in patients with systolic left ventricular dysfunction. Again, no prospective data are available to determine the relative benefits of mitral valve repair in this patient population.

The advent of mechanical circulatory support in the past few years has again dramatically altered the landscape for heart transplantation (108-110). To date, nine active programs in Canada provide mechanical circulatory support, with three

centres providing destination therapy. Advances in device technology will predictably allow for a smaller, more efficient and reliable system. It is foreseeable that in the future, patients listed for heart transplantation will have the option of receiving a biological or a mechanical heart, similar to the choice offered to them today with respect to heart valves. Furthermore, patients who are considered to be unsuitable for cardiac transplantation due to fixed pulmonary hypertension may be ideal candidates for destination therapy and long-term mechanical circulatory support. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial (110) showed that mechanical support provided significantly better short-term survival and quality of life over optimal medical therapy. Almost 1500 patients in Canada are denied cardiac transplantation annually due to our stringent screening process and may potentially benefit from mechanical circulatory support. Other centrifugal and coaxial pumps are under investigation.

Novel surgical therapies include left ventricular remodelling, mechanical circulatory assistance and, more recently, isolated cell transplantation or gene therapy (111-116). The advent of cell transplantation provides great promise for the future because it may be a useful adjunct to several of the previously mentioned therapies. Furthermore, some of the early failures seen with left ventricular remodelling may be prevented with adjuvant cell therapy, and in the case of mechanical circulatory assistance, adjuvant cell transplantation may increase the proportion of patients who are successfully bridged to recovery. However, the era of cell transplantation is only dawning. Several key issues remain unanswered, including the potential side effects of cell transplant therapy. Ongoing prospective clinical trials of angiogenesis by either gene or cell therapy should provide important new data in the next three years.

Practical tip

- The role of surgical revascularization in patients with heart failure and no evidence of reversible ischemia or viable myocardium remains unknown, and these patients should be offered revascularization only in the context of a clinical trial.

ASSESSMENT OF THE ELDERLY HEART FAILURE PATIENT

Recommendations

- The elderly patient with known or suspected heart failure should be assessed for relevant comorbid conditions, including cognitive impairment, dementia and depression, that may affect treatment, adherence to therapy, follow-up or prognosis (level I, class C).
- In hospitalized elderly heart failure patients, delirium should be considered when clinically appropriate (level I, class C).
- In the care of elderly heart failure patients with cognitive impairment, a capable caregiver should be identified (level I, class C).
- Heart failure therapies in elderly heart failure patients should be similar to those in younger patients, although their use may depend primarily on concomitant conditions (level I, class B).

TABLE 5
Atypical clinical features of heart failure in the frail elderly

Symptoms and syndromes	Signs
Delirium	Ankle edema: may reflect venous insufficiency, drug effects, immobility,
Falls	malnutrition
Sudden functional decline	Sacral edema
Sleep disturbances	Pulmonary rales/crackles are nonspecific
Nocturia or nocturnal incontinence	Dyspnea less likely if patient is sedentary

- Elderly heart failure patients who are frail and have a high comorbid disease burden should be followed up in a disease management setting (level I, class A).
- Frail elderly heart failure patients should be referred to a geriatrician for comprehensive geriatric assessment (level I, class B).
- The primary care physician or provider should be involved in the disease management plan of frail elderly heart failure patients (level I, class C).

Although most clinical trials of therapy have studied patients with an average age in the mid-60s, heart failure is common among the elderly, who bear a greater burden of comorbidity and polypharmacy (117), as well as psychogeriatric comorbidities, caregiver burden, health service use, functional decline and frailty (118-120). Frailty characterizes elderly persons with a progressively eroding ability to independently perform activities of daily living, such as bathing, toileting, dressing, grooming and feeding (121). These associations have ramifications on the diagnosis and prognosis of heart failure (122,123) (Table 5). A comprehensive understanding by clinicians of the interaction between heart failure and age-associated syndromes is essential to deal effectively with this growing epidemic.

Heart failure is associated with cognitive impairment in the domains of attention, short-term memory and executive functions (insight, judgement, problem solving and decision-making), and has been associated with nonadherence to treatment, accelerated functional decline and mortality (124-127). Acute and fluctuating cognitive impairment, or delirium, can be precipitated by decompensated heart failure (128). Generally under-recognized by health care providers, delirium is usually reversible, although it may persist well beyond hospital discharge (129). The Confusion Assessment Method is an effective screening instrument for delirium (sensitivity and specificity of 94% to 100% and 90% to 95%, respectively) (130). Chronic cognitive impairment can occur in patients with stable heart failure and is known as dementia if it impinges on independent function (such as adherence to prescribed therapy). A number of screening instruments for dementia exist; although none has clearly been shown to be superior to the widely used and studied Mini-Mental State Examination, the Mini-Cog is briefer (131,132). Cognitive impairment reported by a caregiver should not be overlooked (131).

Symptoms of depression are common in heart failure patients (133). Depression reduces quality of life; increases the risk of functional impairment, rehospitalization and mortality; and may reduce adherence to prescribed therapy (134). Depression and heart failure share common clinical features in elderly patients, including weight gain, sleep disturbances, fatigue, poor energy and cognitive disturbances (134). A number of instruments exist to screen for depression in the elderly, and while none is

TABLE 6
Causes of orthostatic hypotension

Medications	Antipsychotics
	Tricyclics
	Diuretics
	Antihypertensives and vasodilators
	Alpha-antagonists
	Antiparkinsonian agents
Medical conditions	Adrenal insufficiency
	Bed rest, deconditioning
	Postprandial hypotension
	Heat-induced vasodilation
	Systolic hypertension
	Volume depletion
	Peripheral neuropathy
	Parkinsonian syndromes
	Autonomic failure

clearly superior, the Geriatric Depression Scale may be advantageous in identifying patients with mild depression (135). Short versions of the Geriatric Depression Scale have been validated and have acceptable psychometric properties (136).

Pharmacotherapy of heart failure in elderly patients

A few randomized trials of therapies conducted specifically in elderly populations, in conjunction with a multitude of data from observational data sets, suggest that most recommendations on heart failure therapies are applicable to elderly patients. Observational data suggest that ACE inhibitor use in elderly heart failure patients may preserve cognition, slow functional decline, and reduce hospitalizations and perhaps even mortality, even in patients with relative contraindications, such as mild to moderate renal impairment (137-139). The beta-blocker nebivolol has been studied in 2128 patients 70 years of age or older with clinical evidence of heart failure regardless of ejection fraction (140). After a follow-up of less than two years, a significant benefit for nebivolol was seen with reduction of the combined primary end point of mortality and cardiovascular hospitalization. The Japanese Diastolic Heart Failure Study (141) will further evaluate the effects of the beta-blocker carvedilol in 800 elderly Japanese patients with heart failure and a documented ejection fraction greater than 40%.

Elderly patients are vulnerable to adverse drug events (ADEs) due to the growing complexity of medication regimens, age-related physiological changes and a higher burden of comorbid illnesses (142). Cardiovascular medications are frequently associated with ADEs in the elderly (143). Digoxin toxicity can occur at therapeutic serum concentrations (144). Falls are common presentations of ADEs in the elderly, often from postural hypotension. In randomized trials of medications for heart failure, titration to target doses is less frequently successful in older patients due to higher side effect rates. As such, care must be taken with titration of medications to target doses to avoid ADEs. In particular, orthostatic hypotension is a frequent side effect in elderly patients, but if recognized, it can be managed to allow for use of evidence-based therapies (Table 6).

Cardiovascular medications in general, and heart failure medications in specific, are underprescribed to older patients, despite the observation that, as a result of a higher baseline incidence of cardiovascular events, the absolute benefit of

evidenced-based therapies may be greater in the elderly population (145,146).

Management programs for heart failure in the elderly

Systematic reviews (147) support the role of heart failure management programs in elderly heart failure populations. While active involvement of caregivers in patient monitoring and medication adjustment is common to studies showing benefit, the optimal way of providing heart failure management remains an ongoing subject of debate. The precise design of such care delivery systems depends, in part, on local resources and infrastructure. Comprehensive geriatric assessment, shown to improve function, prevent hospitalization and institutionalization, reduce the risk of adverse drug reactions and improve suboptimal prescribing, may have a role in the management of frail elderly patients with heart failure (148-150).

The occurrence of diabetes mellitus and renal insufficiency in older heart failure patients carries a significantly worse prognosis and a greater likelihood of ADEs. The potential for contradictory recommendations may arise when these comorbidities are managed in separate settings. Conflicting advice from multiple care providers can result in patient confusion, nonadherence and adverse outcomes. Recommendations to limit diuretic use to maintain renal function or dietary advice to control blood glucose that results in increased sodium intake may lead to worsening heart failure symptoms. An integrative approach to care is required, based on shared therapeutic goals and involving all care providers, including the primary care physician and the patient.

Practical tips

- Depression in elderly heart failure patients should be suspected when many chronic physical complaints persist despite optimal heart failure therapy.
- Heart failure medications may need to be introduced in lower doses and titrated more slowly.
- Supine blood pressure should be measured after a patient has rested for 15 min.
- Standing (not sitting) blood pressure should be measured within three to five minutes. Blood pressure may drop immediately after standing. Orthostatic hypotension is defined as a fall of greater than 20 mmHg in SBP or greater than 10 mmHg in diastolic blood pressure on standing.
- Repeated measurements at different times of the day are advisable because orthostatic hypotension is not consistently present in an individual.
- Orthostatic hypotension may be more likely to be observed in the morning.

Ethical and end-of-life issues

Recommendations

- Patients with heart failure should be approached early in the heart failure disease process regarding their prognosis, advanced medical directives and wishes for resuscitative care. These decisions should be reviewed regularly and specifically after any change in the patient's condition (level I, grade C).
- A substitute decision-maker (proxy) should be identified. (level I, grade C).

- Where possible, a living will should be discussed with patients to clarify wishes for end-of-life care (level I, grade C).
- As patients near the end of life, physicians should readdress goals of therapy – balancing quantity and quality of life, with a shift of focus to quality of life. Palliative care consultation should be considered (level I, grade C).
- Psychosocial issues (eg, depression, fear, isolation, home supports and need for respite care) should be re-evaluated routinely (level I, grade C).
- Caregivers of patients with advanced heart failure should be evaluated for coping and degree of caregiver burden (level I, grade C).

Death from heart failure is due to sudden cardiac death, brady- or tachyarrhythmias, or progressive heart failure. Although there are multiple prognostic markers in heart failure, including ejection fraction (151,152), predicting time of death is notoriously challenging, especially given the cyclical nature of the disease. Recent technological advances have led to increased complexity of care and decision-making at the end of life. As a result, advanced care planning for patients with CHF must be addressed earlier in the course of the disease, allowing patients the opportunity to review the issues surrounding death from heart failure before the development of an acute exacerbation.

NYHA class II patients have a better prognosis; however, they are at a proportionally higher risk of sudden cardiac death ('drop'). Patients with class IV symptoms have a one-year mortality as high as 75% and a significantly higher risk of dying of progressive heart failure characterized by increasing shortness of breath, orthopnea, and decreasing blood pressure and level of consciousness ('drown') (153-155). Patients in NYHA class II to III who receive an ICD may progress to class IV symptoms, with the likely mode of death changing from drop to drown.

Patient preferences suggest that critically ill patients living with heart failure want treatment at the end of life (156); however, these preferences are not stable over time. This may reflect the cyclical nature of CHF, with decision-making being dependent on symptomatic status. In fact, patients with CHF assign a higher degree of importance to symptom management than to survival and are more likely to decline treatment when the likelihood of an adverse event increases (157,158).

Physician preferences for treatment also influence decision-making at end of life. In the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) (156), 24% of physicians did not correctly perceive their patient's resuscitation preference. Physician preference was based on the physician's resuscitation preference if he or she were in the patient's condition. Although these patients were ill and many physicians expected them to die within two months, only 25% of patients reported that they had discussed preferences for resuscitation with their physicians. Open and honest dialogue with patients and their families regarding treatment at end of life is necessary to guarantee that care reflects patient preferences and avoids unnecessary conflict among the patient, family and clinicians during a very difficult time. Suggested domains of care that should be considered at the end of life are given in Table 7 (159).

It is critical with the current technologically advanced therapy that programs proactively include a comprehensive

TABLE 7
End-of-life domains in treatment guidelines for life-limiting diseases

1. Necrology (death statistics, including sex, age at death and any racial disparities)
2. Natural history (prognosis, time course, mode of death and symptoms)
3. Pain assessment and management
4. Nonpain symptom assessment and management (eg, dyspnea, nausea and vomiting, delirium and fatigue)
5. Psychological issues (depression, anxiety, fear, loneliness and emotional awareness)
6. Social issues (interpersonal relationships with spouses or partners, family and friends; supporting these relationships)
7. Spiritual issues (abandonment, completion of tasks, acceptance, religious tasks and choices)
8. Patient or family values (any discussion regarding patient and family goals and values, including advanced directives and 'do not resuscitate')
9. Family roles and responsibilities (communication of patient and family member roles during the process, grief and bereavement, caregiver role and support)
10. Financial issues (cost to patient and family, not insurer or societal cost)
11. Goals of care (goals of care related to quality of life and end-of-life care)
12. Ethics, laws and policies (individual versus organization ethics, patients' self-determination, double effect, legal aspects of withdrawal and withholding of life support)
13. Physician roles in advocacy and policy (including pronouncement, autopsy, organ donation, advocacy and changing institutional policy)
14. Physician communication with patient and family (including communication with patient and family about personal grief and bereavement)
15. Settings of care (options for location of end-of-life care, referral to hospice and funeral arrangements)

process for potential device withdrawal that includes detailed informed consent and advance care planning. As increasing numbers of ICDs are implanted, there will be a greater number of patients with terminal CHF with active ICDs. Turning off the defibrillator function of an ICD in patients with advanced heart failure may change the mode of death from progressive heart failure to sudden death, often a more preferable and less symptomatic form of death (160,161).

Advanced directives, or living wills, enable competent persons to maintain control over their medical care should they lose their decision-making capacity (162). Advanced directives determine what decisions are to be made and who makes the decisions (162,163). Incorporating this early in the care of the heart failure patient allows patient wishes to be upheld throughout the disease course. Advanced directives require communication among patients, families and health care providers (163). Given the episodic nature of heart failure, issues regarding therapy should be revisited throughout the course of the disease. It is critical that physicians help capable patients clarify and regularly update their views about these issues with both complicated (eg, ventilation) and simple (eg, IV fluids) therapies (162).

Quality end-of-life care has three crucial elements: support of dying patients and their families; control of pain and other symptoms; and decisions on the use of life-sustaining therapies (164). End-of-life care incorporates features of truth-telling,

TABLE 8
Advanced directives

Provincial variations exist in the type of advanced directive that is legal in that province. It is important to prepare an advanced directive that is legal in your province; if both instructive and proxy are permitted, both should be prepared. In provinces where advanced directives are not legally binding, they continue to be useful to open lines of communication between the patient, his or her family, and the health care professionals, and help to guide future health care decisions. The table below indicates what is legal in each province.

Advanced directives indicate a patient's wishes when they are no longer able to express them. They come into effect only when the patient is no longer competent to make decisions. Instructive directives, also known as a 'living will', inform health care professionals what or how health care decisions are to be made. They may contain specific instructions or may define general principles to be followed when health care decisions are made. Proxy directives, also known as 'substitute decision-maker' or 'durable power of attorney for health care', define who will make health care decisions when the patient is no longer able to make these decisions.

Province or territory	Instructive	Proxy
British Columbia	Yes	Yes
Yukon	No	Yes
Alberta	Yes	Yes
Nunavut	No legislation	No legislation
Saskatchewan	Yes	Yes
Manitoba	Yes	Yes
Ontario	Yes	Yes
Quebec	No	Yes
New Brunswick	No legislation	No legislation
Nova Scotia	No	Yes
Prince Edward Island	Yes	Yes
Newfoundland and Labrador	Yes	Yes

Adapted from reference 171

consent, capacity, substitute decision-making, advance care planning and appropriate use of life-sustaining treatment (164). Symptom control is especially important for patients with progressive heart failure because many patients will feel increasing dyspnea and a sensation of drowning at the end of life. Although heart failure physicians are comfortable with the use of diuretics for symptom control, many patients will require short- or long-acting narcotics for dyspnea.

Caregivers for people with chronic illnesses, such as heart failure, experience an increased morbidity and mortality. Caregiver burden is an independent risk factor for mortality, as well as emotional distress and loneliness (165). Although it is important for caregivers to be involved in all aspects of care, as the number of care tasks increase, as well as the perceived degree of difficulty in performing these tasks, so does the degree of depression among caregivers (166). Younger caregivers experienced a greater degree of distress than did their older counterparts (167). Female spouses providing more than 9 h of caregiving activities per week had a twofold increased risk of developing coronary artery disease (168).

Practical tips

- Engage patients and families in open and honest discussion about the prognosis of heart failure, including possible modes of death.

- Sample living wills are available from the University of Toronto Web site (<www.utoronto.ca/jcb/outreach/living_wills.htm>).
- Provincial variations exist regarding the legality of the various components of advanced care directives (instructive versus proxy) (Table 8).
- Effective communication and documentation is essential to ensure continuity of care between inpatient and outpatient settings.

CONCLUSIONS

The provision of optimal care to patients with heart failure presents many challenges to the patient, their family or caregivers, the physician, other health care providers and the health care system. An accurate and timely diagnosis is critical to initiate treatment that will relieve symptoms, improve quality of life, reduce hospitalizations and prolong survival. The past 20 years have seen dramatic changes in our understanding of heart failure and the introduction of many new treatment modalities. These consensus recommendations should provide an evidence-based road map to translate knowledge into practice and allow health care practitioners to make the best clinical judgments and decisions for their individual patient. Practical tools to improve implementation are being developed by a Clinical Practice and Health Outcomes Impact Working Group of the CCS, which is also identifying potential organizational barriers to implementation and specific measurable outcome audit criteria. Because new evidence will continue to be published, these recommendations will be updated in 12 months. Our goal is that this will improve the delivery of best care and practices to heart failure patients in Canada.

REFERENCES

- Johansen H, Strauss B, Arnold JMO, Moe G, Liu P. On the rise: The current and projected future burden of congestive heart failure hospitalization in Canada. *Can J Cardiol* 2003;19:430-5.
- Johnstone DE, Abdulla A, Arnold JMO, et al. Report of the Canadian Cardiovascular Society's Consensus Conference on the diagnosis and management of heart failure. *Can J Cardiol* 1994;10:613-31.
- Liu P, Arnold JMO, Belenkie I, et al. The 2001 Canadian Cardiovascular Society consensus guideline update for the management and prevention of heart failure. *Can J Cardiol* 2001;17(Suppl E):5E-25E.
- Liu P, Arnold JMO, Belenkie I, et al. The 2002/3 Canadian Cardiovascular Society consensus guideline update for the diagnosis and management of heart failure. *Can J Cardiol* 2003;19:347-56.
- 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.
- The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th edn. Boston: Little, Brown, 1994.
- Piepoli MF, Flather M, Coats AJ. Overview of studies of exercise training in chronic heart failure: The need for a prospective randomized multicentre European trial. *Eur Heart J* 1998;19:830-41.
- McKelvie RS, Teo KK, McCartney N, Humen D, Montague T, Yusuf S. Effects of exercise training in patients with congestive heart failure: A critical review. *J Am Coll Cardiol* 1995;25:789-96.
- Piepoli MF, Davos C, Francis DP, Coats AJ; ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;328:189-92.
- Pina IL, Apstein CS, Balady GJ, et al; American Heart Association Committee on exercise, rehabilitation, and prevention. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation* 2003;107:1210-25.
- Stone JA, Cyr C, Friesen M, Kennedy-Symonds H, Stene R, Smilovitch M; Canadian Association of Cardiac Rehabilitation. Canadian guidelines for cardiac rehabilitation and atherosclerotic heart disease prevention: A summary. *Can J Cardiol* 2001;17(Suppl B):3B-30B.
- Working Group on Cardiac Rehabilitation and Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. Recommendations for exercise testing in chronic heart failure patients. *Eur Heart J* 2001;22:37-45.
- Smart N, Marwick TH. Exercise training for patients with heart failure: A systematic review of factors that improve mortality and morbidity. *Am J Med* 2004;116:693-706.
- Wait Time Alliance for Timely Access to Health Care. It's About Time: Achieving Benchmarks and Best Practices in Wait Time Management. Ottawa: Canadian Medical Association, 2005.
- McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: A systematic review of randomized trials. *J Am Coll Cardiol* 2004;44:810-9.
- Gwadry-Sridhar FH, Flintoft V, Lee DS, Lee H, Guyatt GH. A systematic review and meta-analysis of studies comparing readmission rates and mortality rates in patients with heart failure. *Arch Intern Med* 2004;164:2315-20.
- Holland R, Battersby J, Harvey I, Lenaghan E, Smith J, Hay L. Systematic review of multidisciplinary interventions in heart failure. *Heart* 2005;91:899-906.
- Bradley TD, Logan AG, Kimoff RJ, et al; CANPAP Investigators. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005;353:2025-33.
- The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the

ACKNOWLEDGEMENTS: This consensus conference was supported by the Canadian Cardiovascular Society. The authors are indebted to John H Parker and Lise Hodgson of the Canadian Cardiovascular Society, Gordon Marchiori PhD and Kim Harrison for logistic and administrative support.

SECONDARY PANELISTS: Tom Ashton MD FRCPC, Penticton, British Columbia; Victor Huckell MD FRCPC, University of British Columbia, Vancouver, British Columbia; Debra Isaac MD FRCPC, University of Calgary, Calgary, Alberta; Marie-Helene Leblanc MD FRCPC, Hopital Laval, Sainte-Foy, Quebec; Gary E Newton MD FRCPC, Mount Sinai Hospital, Toronto, Ontario; Joel Niznick MD FRCPC, The Ottawa Hospital, General Campus, Ottawa, Ontario; Sherryn N Roth MD FRCPC, Scarborough General Hospital, Toronto, Ontario; Denis Roy MD FRCPC, Institut de Cardiologie de Montreal, Montreal, Quebec; Stuart Smith MD FRCPC, St Mary's Hospital, Kitchener, Ontario; Bruce A Sussex MD FRCPC, Health Sciences Centre, St John's Newfoundland; Salim Yusuf MD FRCPC, McMaster University, Hamilton, Ontario.

The following primary panel members also represented their respective societies:

Ross Tsuyuki, Canadian Pharmacists Association; Anna Svendsen, Canadian Nurses Association; George Heckman, Canadian Geriatrics Society; Errol J Sequeira, College of Family Physicians of Canada.

CONFLICT OF INTEREST: The panelists had complete editorial independence in the development and writing of this manuscript, and functioned on a pro bono basis. A full description of the planning of this consensus conference and the ongoing process (including the needs assessment, the methods of searching for and selecting the evidence for review, and the conflict of interest statements of panel members) is available at <www.ccs.ca>.

- Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
20. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
 21. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
 22. 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.
 23. 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.
 24. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821-8.
 25. 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.
 26. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet* 1999;353:9-13.
 27. Merit-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Interventional Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.
 28. Packer M, Coats AJ, Fowler MB, et al; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.
 29. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. *Lancet* 2001;357:1385-90.
 30. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: A systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;355:1575-81.
 31. Dulin BR, Haas SJ, Abraham WT, Krum H. Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. *Am J Cardiol* 2005;95:896-8.
 32. Shekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: A meta-analysis of major clinical trials. *J Am Coll Cardiol* 2003;41:1529-38.
 33. Willenheimer R, van Veldhuisen DJ, Silke B, et al; CIBIS III Investigators. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: Results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation* 2005;112:2426-35.
 34. Granger CB, McMurray JJ, Yusuf S, et al; CHARM Investigators and Committees. 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.
 35. Pfeffer MA, McMurray JJ, Velazquez EJ, et al; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-906. (Erratum in 2004;350:203)
 36. McMurray JVV, Östergren J, Swedberg K, et al; CHARM Investigators. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: The CHARM-Added trial. *Lancet* 2003;362:767-71.
 37. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
 38. Dimopoulos K, Salukhe TV, Coats AJ, Mayet J, Piepoli M, Francis DP. Meta-analyses of mortality and morbidity effects of an angiotensin receptor blocker in patients with chronic heart failure already receiving an ACE inhibitor (alone or with a beta-blocker). *Int J Cardiol* 2004;93:105-11.
 39. Pitt B, Zannad F, Remme WJ, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
 40. Pitt B, Williams G, Remme W, et al. The EPHEsus trial: Eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. *Cardiovasc Drugs Ther* 2001;15:79-87.
 41. Taylor AL, Ziesche S, Yancy C, et al; African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351:2049-57. (Erratum in 2005;352:1276)
 42. Gattis WA, Hasselbald V, Whelan DJ, O'Connor CM. Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: Results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. *Arch Intern Med* 1999;159:1939-45.
 43. Tsuyuki RT, Fradette M, Johnson JA, et al. A multicenter disease management program for hospitalized patients with heart failure. *J Card Fail* 2004;10:473-80.
 44. Tsuyuki RT. Drug-induced congestive heart failure. In: Tisdale JE, Miller D, eds. *Drug-Induced Diseases*. Bethesda: ASHP Publications, 2005.
 45. Amabile CM, Spencer AP. Keeping your patient with heart failure safe. A review of potentially dangerous medications. *Arch Intern Med* 2004;164:709-20.
 46. Feenstra J, Grobbee DE, Remme WJ, Stricker BH. Drug-induced heart failure. *J Am Coll Cardiol* 1999;33:1152-62.
 47. Hemmelgarn BR, McAllister FA, Myers MG, et al. The 2005 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 1 – blood pressure measurement, diagnosis and assessment of risk. *Can J Cardiol* 2005;21:645-56.
 48. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: Diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002;105:1387-93.
 49. 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.
 50. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis* 2005;47:320-32.
 51. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function: Clinical approaches to diagnosis and treatment of diastolic heart failure. *Arch Intern Med* 1996;156:146-57.
 52. Massie BM, Fabi MR. Clinical trials in diastolic heart failure. *Prog Cardiovasc Dis* 2005;47:389-95.
 53. Yusuf S, Pfeffer MA, Swedberg K, et al; CHARM Investigators and Committees. 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. Hasenfuss G, Holubarsch C, Hermann HP, Astheimer K, Pieske B, Just H. Influence of the force-frequency relationship on haemodynamics and left ventricular function in patients with non-failing hearts and in patients with dilated cardiomyopathy. *Eur Heart J* 1994;15:164-70.
 55. Kass DA. Force-frequency relation in patients with left ventricular hypertrophy and failure. *Basic Res Cardiol* 1998;93:108-16.
 56. Yu CM, Sanderson JE. Right and left ventricular diastolic function in patients with and without heart failure: Effect of age, sex, heart rate, and respiration on Doppler-derived measurements. *Am Heart J* 1997;134:426-34.
 57. Kamamura K, Shannon RP, Pasipoulourides A, et al. Alterations in left ventricular diastolic function in conscious dogs with pacing-induced heart failure. *J Clin Invest* 1992;89:1825-38.
 58. Boos CJ, Carlsson J, More RS. Rate or rhythm control in persistent atrial fibrillation? *QJM* 2003;96:881-92.
 59. Heart Disease and Stroke Statistics 2004. American Heart Association, American Stroke Association, 2003.
 60. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. *Am Heart J* 1999;137:352-60.

61. Aghababian RV. Acutely decompensated heart failure: Opportunities to improve care and outcomes in the emergency department. *Rev Cardiovasc Med* 2002;3(Suppl 4):S3-9.
62. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997;157:99-104.
63. Johansen H, Strauss B, Arnold JM, Moe G, Liu P. On the rise: The current and projected future burden of congestive heart failure hospitalization in Canada. *Can J Cardiol* 2003;19:430-5.
64. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2001;38:2101-13.
65. Hunt SA; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005;46:e1-82.
66. Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: The Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26:384-416.
67. Didomenico RJ, Park HY, Southworth MR, et al. Guidelines for acute decompensated heart failure treatment. *Ann Pharmacother* 2004;38:649-60.
68. Emerman CL. Treatment of the acute decompensation of heart failure: Efficacy and pharmacoeconomics of early initiation of therapy in the emergency department. *Rev Cardiovasc Med* 2003;4(Suppl 7):S13-20.
69. Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): Opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med* 2003;4(Suppl 7):S21-30.
70. Brater DC. Diuretic therapy. *N Engl J Med* 1998;339:387-95.
71. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 1985;103:1-6.
72. 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.
73. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: Derivation and validation of a clinical model. *JAMA* 2003;290:2581-7.
74. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: Classification and regression tree analysis. *JAMA* 2005;293:572-80.
75. Januzzi JL Jr, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005;95:948-54.
76. 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.
77. McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: Analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002;106:416-22.
78. Albert NM, Eastwood CA, Edwards ML. Evidence-based practice for acute decompensated heart failure. *Crit Care Nurse* 2004;24:14-6, 18-24, 26-9.
79. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: Bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996;28:376-82.
80. Jain P, Massie BM, Gattis WA, Klein L, Gheorghide M. Current medical treatment for the exacerbation of chronic heart failure resulting in hospitalization. *Am Heart J* 2003;145(2 Suppl):S3-17.
81. Steimle AE, Stevenson LW, Chelimsky-Fallick C, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. *Circulation* 1997;96:1165-72.
82. Dupuis J, Lalonde G, Lebeau R, Bichet D, Rouleau JL. Sustained beneficial effect of a seventy-two hour intravenous infusion of nitroglycerin in patients with severe chronic congestive heart failure. *Am Heart J* 1990;120:625-37.
83. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: Differing hemodynamic effects and individual patient responsiveness. *Circulation* 1986;73:III75-83.
84. 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.
85. Pang D, Keenan SP, Cook DJ, Sibbald WJ. The effect of positive pressure airway support on mortality and the need for intubation in cardiogenic pulmonary edema: A systematic review. *Chest* 1998;114:1185-92.
86. Poponick JM, Renston JP, Bennett RP, Emerman CL. Use of a ventilatory support system (BiPAP) for acute respiratory failure in the emergency department. *Chest* 1999;116:166-71.
87. Tsuyuki RT, McKelvie RS, Arnold JM, et al. Acute precipitants of congestive heart failure exacerbations. *Arch Intern Med* 2001;161:2337-42.
88. Tang AS, Ross H, Simpson CS, et al. Canadian Cardiovascular Society/Canadian Heart Rhythm Society position paper on implantable cardioverter defibrillator use in Canada. *Can J Cardiol* 2005;21(Suppl A):11A-8A.
89. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;101:1297-302.
90. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576-83.
91. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;102:748-54.
92. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. *Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J* 2000;21:2071-8.
93. Moss AJ, Zareba W, Hall WJ, et al; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-83.
94. Bardy GH, Lee KL, Mark DB, et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-37. (Erratum in 2005;352:2146)
95. Kadish A, Dyer A, Daubert JP, et al; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;350:2151-8.
96. Hohnloser SH, Kuck KH, Dorian P, et al; DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-8.
97. Bristow MR, Saxon LA, Boehmer J, et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.
98. Cleland JG, Daubert JC, Erdmann E, et al; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.
99. McAlister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: Cardiac resynchronization in patients with symptomatic heart failure. *Ann Intern Med* 2004;141:381-90.
100. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: A meta-analysis of randomized controlled trials. *JAMA* 2003;289:730-40.
101. Myers WO, Schaff HV, Gersh BJ, et al. Improved survival of surgically treated patients with triple vessel coronary artery disease and severe

- angina pectoris. A report from the Coronary Artery Surgery Study (CASS) registry. *J Thorac Cardiovasc Surg* 1989;97:487-95.
102. Doenst T, Velazquez EJ, Beyersdorf F, et al; STICH investigators. To STICH or NOT to STICH: We know the answer, but do we understand the question? *J Thorac Cardiovasc Surg* 2005;129:246-9.
 103. Mickleborough LL, Merchant N, Ivanov J, Rao V, Carson S. Left ventricular reconstruction: Early and late results. *J Thorac Cardiovasc Surg* 2004;128:27-37.
 104. Dor V, Di Donato M, Sabatier M, Montiglio F, Civaia F; RESTORE Group. Left ventricular reconstruction by endoventricular circular patch plasty repair: A 17-year experience. *Semin Thorac Cardiovasc Surg* 2001;13:435-47.
 105. Bolling SF, Deeb GM, Brunsting LA, Bach DS. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. *J Thorac Cardiovasc Surg* 1995;109:676-82.
 106. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2005;45:381-7.
 107. Badhwar V, Bolling SF. Mitral valve surgery in the patient with left ventricular dysfunction. *Semin Thorac Cardiovasc Surg* 2002;14:133-6.
 108. Stevenson LW, Kormos RL, Barr ML, et al; American College of Cardiology Steering Committee. Mechanical cardiac support 2000: Current applications and future trial design: June 15-16, 2000 Bethesda, Maryland. *Circulation* 2001;103:337-42.
 109. Hunt SA, Frazier OH. Mechanical circulatory support and cardiac transplantation. *Circulation* 1998;97:2079-90.
 110. Rose EA, Gelijns AC, Moskowitz AJ, et al; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med* 2001;345:1435-43.
 111. Menashe P, Hagege AA, Scorsin M, et al. Myoblast transplantation for heart failure. *Lancet* 2001;357:279-80.
 112. Taylor DA, Atkins BZ, Hungspreugs P, et al. Regenerating functional myocardium: Improved performance after skeletal myoblast transplantation. *Nat Med* 1998;4:929-33. (Erratum in 1998;4:1200)
 113. Wang J-S, Shum-Tim D, Galipeau J, Chedrawy E, Eliopolous N, Chiu R-J. Marrow stromal cells for cellular cardiomyoplasty: Feasibility and potential clinical advantages. *J Thorac Cardiovasc Surg* 2000;119:999-1006.
 114. Soonpaa MH, Koh GY, Klug MG, Field LG. Formation of nascent intercalated disks between grafted fetal cardiomyocytes and host myocardium. *Science* 1994;264:98-101.
 115. Yau TM, Fung K, Weisel RD, Fujii T, Mickle DA, Li R-K. Enhanced myocardial angiogenesis by gene transfer with transplanted cells. *Circulation* 2001;104(Suppl 1):I218-22.
 116. Koh GY, Kim SJ, Klug MG, et al. Targeted expression of transforming growth factor-beta1 in intracardiac grafts promotes vascular endothelial cell DNA synthesis. *J Clin Invest* 1995;95:114-21.
 117. Heiat A, Gross CP, Krumholz HM. Representation of elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002;162:1682-8.
 118. Ferrucci L, Guralnik JM, Pahor M, Corti MC, Havlik RJ. Hospital diagnoses, Medicare charges, and nursing home admissions in the year when older persons become severely disabled. *JAMA* 1997;277:728-34.
 119. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. *Am Heart J* 1999;137:352-60.
 120. Newman AB, Gottdiener JS, Mcburnie MA, et al; Cardiovascular Health Study Research Group. Association of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001;56:M158-66.
 121. Rockwood K, Fox RA, Stolee P, Robertson D, Beattie BL. Frailty in elderly people: An evolving concept. *CMAJ* 1994;150:489-95.
 122. Jarrett PG, Rockwood K, Carver D, Stolee P, Cosway S. Illness presentation in elderly patients. *Arch Intern Med* 1995;155:1060-4.
 123. Tresch DD. The clinical diagnosis of heart failure in older patients. *J Am Geriatr Soc* 1997;45:1128-33.
 124. Almeida OP, Flicker L. The mind of a failing heart: A systematic review of the association between congestive heart failure and cognitive functioning. *Intern Med J* 2001;31:290-5.
 125. Roman GC. Vascular dementia: Distinguishing characteristics, treatment, and prevention. *J Am Geriatr Soc* 2003;51(5 Suppl):S296-304.
 126. Ekman I, Fagerberg B, Skoog I. The clinical implications of cognitive impairment in elderly patients with chronic heart failure. *J Cardiovasc Nurs* 2001;16:47-55.
 127. Zuccala G, Pedone C, Cesari M, et al. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. *Am J Med* 2003;115:97-103.
 128. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *JAMA* 1990;263:1097-101.
 129. Kelly KG, Zisselman M, Cuttillo-Schmitter T, Reichard R, Payne D, Denman SJ. Severity and course of delirium in medically hospitalized nursing facility residents. *Am J Geriatr Psychiatry* 2001;9:72-7.
 130. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RJ. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941-8.
 131. Patterson CJ, Gass DA. Screening for cognitive impairment and dementia in the elderly. *Can J Neurol Sci* 2001;28(Suppl 1):S42-51.
 132. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: Validation in a population-based sample. *J Am Geriatr Soc* 2003;51:1451-4.
 133. Gottlieb SS, Khatta M, Friedmann E, et al. The influence of age, gender, and race on the prevalence of depression in heart failure patients. *J Am Coll Cardiol* 2004;43:1542-9.
 134. Joynt KE, Whellan DJ, O'Connor CM. Why is depression bad for the failing heart? A review of the mechanistic relationship between depression and heart failure. *J Card Fail* 2004;10:258-71.
 135. Pignone M, Gaynes BN, Rushton JL, et al, for the Research Triangle Institute - University of North Carolina Evidence-based Practice Center. Screening for Depression: Systematic Evidence Review <<http://www.ahrq.gov/downloads/pub/prevent/pdfser/depser.pdf>> (Version current at December 6, 2005).
 136. Almeida OP, Almeida SA. Short versions of the Geriatric Depression Scale: A study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. *Int J Geriatr Psychiatry* 1999;14:858-65.
 137. Ahmed A, Kiefe CI, Allman RM, Sims RV, DeLong JF. Survival benefits of angiotensin-converting enzyme inhibitors in older heart failure patients with perceived contraindications. *J Am Geriatr Soc* 2002;50:1659-66.
 138. Gambassi G, Lapane KL, Sgadari A, et al. Effects of angiotensin-converting enzyme inhibitors and digoxin on health outcomes of very old patients with heart failure. *Arch Intern Med* 2000;160:53-60.
 139. Zuccala G, Onder G, Marzetti E, et al. Use of angiotensin-converting enzyme inhibitors and variations in cognitive performance among patients with heart failure. *Eur Heart J* 2005;26:226-33.
 140. Flather MD, Shibata MC, Coats AJ, et al; SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215-25.
 141. Hori M, Kitabatake A, Tsutsui H, et al; The J-DHF Program Committee. Rationale and design of a randomized trial to assess the effects of beta-blocker in diastolic heart failure; Japanese Diastolic Heart Failure Study (J-DHF). *J Card Fail* 2005;11:542-7.
 142. Merle L, Laroche ML, Dantoine T, Charnes JP. Predicting and preventing adverse drug reactions in the very old. *Drugs Aging* 2005;22:375-92.
 143. Gurwitz JG, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003;289:1107-16.
 144. Miura T, Kojima R, Sugiura Y, Mizutani M, Takatsu F, Suzuki Y. Effect of aging on the incidence of digoxin toxicity. *Ann Pharmacother* 2000;34:427-32.
 145. Cleland JG, Cohen-Solal A, Aguilar JC, et al; IMPROVEMENT OF Heart Failure Programme Committees and Investigators. Improvement programme in evaluation and management; Study Group on Diagnosis of the Working Group on Heart Failure of The European Society of Cardiology. Management of heart failure in primary care (the IMPROVEMENT OF Heart Failure Programme): An international study. *Lancet* 2002;360:1631-9.
 146. Heckman GA, Misiaszek B, Merali F, et al. Management of heart failure in Canadian long-term care facilities. *Can J Cardiol* 2004;20:963-9.
 147. Gonseth J, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure:

- A systematic review and meta-analysis of published reports. *Eur Heart J* 2004;25:1570-95.
148. Stuck AE, Siu AL, Wieland GD, Adams A, Rubenstein LZ. Comprehensive geriatric assessment: A meta-analysis of controlled trials. *Lancet* 1993;342:1032-6.
 149. Schumaker KE, Hanlon JT, Pieper CF, et al. Effect of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med* 2004;116:394-401.
 150. Chin MH, Wang JC, Zhang JX, Sachs GA, Lang RM. Differences among geriatricians, general internists, and cardiologists in the care of patients with heart failure: A cautionary tale of quality assessment. *J Am Geriatr Soc* 1998;46:1349-54.
 151. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 1991;325:1468-75.
 152. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. *N Engl J Med* 1998;339:1810-6.
 153. 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.
 154. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-81.
 155. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001;345:1435-43.
 156. Krumholz HM, Phillips RS, Hamel MB, et al. Resuscitation preferences among patients with severe congestive heart failure: Results from the SUPPORT project. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *Circulation* 1998;98:648-55.
 157. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). The SUPPORT Principal Investigators. *JAMA* 1995;274:1591-8. (Erratum in 1996;275:1232)
 158. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. *N Engl J Med* 2002;346:1061-6.
 159. Mast KR, Salama M, Silverman GK, Arnold RM. End-of-life content in treatment guidelines for life-limiting diseases. *J Palliat Med* 2004;7:754-73.
 160. Workman S. End-of-life care and congestive heart failure. *Arch Intern Med* 2003;163:737.
 161. Dickens BM. Legal implications of ICD therapy. *Can J Cardiol* 2000;16:1318-23.
 162. Hebert PC. *Doing Right: A Practical Guide to Ethics for Medical Trainees and Physicians*. Toronto: Oxford University Press, 1996:31.
 163. Singer PA, Robertson G, Roy DJ. Bioethics for clinicians: 6. Advance care planning. *CMAJ* 1996;155:1689-92.
 164. Singer PA, MacDonald N. Bioethics for clinicians: 15. Quality end-of-life care. *CMAJ* 1998;159:159-62.
 165. Schulz R, Beach SR. Caregiving as a risk factor for mortality: The Caregiver Health Effects Study. *JAMA* 1999;282:2215-9.
 166. Saunders MM. Family caregivers need support with heart failure patients. *Holist Nurs Pract* 2003;17:136-42.
 167. Dracup K, Evangelista LS, Doering L, Tullman D, Moser DK, Hamilton M. Emotional well-being in spouses of patients with advanced heart failure. *Heart Lung* 2004;33:354-61.
 168. Lee S, Colditz GA, Berkman L, Kawachi I. Caregiving and risk of coronary heart disease in U.S. women: A prospective study. *Am J Prev Med* 2003;24:113-9.
 169. Pfeffer MA, Greaves SC, Arnold JM, et al. Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial. *Circulation* 1997;95:2643-51.
 170. Tatro DE, ed. *Drug Interaction Facts. Facts and comparisons*. St Louis: A Wolters Kluwer Company, 1998.
 171. Dalhousie University. End of Life Project. <<http://as01.ucis.dal.ca/dhli/default.cfm>> (Version current at December 6, 2005).