

The 2001 Canadian Cardiovascular Society Consensus Guideline Update for the Management and Prevention of Heart Failure

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The Canadian Cardiovascular Society (CCS) heart failure treatment consensus guidelines were previously published in 1994 (1). The document expertly outlined some of the fundamental treatment strategies that remain truisms today. However, significant advances in the understanding and treatment of heart failure have accumulated since 1994. Most notable are the use of beta-blockers and other neurohumoral modulators; also, the increased adoption of heart failure clinics has transformed the treatment landscape for heart failure in Canada. The currently revised guidelines incorporate these new data into a clinical practice guideline format using an evidence-based approach. The expert panel very carefully evaluated each recommendation in light of the evidence available in the context of the unique Canadian health care system and standards of practice. The purpose of the guidelines is to provide practical advice for all health care practitioners who treat heart failure patients.

To formulate the current version of the guidelines, in addition to the individual heart failure experts recommended by the CCS Council, individuals with expertise in cardiac transplantation, arrhythmias, pharmaceutical sciences, clinical trials, guideline dissemination and professional education were included. The group conducted a systematic MEDLINE search, and obtained copies of all the currently available American and European heart failure guidelines, both in print and electronic forms, and Cochrane collaborative reviews. The evidence was then evaluated according to the criteria discussed below, and the consensus statements were proposed, debated, revised and voted on using conference calls and the Delphi system during a face-to-face meeting. The document was then peer reviewed by the entire CCS membership using a unique first-time electronic dissemination system through both electronic mail and posting on the CCS Web site. We received an unprecedented amount of electronic feedback, totalling over 200 responses, and incorporated all the suggestions that are evidence based, innovative and user friendly into the new version of the guidelines.

The preparation of these guidelines was financially supported only by the CCS, without the influence of or funding from industry partners.

LEVELS OF EVIDENCE

Grade A recommendation

Level 1 evidence: Large-scale randomized trials or meta-analysis with clear-cut results

Grade B recommendation

Level 2 evidence: Small-scale randomized trials or meta-analysis with less certain results

Grade C recommendation

Level 3 evidence: Nonrandomized contemporaneous controls

Level 4 evidence: Nonrandomized historical controls

Level 5 evidence: Case series and expert opinion

HEART FAILURE: A DEFINITION

Heart failure is a pathophysiological state in which the heart is unable to pump blood throughout the circulatory system to meet the peripheral demands of the metabolizing tissues. It is often caused by a defect in myocardial contraction and relaxation, and accompanied by elevated cardiac filling pressures. It may also occur when the normal heart is suddenly presented with excessive demands or severe impairment of its filling.

HEART FAILURE: AN EMERGING EPIDEMIC

Heart failure is the most rapidly rising cardiovascular condition to affect the lives of Canadians. This is in distinct contrast to the declining mortality from cardiovascular disease in general and acute conditions, such as myocardial infarction (MI), in particular (2). Over 350,000 Canadians are afflicted with the condition, and the one-year mortality after diagnosis ranges between 25% and 40% (3).

In contrast to MI, heart failure is a chronic condition that is characterized by episodic clinical deterioration interspersed with asymptomatic or minimally symptomatic periods of apparent stability. The acute deterioration often brings the patient to the hospital or the physician's office, where acute treatment is instituted. However, in contrast to the usual perception, heart failure is not 'cured' with the relief of congestive symptoms. The disease often progresses asymptotically with continuing enlargement and adverse remodelling, leading ultimately to chronic debility and increased mortality (4).

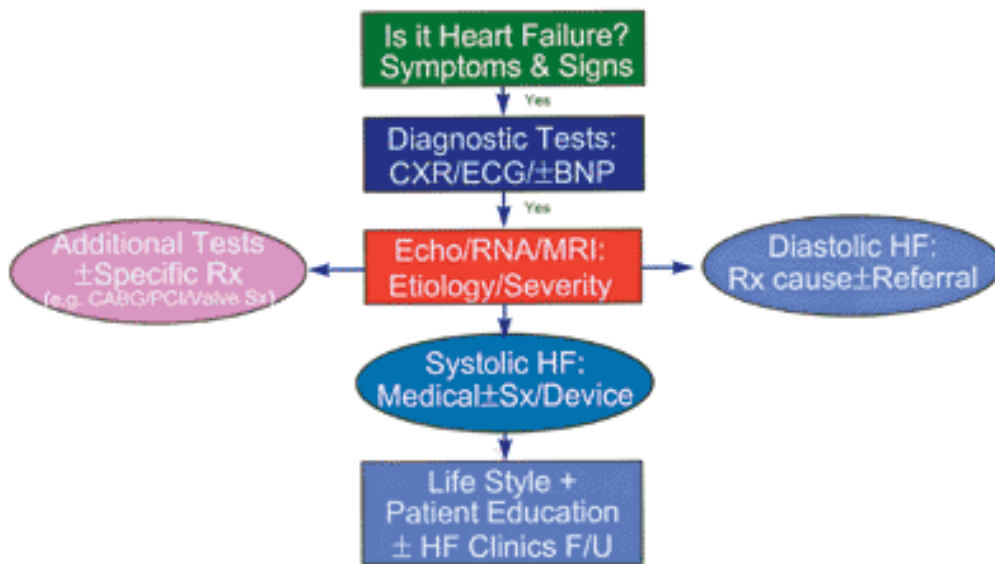
Heart failure also greatly affects the health care system. Heart failure remains the most common diagnosis that brings a patient to hospital for a medical admission (5). Each hospitalization averages eight days of inpatient stay in Canada, accruing a cost of over \$1 billion per year for inpatient hospital care alone. The patients are also usually on a complex regimen of medications, and when unstable, may require repeated admissions to hospital, adding further to the cost of care.

It is evident from the data accumulated that effective treatment strategies are becoming increasingly available to improve both the quantity and quality of life of heart failure patients. Adoption of these new treatment guidelines should improve the survival and the quality of life of these patients, and decrease the requirement of hospitalization and potential costs to the health care system.

GENERAL STRATEGIES IN THE TREATMENT OF HEART FAILURE

Recommendations

- When heart failure has been identified, it is necessary to search for specific or treatable causes that may be reversible for the individual patient.
- Treatment plans for patients with heart failure should take into account the complexity of the syndrome, including comorbid conditions, the presence or absence of systolic dysfunction, the severity of the systolic dysfunction when present and presenting symptomatology. (Grade C)
- In drawing up such a treatment plan, physicians should consider the important contribution that can be provided by other health care professionals, including but not limited to nurses, dietitians, pharmacists, rehabilitation specialists, social workers and home care providers. (Grade A)
- The goals of treatment are to improve the patient's quantity and quality of life, to reduce symptoms and hospitalizations, and to coordinate care that is patient centred and evidence based. (Grade C)
- Vaccination to prevent influenza and pneumonia is recommended for patients with heart failure. (Grade C)
- Increased general awareness of the care of patients with heart failure in health care institutions and the community should be a priority in reducing the overall burden of the disease.



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Figure 1) Modified diagnostic algorithm for both systolic and diastolic heart failure. Basic screening tests are recommended, and if heart failure is confirmed, ventricular function should be assessed by one of the imaging techniques. Identification and treatment of specific etiology is particularly emphasized, and the role of heart failure/function clinics in facilitating the treatment is increasingly being recognized. BNP Brain natriuretic peptide; CABG Coronary artery bypass graft surgery; CXR Chest x-ray; ECG Electrocardiogram; F/U Follow-up; HF Heart failure; MRI Magnetic resonance imaging; PCI Percutaneous coronary intervention; Rx Therapy; Sx Surgery

SPECIAL CONSIDERATIONS IN THE TREATMENT OF HEART FAILURE

The role of heart failure/function clinics

- Specialized heart failure/function clinics and transitional care programs, staffed by physicians and health care professionals with an interest and expertise in heart failure, should be considered for the assessment and management of patients with complex heart failure who are at higher risk of morbidity and mortality. (Grade B)
- Such clinics should also be a resource for physicians, patients and their families. (Grade C)
- Patients who may particularly benefit from the care of a heart failure clinic are those who are not responsive to treatment; experience deterioration while on treatment; were recently seen in the emergency department; require prompt access to care by someone with expertise in heart failure; or whose diagnosis is unclear.
- Telemonitoring by clinic nurses of patients at high risk for deterioration can provide the uninterrupted care required by patients as they move back into the community.

Compliance

- Strategies to improve compliance for patients with heart failure should be part of the planning and implementation of care. (Grade C)

Investigations

- Basic investigations commonly required for heart failure patients include electrocardiogram, chest x-

ray, routine blood work, including evaluation of renal and liver function, and risk factor assessment. There should also be an objective and careful evaluation of ventricular function and chamber size, such as using nuclear or echocardiographic techniques (Figure 1).

- Ischemic heart disease, if suspected to be present, should be appropriately investigated and treated.

PHARMACOLOGICAL THERAPIES FOR SYSTOLIC HEART FAILURE ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR ANTAGONISTS

Recommendations for the use of angiotensin-converting enzyme inhibitors

- Angiotensin-converting enzyme (ACE) inhibitors should be prescribed as soon as safely possible following acute MI for all patients (unless contraindicated or not tolerated) and continued for six weeks. Therapy should be continued indefinitely in those with either left ventricular ejection fraction (LVEF) less than 40% or clinical evidence of congestive heart failure (CHF), even if only transient. (Grade A, Level 1)
- ACE inhibitors should be prescribed as soon as safely possible for all asymptomatic patients with LVEF less than 35% to 40%, unless contraindicated or not tolerated. (Grade A, Level 1)
- ACE inhibitors should be prescribed as soon as safely possible for all patients with symptomatic congestive heart failure, New York Heart Association (NYHA) functional class II to IV, unless contraindicated or not tolerated. (Grade A, Level 1)
- The target ACE inhibitor dose should be either the dose used in placebo controlled mortality trials, for specific ACE inhibitors for which data exist, or the maximum tolerated (or recommended) dose for ACE inhibitors for which no mortality data exist. Where appropriate, ACE inhibitors with efficacy data in the treatment of heart failure should be considered. (Grade A, Level 1)

Recommendations for the use of angiotensin II receptor antagonists

- ACE inhibitors remain the therapy of choice for CHF, and are preferable to angiotensin II receptor antagonists (ARBs). However, ARBs may be considered for those who cannot tolerate ACE inhibitors due to cough. (Grade B, Level 2)
- ARBs may be considered as adjunctive therapy when either beta-blockers or ACE inhibitors are not tolerated. Top priority must be given to the initiation of ACE inhibition and beta-blockade. (Grade B, level 2)
- Current evidence does not support the routine use of combination triple therapy of beta-blocker plus ACE inhibitor plus ARB in the management of CHF. However, patients with advanced symptoms and who are on maximal therapy, and who have adequate renal function and blood pressure may be referred for the consideration of combination ACE inhibitor plus ARB therapy, with the aim to reduce hospitalization and improve quality of life. (Grade C, Level 3)

Practical tips

- There is no evidence to suggest that there is a 'best' ACE inhibitor for the treatment of heart failure; however, it is useful to consider those with efficacy in heart failure treatment based on clinical evidence. It is likely more important to use ACE inhibitors in higher doses or doses used in trials.
- Studies evaluating ACE inhibitors in left ventricular (LV) dysfunction generally include patients with serum creatinine levels less than 220 mmol/L, potassium less than 5.5 mmol/L and systolic blood pressure (BP) greater than 80 to 85 mmHg, and without a history of angioedema due to ACE inhibitors.

EVIDENCE AND RATIONALE

ACE inhibitors and CHF

All ACE inhibitors inhibit ACE, which results in the suppression of angiotensin II generation from angiotensin I and inhibition of bradykinin breakdown. The effects of ACE inhibitors occur both in plasma and tissue. The precise mechanism by which ACE inhibitors exert their clinical benefits remains unknown, though it is likely through some combination of the two above-mentioned effects. The latter effect leads to the ACE inhibitor cough – a dry, low grade, usually nonparoxysmal cough in the absence of ongoing venous congestion.

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial (6), published in 1987, was the first of several landmark trials that demonstrated that ACE inhibitors significantly reduced mortality in chronic CHF due to LV systolic dysfunction (when LVEF is less than 35% to 40%). Since then, clinical trials involving nearly 100,000 patients, randomly assigned to groups treated with ACE inhibitors or placebo, have been published. The results of these trials have firmly established ACE inhibitors as first-line therapy for chronic CHF, whether symptomatic or asymptomatic (7-10). An overview of the literature shows that ACE inhibitors reduce total mortality, total hospitalizations, worsening heart failure and recurrent MI by 20% to 25% when used for patients with LV systolic dysfunction (11). Indeed, additional observations seen in these studies have led to research of further questions. The result has been the expansion of the therapeutic uses for ACE inhibitors to new indications, such as chronic ischemic heart disease, regardless of EF, and diabetic renal disease (12) (see 'Prevention' below).

Important ancillary data from these trials have confirmed the central role of neurohumoral activation in the cause and progression of chronic CHF. Suppression of neurohumoral activation is strongly linked to improvements in hemodynamics, cardiac remodelling, symptoms and mortality benefit (13). In general, patients with more advanced illness derive greater benefit than those earlier in the course of disease. There are currently no mortality data to support the use of ACE inhibitors for patients with chronic CHF and EF greater than 40% (CHF with preserved LV function) in the absence of another indication for ACE inhibitor therapy.

Use and side effects of ACE inhibitors

ACE inhibitors should be introduced as soon as safely possible and in a stepwise fashion. Dose titration should be performed every seven to 14 days or sooner if the patient is in hospital. Baseline serum electrolyte and creatinine levels should be documented and tests repeated seven to 14 days later or before each titration. The target dose should be equal to the dose regimens used in clinical trials or the maximally tolerated dose (Table 1).

Side effects of ACE inhibitors include cough – a class effect that leads to discontinuation in up to 5% of patients. It is important to remember that cough can occur in up to 40% of patients with CHF and is most frequently a manifestation of uncontrolled CHF rather than ACE inhibition (14). Hypotension, renal dysfunction and hyperkalemia may occur. With renal dysfunction and hypotension, overdiuresis is frequently a contributing factor, and the reduction of concomitant diuretics may improve or reverse the problem. Other side effects include skin rash, taste disturbance and angioedema, which, though rare, can be life-threatening.

Contraindications to ACE inhibitor therapy include previously documented intolerance, severe hyperkalemia, greater than 5.0 mmol/L (in absence of potassium supplements or potassium-sparing diuretics), symptomatic hypotension with systolic BP less than 80 mmHg, bilateral renal artery stenosis or progressive renal insufficiency. An important point regarding side effects is the frequent misconception that elderly patients cannot tolerate or benefit from ACE inhibitors. In fact, elderly patients with CHF are less likely to receive these medications, while evidence shows that they derive at least equal benefit from ACE inhibitor therapy. In the recently completed Evaluation of Losartan in the Elderly Study (ELITE) II (15), 3152 patients were randomly assigned to groups treated with either captopril (n=1574) or losartan (n=1578), and were followed for a mean 555 days. Over 85% of these patients were older than 65 years of age and only 2% of patients withdrew from the study medication due to renal impairment. Thus, ACE inhibitors should be strongly considered in elderly patients with baseline creatinine levels less than 220 mmol/L and

potassium levels less than 5.0 mmol/L.

Dosage and class effect of ACE inhibitors

The 2001 CCS guidelines reaffirm the central role of ACE inhibitor therapy for the management of chronic CHF with EF less than 40%. Previous guidelines suggested duplication of dose regimens used in clinical trials when applied to the bedside. Recent publications show that high-dose ACE inhibitor therapy is superior to low-dose therapy; possibly half the benefits of ACE inhibitor therapy are related to the use of high doses. While there are many ACE inhibitors available, it is useful to consider those with clinical evidence of benefit when starting a new patient on this class of medications.

Table 1
Recommended initiating and target doses of commonly used angiotensin-converting enzyme (ACE) inhibitors based on clinical trial data

ACE inhibitor	Initiating dose	Target dose
Captopril	6.25-12.5 mg tid	25-50 mg tid
Enalapril	1.25-2.5 mg bid	10 mg bid
Ramipril	1.25-2.5 mg bid	5 mg bid*
Lisinopril	2.5-5 mg od	20-35 mg od

**In the Healing and Early Afterload Reduction Therapy (HEART) study (79), 10 mg od was also found to be effective after myocardial infarction*

The largest randomized trial comparing high-dose with low-dose ACE inhibitor therapy was the Assessment of Treatment with Lisinopril and Survival (ATLAS) study (16). In this trial, 3164 patients with chronic CHF were randomly assigned to groups treated with low doses (2.5 to 5 mg daily, n=1596) or high doses of lisinopril (32.5 to 35 mg daily, n=1568). After a median 45 months of follow-up, there was a 12% reduction in the composite end point of mortality and total hospitalizations ($P=0.002$), and a nonsignificant 8% reduction in total mortality ($P=0.128$) and a 24% reduction in CHF hospitalizations ($P=0.002$) in patients receiving the high dose. Smaller studies using other ACE inhibitors have shown similar results. These data support ACE inhibitor prescription with the intent of attaining the highest recommended (or tolerated) dose for that particular ACE inhibitor or the same regimen used in CHF clinical trials.

The use of ACE inhibitors in patients with LVEF greater than 40% can follow the section on prevention below.

Angiotensin II receptor antagonists

ARBs, which block the angiotensin AT1 receptor specifically, are well tolerated, with a side effect profile similar to that of placebo. Their efficacy in heart failure treatment is, however, less clear. The enthusiasm for ARBs in heart failure treatment was stimulated by the ELITE I trial (17) in which 722 patients with class II to IV heart failure were randomly assigned to groups treated with losartan 50 mg/day or captopril 50 mg tid. The primary end point of the study was renal dysfunction, and was not different between the two arms of the study (17). However, unexpectedly, the patients showed a highly significant reduction in mortality in the losartan arm (17 of 352 died) compared with the captopril arm (32 of 370 died). There was no difference in hospitalization rates. To explore this effect further, a second larger trial, ELITE II (Losartan Heart Failure Survival Study) (15), was conducted. Overall, 3152 patients (mean age 71.6 years) were randomly assigned to groups treated with captopril 150 mg/day or losartan 50 mg/day, and followed for a mean 555 days (15). The primary end point was total mortality, and of 1574 captopril patients, 250 died, while 280 of 1578 losartan patients died ($P=0.12$). The secondary end point was resuscitated cardiac arrest or sustained ventricular tachycardia, and a trend in favour of captopril ($P=0.08$) was noted. Losartan was significantly better tolerated than captopril ($P=0.001$, 14.3% versus 9.4% discontinuation rate). Thus, ELITE II failed to demonstrate the superiority of losartan over captopril. This should not, however, be interpreted as equivalence of the two agents. On the basis of this study and the total CHF literature, ACE

inhibitors remain the therapy of choice for chronic CHF due to LV systolic dysfunction. For those who cannot tolerate ACE inhibitor due to cough, ARBs may be considered. While ARBs have not been proven to be superior to combination hydralazine/nitrates, it is unlikely that they will be less efficacious, and very likely, that they will be better tolerated. However, there are no current or planned trials comparing ARBs with hydralazine/nitrates in ACE inhibitor-intolerant patients with CHF due to LV dysfunction. Thus, optimal therapy for ACE inhibitor-intolerant patients has yet to be determined. One ongoing trial, the Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM) trial (18), has three arms, one of which is to compare candesartan with placebo in patients with CHF due to LV systolic dysfunction (n=1700) who are intolerant to ACE inhibitors. While hydralazine/nitrate therapy was allowed in CHARM, it was not mandatory or restricted to the placebo treatment groups. As such, only indirect comparisons of candesartan with hydralazine/ nitrates will be possible in this study. The results are expected in 2002.

There may be a rationale for combination ACE inhibitor/ARB therapy. Although both agents cause similar hemodynamic changes, each effects its changes through a different mechanism (19). When ARBs are used in combination with ACE inhibitors, further improvements in hemodynamic and exercise variables occur (20). Indeed, in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study (21) involving over 700 patients with CHF, the combination of ACE inhibitor/ARB therapy (enalapril plus candesartan) was associated with attenuation of LV remodelling and improvements in neurohumoral activation compared with either agent alone. Preliminary but yet unpublished data are available from the much larger Valsartan Heart Failure Study (Val-HEFT), which enrolled 5010 patients with chronic, stable mild to moderate CHF on ACE inhibitor therapy, and randomly assigned them to either additional ARB (valsartan up to 160 mg orally bid, n=2511) or placebo (n=2499) treatment. There were two primary end points – all-cause mortality and a composite of all-cause mortality and morbidity (including heart failure admissions, need for intravenous inotropic therapy and resuscitated sudden cardiac arrest). After a mean 1.8-year follow-up, there was no difference in all-cause mortality (495 or 19.7% in the valsartan arm, and 484 or 19.4% in the placebo arm, P=0.8). However, there was a 13.3% reduction in the composite primary end point (723 or 28.8% in the valsartan arm versus 801 or 32.1% in the placebo arm, P<0.009). In terms of heart failure hospitalizations, there were 349 admissions (13.9%) in the valsartan arm and 463 admissions (18.5%) in the placebo arm (P<0.00002). Thus, the Val-HEFT trial did not show a reduction in all-cause mortality, but there was a reduction in morbidity when ARB was added to ACE inhibitors.

Additionally, 7% (366) of patients randomly assigned to treatment in Val-HEFT were not on ACE inhibitors at the study entry. In this group, there was a 44% reduction in the composite primary end point in the valsartan arm. Another prespecified subgroup analysis involved beta-blockade treatment. The valsartan arm demonstrated a significant reduction in the primary composite end point in patients without beta-blocker therapy. In the approximately 1500 patients on beta-blocker therapy, there was a slight and nonsignificant trend toward increase in the composite primary end point events in the valsartan arm. This observation will need to be confirmed with other ongoing studies, but suggested that adding ARB to an existing regimen of beta-blockers and ACE inhibitors is not associated with greater benefit.

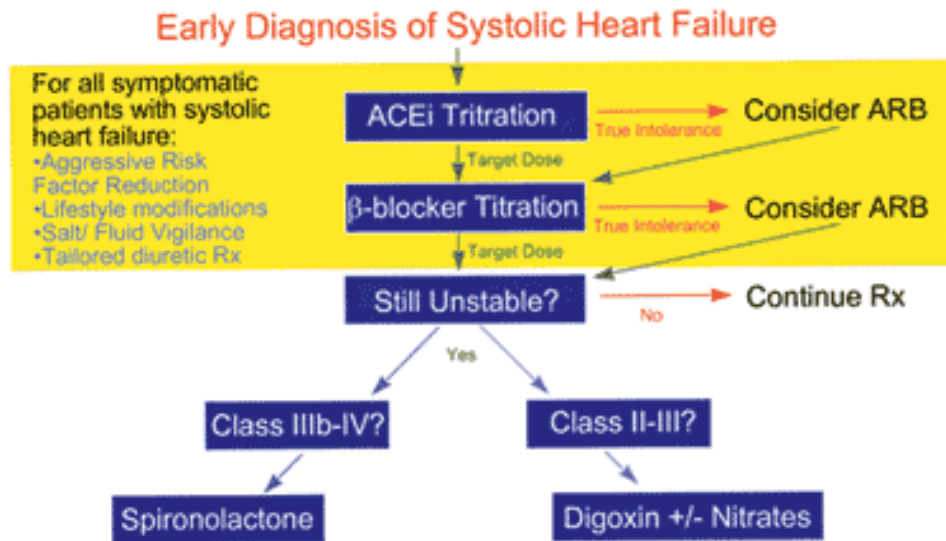
One arm of another trial (18), the CHARM combination arm (n=2500), has a similar design as Val-HEFT but with significant differences. This trial has high-dose candesartan (up to 32 mg orally once daily) as the intervention, with a follow-up of two years. Baseline characteristics of the CHARM versus Val-HEFT populations indicate CHARM to have a more advanced level of CHF, and higher beta-blocker and spironolactone usage. Data from this trial will shed further light on the concept of multiple neurohumoral blockade, including inhibition of ACE, beta-receptors, aldosterone and angiotensin II.

As a result of these data, caution is warranted in consideration of combination ACE inhibitor/ARB therapy. The committee feels that the highest priority should be given to initiation of ACE inhibitor and beta-blocker therapy, and if either of these two treatments cannot be tolerated, ARB therapy should be considered as an alternative (Figure 2). In functional class IV patients, current evidence favours the combination of spironolactone, ACE inhibitors and beta-blockers as the standard. Because only 2% of patients in Val-HEFT were on spironolactone at the study entry, there are insufficient data to recommend routine combination of ACE inhibitor/ARB/spironolactone.

As previously mentioned, patients with CHF with preserved LV function (LVEF greater than 40%) currently

have no proven therapy for reduction of mortality. One ongoing trial, the Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) trial, randomly assigned 1000 elderly patients with diastolic heart failure to perindopril 4 mg once daily or placebo treatment. Results will be available in 2003. The final arm of the CHARM trial (n=3000) involves the random assignment of patients with diastolic heart failure to either candesartan or placebo treatment. The use of concomitant ACE inhibitor therapy (if indicated) has been allowed in the CHARM trial.

Pharmacological Therapy in Heart Failure



[[Click](#) to enlarge]

Figure 2) Pharmacological algorithm in the treatment of systolic heart failure. ACE inhibitors and beta-blockers are the mainstay of pharmacological treatment. Diuretics are important for symptom management and should be tailored to the patient's condition. ACEi Angiotensin converting enzyme inhibitor; ARB Angiotensin receptor blocker; Rx Therapy

BETA-ADRENERGIC RECEPTOR BLOCKERS IN CHF

Recommendations

- Beta-adrenergic receptor blockers are strongly recommended in all patients with NYHA class II to III heart failure and LVEF 40% or less to reduce mortality, hospitalizations, improve cardiac function and quality of life, unless contraindicated. (Grade A, Level 1)
- Following the Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) trial (22), beta-blockers are now also indicated in patients with stable class IV heart failure (Grade A, Level 1). It is important to keep in mind that the class IV heart failure patient is a moving target, and the patient must be stable before considering beta-blockers.
- Beta-blockers are recommended for patients with LV systolic dysfunction who are asymptomatic in NYHA class I with LVEF less than 40%, particularly after MI. (Grade A)

Practical tips

- Beta-blockers should be initiated with low doses (eg, 3.125 to 6.25 mg carvedilol bid, 1.25 mg of

bisoprolol once daily or 6.25 to 12.5 mg metoprolol bid), and the doses should be increased slowly at intervals of two or more weeks. These agents may not be tolerated during the first attempt at initiation; however, subsequent attempts may be successful. Patients with significant fluid overload are not good candidates for beta-blockers until it is corrected.

- Beta-blockers are relatively contraindicated in patients with severe bronchospasm (requiring regular bronchodilator therapy) or advanced heart block (without pacing), and considered carefully in those with bradycardia (less than 60/min). Diabetes is not a contraindication.
- Patients should be assessed clinically for worsening of heart failure and other potential adverse effects (hypotension and bradycardia, in particular) before each dose titration. Persistence with the beta-blocker if symptoms or signs of failure worsen is important because patients who develop manageable side effects will often improve with time, commonly over two to 12 weeks. Objective improvement in cardiac function may not be fully achieved for up to one year.
- Abrupt withdrawal or major reduction in the dose of the drugs should be avoided. The exceptions include severe drug reaction, requirement of intravenous inotropic agent or substantial difficulty in management of the heart failure with vasodilators and diuretics.
- Acute CHF should be optimized with standard therapy, which generally includes ACE inhibitors and diuretics, before starting the beta-blocker.
- Beta-blockers may be used with other vasodilators, spironolactone, amiodarone and digoxin.

Table 2
Summary of the currently available heart failure trials involving beta-blockers, and a comparison of the number needed to treat as a basis for comparison

Clinical trial	Active therapy	Class	n	Placebo mortality (per year)	Treated mortality (per year)	Number needed to treat/year
United States Carvedilol (28)	Carvedilol	II-III	1094	9%	3%	16
CIBIS II (26)	Bisoprolol	II-IV	2647	13.2%	8.8%	23
MERIT (25)	Metoprolol XL	II-IV	3991	11.0%	7.2%	26
BEST (36)	Bucindolol	III-IV	2708	16.8%	15.1%	59
COPERNICUS (22)	Carvedilol	III-IV	2289	18.5%	11.4%	15

BEST Beta-blocker Evaluation of Survival Trial; CIBIS II The Cardiac Insufficiency Bisoprolol Study II; COPERNICUS Carvedilol Prospective Randomised Cumulative Survival; MERIT Metoprolol CR/XL Randomised Intervention Trial

EVIDENCE FOR BETA-BLOCKERS

The most dramatic changes from the previous guidelines for heart failure involve the recommendations on beta-blockers. There was no level 1 evidence to support the use of beta-blockers in 1994, but definitive evidence for the use of beta-blockers has emerged in the past four years to transform the treatment of heart failure. The benefits of beta-blockers for heart failure are demonstrated in both ischemic and nonischemic forms of heart failure, and include reduction in mortality (20% to 65%; most studies showed a reduction of approximately 33%, with one study using carvedilol demonstrating a 65% reduction), progression of failure and rehospitalizations (approximately 25%) (23-31). There is also improvement in symptoms and feeling of well-being, but only equivocal changes in measured exercise capacity (32). LV end-diastolic and end-systolic volumes are consistently decreased and LVEF is increased, sometimes remarkably (33,34). The benefits appear to be similar across different demographics, including age (up to 80 years in the clinical trials) (35).

The majority of heart failure trials using beta-blockers involve patients in class II-III heart failure who have been stable for at least one month. For patients in severe heart failure, only the COPERNICUS trial using carvedilol has shown a significant benefit, while the Beta-blocker Evaluation of Survival Trial (BEST) (36) using bucindolol has failed to show a benefit. It is important to emphasize that the patients who were enrolled in the COPERNICUS trial included patients with advanced heart failure with symptoms at rest or minimal exertion, and LVEF of less than 25%. However, patients who were unstable were excluded,

including patients who were in the intensive care unit and who were on intravenous inotropes or vasodilators. A brief summary of some of the representative major clinical trials is outlined in Table 2. Please keep in mind that all the patients are on background therapy of ACE inhibitors and diuretics.

No definitive clinical trial has randomly assigned patients with asymptomatic LV dysfunction to treatment with beta-blockers or placebo. However, in the setting of post-MI, the recent Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial (37) randomly assigned 1959 patients with LV dysfunction after MI (already treated with thrombolytic therapy and ACE inhibitors) to carvedilol or placebo treatment. The results showed a 23% reduction in all-cause mortality, and beneficial effects of carvedilol on cardiovascular mortality and nonfatal MI (37). This result suggested the positive benefit of beta-blockade in patients with LV dysfunction following recent MI.

The pathophysiological pathways contributing to morbidity and mortality in CHF include those mediated by the beta-receptors that are activated by the sympathetic nervous system. This includes neuroendocrine activation, peripheral vasoconstriction, impaired sodium excretion, myocardial ischemia, arrhythmias and promotion of apoptosis. The actions of the available beta-blockers vary among those that are beta-1 selective blockers (metoprolol and bisoprolol), beta-1 and beta-2 blockers (propranolol and bucindolol), and beta-1, beta-2 and alpha-1 blockers (carvedilol). While metoprolol, bisoprolol and carvedilol have been shown to be beneficial in large randomized, clinical trials, it is not yet clear how much of the benefit is a class effect or whether efficacy will be shown to be different with the different agents (38,39). The trial results with metoprolol, bucindolol and carvedilol suggest that important differences may exist. A large randomized, clinical trial designed to compare carvedilol with metoprolol is still in progress. Until the results are available, metoprolol, bisoprolol and carvedilol can all be considered for clinical use in heart failure treatment in Canada. There are limited data on the differences between long- and short-acting metoprolol, even though it is the former that was used in the Metoprolol CR/XL Randomised Intervention Trial (MERIT) trial (40). At this time, low-dose tablets are not always available for all the preparations, which may create difficulty for some patients who need to start at extremely small doses of these agents.

Physicians who are not yet experienced in the use of beta-blockers should consider initiation of treatment in conjunction with a physician experienced in heart failure management. This may include the local heart failure clinic. Patients with severe symptoms will require expert heart failure assessment for the appropriate timing and dose of beta-blocker usage, and will require very close monitoring to avoid deterioration (Table 3).

The most optimal target doses are not clear at this time. Maximum doses are usually up to 50 mg carvedilol bid and up to 200 mg metoprolol CR/XL once daily, although many patients will only tolerate lower doses. Benefits are evident even at low doses of carvedilol, so doses lower than target should be maintained when the higher ones cannot be achieved. However, achieving higher tolerated doses if possible is still desirable because a dose-response relationship of beta-blockers and improvement in LVEF have been suggested.

Adverse effects most often seen during dose titration include worsening of failure, hypotension and bradycardia. Nonspecific symptoms due to the beta-blockade are also common. Optimal use of vasodilators and diuretics before implementation of the beta-blocker will minimize these occurrences. If failure increases, increasing the dose of vasodilators, if the BP and symptoms permit, and/or diuretics is usually effective in controlling the failure. A pacemaker may be indicated for patients with severe bradycardia, if the benefit of beta-blocker therapy outweighs the risks associated with pacemaker implantation. The patient may need to be re-evaluated frequently during the period of drug titration, and the medical regimen may need to be intensified.

ALDOSTERONE ANTAGONISM IN HEART FAILURE

Recommendations

- Patients with severe symptomatic heart failure (class IIIb and IV), who are already on standard medications (ACE inhibitor, with or without digoxin or beta-blockers), should be strongly considered for an aldosterone antagonist (eg spironolactone). (Grade A, Level 1)

Practical tip

- The patient should have a baseline creatinine level less than 200 mg/L and a potassium level less than 5.0 mEq/L before initiation. The average maintenance dose of spironolactone is low at 25 mg/day. The patient must be followed within five days of initiation with reassessment of potassium and renal function, and the dose adjusted as appropriate. There should be periodic follow-up, especially if concomitant diuretics or weight are changed.

THE EVIDENCE

The Randomized ALdactone Evaluation Study (RALES) (41) enrolled 1663 patients with class III/IV heart failure, and with LVEF less than 35%, serum creatinine less than 2.5 mg/dL and a serum potassium level less than 5 mmol/L who were already on an ACE inhibitor as tolerated, diuretics and/or digoxin. The patients were randomly assigned to treatment with spironolactone (25 mg once daily, n=822) or placebo (n=841), and clinical events were followed, with total mortality being the primary end point. The average dose of spironolactone ultimately used was 27 mg/day.

The RALES trial was terminated prematurely after two years of follow-up due to a significant benefit on total mortality in the active treatment group. The patients who were treated with spironolactone had an overall 30% reduction in mortality ($P < 0.001$), with a baseline mortality of 46% in the placebo group at the end of two years. The benefit was observed across all major subgroups examined. In addition, there was a 31% reduction in deaths due to cardiac causes and a 35% reduction in hospitalizations for heart failure. The number needed to treat per year to save one life is extremely low at 15. There was also a significant improvement in symptoms of heart failure in terms of NYHA classification. The only side effect was an increase in gynecomastia and breast pain in male patients. With the cost of spironolactone being relatively low in many parts of the world, this is indeed the most cost effective treatment for heart failure to date.

The RALES trial demonstrated that aldosterone antagonism in the setting of severe heart failure has an important therapeutic benefit in terms of both mortality and morbidity. Because previous studies have suggested that ACE inhibitors do not adequately suppress aldosterone production, the patient is still at risk for its adverse remodelling influences (42-44). Because the dose of spironolactone used is relatively low, it also suggests that the mechanism of ventricular remodelling and fibrosis, promoted by aldosterone, is an important detrimental process contributing to the progression of heart failure.

It should be emphasized that the aldosterone antagonists have only been evaluated in patients with severe heart failure (class III and IV). The effect in milder heart failure is unknown, and is being evaluated in patients after infarction with ventricular dysfunction, using a next-generation antagonist, eplerenone (EPHESUS trial).

DIGITALIS AND OTHER INOTROPIC DRUGS

Recommendations

- In patients in sinus rhythm and who remain symptomatic on ACE inhibitors and other proven therapies, digoxin is recommended to improve symptoms and reduce hospitalizations. (Grade A, Level 1)
- Intermittent parenteral administration of dopaminergic agents or phosphodiesterase inhibitors is not recommended for routine use; however, short term use may be considered in select patients with intractable heart failure or temporary deterioration after optimization of standard therapy. (Grade B, Level 2)

Table 3
Potential drug interactions of commonly used medications in a patient with heart failure

	ACEI/ARBs	Amiodarone	Beta-blockers	Digoxin	Loop diuretics	Potassium	Spirolactone
ACEI/ARBs							
Amiodarone	—						
Beta-blockers	Decreased BP*	Increased effect of beta-blocker					
Digoxin	—	Increased serum digoxin levels ~2-fold	Decreased HR, decreased AV conduction*, carvedilol may increase dig levels ~25%				
Loop diuretics	Decreased BP*	—	Decreased BP*	Hypokalemia, increased digoxin effect			
Potassium	Increased potassium level	—	—	—	—		
Spirolactone	Decreased BP* Increased potassium level	—	Decreased BP*	May increase digoxin levels	Decreased BP dehydration*	Increased potassium level	
Warfarin	—	Increased warfarin effect	—	—	—	—	—

Possible drug interactions with moderate to major impact are listed. Individual patient responses may vary. * Additive pharmacological effect; ACEI Angiotensin-converting enzyme inhibitor; ARBs Angiotensin II receptor antagonists; AV Atrioventricular; BP Blood pressure; dig Digoxin; HR Heart rate

Practical points

- The usual maintenance dose of digoxin in adult patients is 0.125 to 0.25 mg orally daily, depending on renal function.
- Repeat measurements of digoxin levels are not routinely recommended unless patient noncompliance is suspected or in patients at greater risk of digoxin toxicity, eg, significant loss of

body mass, deterioration of renal function, or at risk of drug interactions, particularly with amiodarone.

- Digoxin levels should be measured immediately before dosage, or 6 h or more after dosage, after steady-state is reached three to four half-lives after a dose adjustment. While therapeutic digoxin levels range up to 2.0 mg/L or higher, lower levels at around 1.0 mg/L appear to be safer than higher levels.

Since the CCS Consensus Conference on Heart Failure was published in 1994, additional data have become available (1), particularly the results of the Digitalis Investigation Group (DIG) mortality trial (45). The results of the few new trials of nonglycosides inotropic agents have not changed the conclusions drawn in the previous conference. While the phosphodiesterase inhibitors continue to be used intravenously to treat acute hemodynamic situations, they have no role to date in the long term management of heart failure because of the potential adverse effect on survival. No additional data are available on the parenteral phosphodiesterase inhibitors, dopaminergic agents, dobutamine and dopamine. Intermittent administration has resulted in hemodynamic improvement, questionable improvement of symptoms and no improvement on survival. Research in this area, however, is continuing. For example, levosimendan, a calcium sensitizer, and enoximone, an orally available mild inotropic agent, are currently being evaluated.

Over the years, a large body of evidence indicates that, in patients with sinus rhythm, digoxin is useful in improving symptoms, increasing exercise tolerance and improving the LVEF, and will result in clinical deterioration when discontinued. The largest prospective, randomized, long term trial of digoxin, the DIG mortality trial, was completed and published in 1997 (45). In 6800 patients with LVEF of 45% or less, with 3397 patients randomly assigned to digoxin and 3403 patients to placebo treatment, mortality was unaffected (34.8% with digoxin and 35.1% with placebo; RR 0.99, 95% CI 0.91 to 1.07, $P=0.80$), after 37 months of follow-up. Treatment was in addition to diuretics and ACE inhibitors. There was a trend toward a decrease in risk of death attributed to worsening heart failure in the digoxin group (RR 0.88, 95% CI 0.77 to 1.01, $P=0.06$). In the digoxin group, there were an absolute 6% fewer hospitalizations overall than in the placebo group. Fewer patients were hospitalized for worsening heart failure (26.8% versus 24.7%, RR 0.72, 95% CI 0.66 to 0.79, $P<0.001$). In the ancillary trial of 988 patients with preserved LV function, the findings on the primary combined outcome of death or hospitalization due to worsening heart failure were consistent with the results of the main trial. It was concluded that digoxin did not reduce overall mortality, but it reduced the rate of overall hospitalization and hospitalization for worsening heart failure.

Routine repeat measurements of digoxin levels are usually not necessary. Digoxin toxicity continues to be a clinical diagnosis encompassing the patient's symptoms, and laboratory and electrocardiographic data. An elevated serum digoxin level is generally inadequate as sole evidence. However, measurements of digoxin levels can be helpful in certain defined situations, such as in suspected patient noncompliance or in patients at greater risk of digoxin toxicity. These include individuals who have rapid loss of body mass, deterioration of renal function or are at risk of drug interactions. To be interpretable, the blood taken for measurement should be taken following standard guidelines, ie, before the next dosage, or 6 h or more after dosage, and after steady-state is reached three to four half-lives after a dose adjustment. In the setting of heart failure, maintaining digoxin levels at around 1.0 mg/L or below appears safer and lowers the risk of toxicity.

THERAPIES FOR ARRHYTHMIAS IN PATIENTS WITH HEART FAILURE OR VENTRICULAR DYSFUNCTION

Recommendations

- Heart failure and arrhythmias occur commonly together and aggravate each other. Treatment must first be aimed at optimal treatment of heart failure and correcting underlying reversible causes that may predispose the patient to arrhythmias. (Grade A, Level 1)
- Patients with heart failure and atrial fibrillation should not be treated with class I antiarrhythmic drugs. (Grade A, Level 1)
- In patients with atrial fibrillation and heart failure, achievement of rate control and full anticoagulation is recommended for optimal heart failure management. The rate can be controlled with beta-blockade, amiodarone or digoxin either alone or in combination, or atrioventricular nodal ablation with permanent pacemaker insertion. (Grade B, Level 2)
- In the setting of recent onset atrial fibrillation in heart failure, cardioversion may be clinically indicated with or without concomitant amiodarone therapy. (Grade C, Level 3)
- Patients surviving cardiac arrest or symptomatic sustained ventricular tachycardia (VT, not within three days of acute MI and not associated with correctable cause), and with LVEF less than 35% should be considered for an implantable cardiac defibrillator (ICD) therapy. (Grade A, Level 1)
- Patients who have had previous MI with LV dysfunction (LVEF 35% or less) and asymptomatic spontaneous nonsustained VT, and who would be suitable candidates for an ICD should undergo an invasive electrophysiological study to determine the inducibility of ventricular arrhythmias. If sustained VT or ventricular fibrillation is induced, the patient should be considered for an ICD. (Grade B, Level 2)
- For heart failure patients with symptomatic ventricular arrhythmias and who do not qualify for an ICD implantation, amiodarone and beta-blockade are the current antiarrhythmic alternatives. (Grade B, Level 2)

Heart failure and arrhythmias are both common conditions, and owing to common risk factors shared by both, they often coexist in the same patient. In addition, there is a potentially reciprocal relationship between heart failure and arrhythmias that complicates the management of either condition. In the setting of heart failure, the atrial and ventricular chambers remodel, subjected to the influences of myocardial injury, increased wall tension, neurohumoral activation and myocardial ischemia, and create a milieu to promote arrhythmias. On the other hand, tachyarrhythmias and the associated uncoordinated contractile pattern may further aggravate heart failure. Therefore, in the treatment of cardiac arrhythmias associated with heart failure, the most important principles are still the treatment of the underlying conditions that led to heart failure and aggravation of arrhythmias. The specific treatment should aim at protection of the injured heart and correction of neurohumoral activation with angiotensin modulators and beta-blockers. These effective pharmacological treatments have been shown to reduce both overall mortality and sudden deaths in large randomized trials (6,25,26). The ischemia should be corrected by revascularization and primary treatment of atherosclerosis, and wall tension reduced by diuretics and afterload reduction. The ventricular rate should be controlled with a combination of beta-blockers and amiodarone, and additional specific measures outlined below.

Atrial fibrillation

The onset of atrial fibrillation (AF) in heart failure can lead to sudden and rapid deterioration of symptoms. The incidence of AF in heart failure ranges from 10% to 50%, and AF is an independent predictor of heart failure mortality and morbidity. Two therapeutic strategies are available for patients with AF and CHF: the first aims at restoring and maintaining sinus rhythm, whereas the second focuses exclusively on optimizing ventricular rate.

Restoration of sinus rhythm electively accompanied by appropriate anticoagulation or urgently guided by transesophageal echocardiography is often effective in reversing the symptoms and should be considered when it is clinically appropriate (46). Amiodarone is more effective than other class I antiarrhythmic agents

in maintaining sinus rhythm after effective cardioversion, and class I agents are contraindicated in this situation due to worsening mortality (47). Metoprolol CR/XL has also been shown to be more effective than placebo in maintaining sinus rhythm (48), although the efficacy of these therapies in the specific setting of heart failure is currently unknown. In patients in whom the ongoing risk of AF is still present, including intermittent episodes, the patient should receive full anticoagulation to maintain the international normalized ratio in the range of 2.0 to 3.0 (49).

In terms of rate control therapy, beta-blocker is the first drug of choice where it is tolerated. The initiation of beta-blocker therapy in symptomatic patients may not be tolerated or the tolerated dose may not be adequate for initial rate control. The addition of amiodarone is often effective in achieving rate control, without evidence of adverse effect on mortality in contrast to other class I antiarrhythmic agents. The addition of digoxin can also be considered, although its benefit is mainly on the resting heart rate, with little influence on the exercise heart rate. Unlike individuals without LV dysfunction, AF in patients with heart failure needs constant review and the patients may need to be referred to an electrophysiology expert for additional considerations, including atrioventricular nodal ablation therapy with permanent pacemaker implantation.

Ventricular tachyarrhythmias

Patients with ventricular arrhythmias and heart failure suffer a much higher mortality rate, and one-half of patients with heart failure will die from tachyarrhythmias. Much of the evidence associated with the treatment of ventricular arrhythmias was reviewed in the 2000 CCS consensus conference on Prevention of Sudden Death from Ventricular Arrhythmias (50); therefore, only a highlight of the relevant discussion and recommendations will be outlined here.

In the setting of secondary prevention following symptomatic ventricular arrhythmias, including cardiac arrest, or syncope in the setting of ventricular dysfunction there were two relevant studies, the Canadian Implantable Defibrillator Study (CIDS) (51) and The Antiarrhythmics Versus Implantable Defibrillators (AVID) (52). These studies included patients whose VT episode caused cardiac arrest or syncope, and those in whom the LVEF was less than 35%. Patients were randomly assigned to receive either an ICD or amiodarone as the primary intended treatment. Meta-analysis of the ICD trials indicated a 27% reduction in mortality with the ICD compared with amiodarone over a mean follow-up period of 2.3 years. The ICD extended life on average by 4.4 months at six years of follow-up. The annual mortality rate with amiodarone was 12.3%, which was reduced to 8.7% with the ICD. The benefit of the ICD in patients with well-tolerated VT is not defined by any of these clinical trials, but is considered minimal. There was an imbalance of beta-blocker usage in these trials, but on final analysis, this probably was not the major reason for the observed efficacy of the ICD. Therefore, the recommendation of the consensus conference for the management of resuscitated ventricular fibrillation or VT, or symptomatic VT in the presence of LVEF less than 35% was to consider the ICD as the first-line treatment. Because the cost effectiveness of ICDs is calculated in the range of \$250,000 per life saved, the access is still relatively limited in some instances to patients at high risk.

In primary prevention in the setting of ventricular dysfunction or MI without a prior event, the evidence is more controversial. Two studies to date have included patients with LV dysfunction and asymptomatic nonsustained VT – Multicenter Automatic Defibrillator Implantation Trial (MADIT) (53) and Multicenter UnSustained Tachycardia Trial (MUSTT) (54). Both studies have demonstrated improved survival with a treatment strategy that included the use of the ICD. Both studies included patients with severely depressed LVEF (the average LVEF in MADIT and MUSTT was 26% and 29%, respectively) and had a high mortality rate in the absence of ICD therapy (approximately 50% after five years). However, the ICD strategy was not randomized in MUSTT, and electrophysiological testing evidence of inducible VT was an inclusion criterion in MADIT. Therefore, the consensus recommendation cautiously suggests that patients who previously have had an MI with LV dysfunction (LVEF 35% or less) and asymptomatic spontaneous nonsustained VT, and who would be suitable candidates for an ICD should undergo an invasive electrophysiological study to determine the inducibility of VT or ventricular fibrillation. If sustained VT or ventricular fibrillation is induced, then the patient should be considered for an ICD. More definitive evidence will have to await the completion of additional prospective studies addressing more clearly the role of ICD in

primary prevention, such as MADIT II and Sudden Cardiac Death in Heart Failure (SCD-HeFT), randomly assigning patients with heart failure or LV dysfunction to ICD or best conventional therapy.

Lifestyle Modifications

Recommendations

- All patients with heart failure should be counselled about lifestyle modifications. This would include support with proper nutrition (including low-salt diet and weight reduction), appropriate treatment of glucose intolerance/diabetes mellitus, appropriate lipid-lowering therapy, advice about alcohol consumption, counselling regarding smoking cessation and advice regarding physical activity. (Grade B, level 2)
- Effective lifestyle modification requires time and specific expertise, and is best conducted as a focused discussion session with planned follow-up.

A history of hypertension or coronary artery disease is often a risk factor for the development of heart failure. Risk factors including smoking, diabetes mellitus and hyperlipidemia have been recognized as being partly responsible for the development of hypertension or coronary artery disease. These risk factors, at least in part, involve lifestyle choices. There are data to suggest that these risk factors also independently promote the development of heart failure (55). Thus, risk factors in patients with heart failure should be addressed and aggressively treated. Sodium and water retention leading to an expansion in the volume of extracellular fluid has been well described in the heart failure syndrome. When normal subjects reduce salt consumption from an average of 10 g/day to 5 g/day (1 g salt equals 0.4 g or 17.1 mmol of sodium), the extracellular fluid volume has been observed to decrease by 1.0 to 1.5 L (56). If a similar effect occurred in a patient with heart failure, the need for diuretic therapy might be reduced. Acute alcohol ingestion causes depression of myocardial contractility and is known, in some cases, to cause a cardiomyopathy. Although it is unclear whether abstinence in those without a history of alcoholism reduces mortality or improves functional status, there are some reports of improvement in ventricular function and clinical well-being (57). Therefore, it would seem reasonable to have patients with alcohol-induced cardiomyopathy abstain from alcohol, while patients with heart failure due to other etiologies may consume small quantities of alcohol.

EXERCISE TRAINING IN HEART FAILURE

Recommendations

- Regular physical activity is recommended for all patients with heart failure.
- Patients with stable NYHA functional class I to III heart failure should be offered a program of exercise training. The program should be individualized for each patient, with the more debilitated patients starting at a lower training intensity and for shorter session times. If the facilities are available, a strength (resistance) training component should be incorporated as part of the overall exercise-training program. (Grade B, Level 2)
- All patients need exercise testing before starting an exercise program.

Traditionally, patients with heart failure have been advised to rest and avoid exercise because of concerns that their condition would further deteriorate. However, a significant amount of data have accumulated that challenge this recommendation, and limiting physical activity may not only be unnecessary but also undesirable because it could lead to further disability (58).

Studies have not demonstrated a relationship between LVEF and peak exercise performance. This finding

suggests that the reduction in exercise capacity may be more importantly influenced by factors other than poor ventricular function. Patients with heart failure have been found to have reduced skeletal muscle strength, skeletal muscle atrophy, impaired muscle blood flow, and abnormalities in skeletal muscle metabolism, biochemistry and histology (59).

A number of studies have examined the effects of exercise training on skeletal muscle function and exercise performance. These studies have generally demonstrated a reversal of the skeletal muscle abnormalities in heart failure with a decrease in sympathetic nervous system activation, improvement in exercise performance and clinical status (58,59). None of the studies to date have been large enough to assess the effects of exercise training on mortality and morbidity, although a recent study suggested that exercise training may decrease clinical events (58).

Exercise training programs should be aimed at reversing the skeletal muscle abnormalities documented in heart failure patients. Ideally, upper and lower body training should take place during each session because the effects of exercise are relatively specific to the muscle groups involved in a particular activity. Aerobic exercise training should be included as part of the exercise program. However, aerobic training alone does not directly improve muscle strength; therefore, either resistance exercise training or interval exercise training should be part of the program (60).

REVASCULARIZATION AND SURGICAL PROCEDURES FOR LV DYSFUNCTION

Recommendations

- Patients with symptomatic myocardial ischemia (angina), operable coronary artery disease and no evidence of severe pulmonary hypertension should be considered for coronary artery bypass grafting. A low LVEF (LVEF less than 35%) or a history of CHF is not a contraindication to surgery. (Grade B, Level 2)
- Patients with chronic coronary artery disease who are asymptomatic (ie, no angina) should be considered for coronary artery bypass grafting for the purpose of improving prognosis if they have objective evidence of significant revascularizable, viable myocardium and no evidence of severe pulmonary hypertension. (Grade C, Level 3)
- Partial ventriculotomy (eg, Batista or Dor procedure) is not recommended, unless future follow-up suggests that there is a benefit. (Grade C, Level 3)
- Patients with idiopathic dilated cardiomyopathy and severe mitral regurgitation and class III to IV symptoms may be considered for mitral valve reconstructive surgery before listing for cardiac transplantation. (Grade C, Level 3)

Survival of patients with ischemic cardiomyopathy and poor LV function is poor. Patients with an LVEF less than 25% have a one-year mortality of 25% and a five-year mortality of 60%. Surgical revascularization should be considered as a treatment option in the management of patients with ischemic LV dysfunction and CHF. As a result of their low EFs, many of these patients, formerly thought to be best treated medically, can undergo safe (perioperative mortality rate 5% to 10%) and effective revascularization with excellent medium-term results. Factors that may affect the outcome of surgical revascularization include the presence of viable myocardium, bypassable coronary vessels, LV dilation, elevated LV end-diastolic pressure, the presence of mitral regurgitation, depressed right ventricular function, redo coronary artery bypass surgery and the presence of comorbid illnesses.

Coronary artery bypass surgery for impaired LV function and symptomatic angina

No randomized trials of coronary surgery have included patients with LVEF less than 35%. However, numerous nonrandomized or retrospective studies have shown a consistent survival advantage for surgical revascularization compared with medical treatment in patients with severe LV dysfunction and symptomatic

angina. These studies show a significantly better three- to five- year survival with coronary artery bypass graft (CABG) (68% to 80%) compared with historical control subjects treated medically (28% to 50%). In addition to improving survival, myocardial revascularization prevents further ischemic injury to functional myocardium, restores function to hibernating myocardium and improves subjective symptoms of heart failure and angina. Furthermore, the benefits of revascularization are more pronounced in the subgroup of patients with more severe LV impairment and higher risk (61). Despite the obvious limitations of these studies, it is reasonable to consider CABG for appropriate patients.

Heart failure patients with evidence of clinical ischemia (eg, exercise-limiting angina, angina occurring at rest or recurrent episodes of 'flash' pulmonary edema thought to be secondary to myocardial ischemia) should undergo coronary angiography as the initial evaluation for consideration of CABG.

CABG for impaired LV function without angina

The ultimate goal of CABG in patients with impaired LV function without angina is to improve survival. There are no controlled studies available on the effect of revascularization in this population of patients. Previous randomized trials of CABG excluded patients with heart failure symptoms (NYHA greater than II). The Coronary Artery Surgery Study (CASS) Registry, which compared the survival of patients with predominant symptoms of heart failure treated medically and surgically, showed an equally poor five-year survival rate of 23% in both groups. In addition, the perioperative mortality rate was in the range of 15% to 20%. However, there are now numerous retrospective studies regarding the revascularization of patients with ischemic cardiomyopathy demonstrating improved medium-term survival (50% to 80% five-year survival) with improvements in LVEF and heart failure symptoms. In addition, in highly selected patients, perioperative mortality rates have fallen to between 2.1% and 6.6%, presumably as a result of advances in the identification of hibernating myocardium and improvements in anesthetic, surgical and myocardial protection techniques. The success of CABG in patients with an ischemic cardiomyopathy without angina is influenced by the presence of significant residual viable myocardium. As expected, there is a consistent relationship between the amount of viable myocardium and the improvement in LV function following revascularization.

The decision to revascularize must balance the risk of myocardial damage at the time of CABG against the benefit of revascularizing hibernating segments. In patients who have predominantly symptoms of heart failure and a low LVEF, the decision to operate should be based on objective evidence of 'hibernating myocardium'. Three techniques are commonly used to assess myocardial viability: dobutamine echocardiography, thallium-201 scintigraphy with late redistribution-24 h reinjection imaging, and positron emission tomography (PET) with [18F] 2-fluoro-2-deoxy-D-glucose (FDG). Substantial regions of myocardial viability that would benefit from revascularization should be demonstrated. Such areas must be perfused by bypassable coronary arteries.

Patients who should be considered for investigations with view to possible CABG include patients with a history of MI but no current angina and patients with neither angina nor a past history of MI but with cardiovascular risk factors.

Percutaneous transluminal coronary angioplasty for LV dysfunction and angina

Percutaneous transluminal coronary angioplasty with or without stenting in patients with multivessel coronary disease and heart failure has not been shown to improve prognosis or surrogate end points, such as LVEF, heart failure symptoms or exercise tolerance. Patients with LV dysfunction and heart failure should be considered for CABG. Percutaneous transluminal coronary angioplasty with or without stenting should be reserved for patients on maximum medical therapy who are ineligible for surgery but require further intervention for symptomatic control of their angina.

Partial left ventriculectomy

Partial left ventriculotomy was pioneered by Batista et al (62) and has been proposed as an alternative treatment for patients with severe symptomatic heart failure caused by a dilated cardiomyopathy. As opposed to the first ventriculectomy, which proposed to remove only aneurysm, the Batista surgery involved resection of LV muscle, and mitral valve repair by putting a suture at the middle portion of the free edge of the anterior and posterior leaflets (Alfieri repair). The earlier reports by Batista et al (62) showed a significant clinical improvement over one year in some patients. These observations were limited by a difficult and a somewhat unreliable follow-up. The Cleveland Clinic experience reported a 58% freedom from death, relisting for cardiac transplantations or the need for LV assist device (LVAD) support in patients who had undergone the Batista procedure (63). This survival was much less than the 82% one-year survival in similar patients with cardiomyopathy. Among the survivors, LVEF and peak oxygen uptake increased, but LV diameter failed to improve. Accordingly, the Batista procedure is not recommended until more studies allow better identification of candidate patients or there are more encouraging follow-up data.

Mitral valve reconstruction

Earlier studies reported that the rate of development of heart failure after mitral valve replacement with normal preoperative LVEF was above 30% at 10 years (64). However, outcome improved when mitral valve replacement was performed with cordal preservation (65). More recently, mitral valve reconstruction by remodelling ring annuloplasty without mitral valve replacement was reported in patients with idiopathic dilated cardiomyopathy with severe mitral regurgitation and class III to IV symptoms (66). A longer term follow-up (24 months) study (66) showed beneficial reverse remodelling, increased LVEF and stroke volume, and improvement in functional class. Based on these data, it is recommended that patients with idiopathic dilated cardiomyopathy and severe mitral regurgitation with or without incidental coronary artery disease, and with class III to IV symptoms undergo such reconstructive surgery before listing for cardiac transplantation. More work needs to be done to better understand who will benefit the most and to confirm the results of a recent study suggesting some benefits in patients with ischemic cardiomyopathy as well (66).

LVAD

After maximal medical therapy for CHF, the only treatment option available for a small number of eligible patients is cardiac transplantation. Unfortunately, the shortage of donor organs restricts the number of available allografts, and a prolonged low-output state leads to further end-organ injury and worsens the perioperative risk at the time of transplantation. In recognition of these trends, the National Heart, Lung and Blood Institute developed the artificial heart program in 1964. The long term objectives of the program were to develop the following.

- Emergency cardiac assist systems to treat acute circulatory insufficiency.
- Temporary cardiac assist systems that could support the circulation for days to months, providing time for recovery or for eventual transplantation.
- Permanent cardiac assist systems that could treat the patient for the remainder of his or her life.
- Total artificial hearts that could permanently replace the native heart.

All four of these objectives have been achieved with clinical success, although the total artificial heart is still being used as a bridge to transplantation (67). Currently available circulatory support devices with United States Food and Drug Administration approval include the centrifugal Biomedicus Pump (Medtronic Inc, USA), the ABIOMED BVS 5000 (ABIOMED Inc, USA), the Thoratec ventricular assist device (Thoratec Labs, USA), the TCI HeartMate pneumatic and vented electric devices (ThermoCardiosystems Inc, USA) and the Novacor LVAS (WorldHeart Corp, Canada). The latter two devices are intracorporeal systems with percutaneous drivelines for power supply. The Biomedicus and ABIOMED pumps are used primarily for short term support in patients with acute cardiogenic or postcardiotomy shock. The Thoratec, HeartMate and Novacor systems are all designed for prolonged support (greater than 30 days) in patients awaiting transplantation. The TCI HeartMate device is currently under investigation for potential destination therapy in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial (68), and the preliminary results favour the LVAD strategy. Further improvements in

device design should allow for smaller, totally implantable devices capable of long term (greater than five years) support.

CARDIAC TRANSPLANTATION

Recommendations

- Patients with class IV heart failure with anticipated poor one-year survival who have failed medical therapy and exhausted all surgical options but have an opportunity for rehabilitation may be referred to a cardiac transplantation centre for evaluation. (Grade C)

General principles

The prevalence of CHF is increasing; however, the donor pool remains at a stable level, thus increasing the mismatch between donor supply and recipient demand. The proportion of patients who undergo transplantation as status 4 recipients (intra-aortic balloon pump or mechanical assist device supported) is increasing. Waiting times continue to increase, and the mortality while waiting is substantial at 25% to 30% per year. The most common indication for transplantation in Canada is coronary artery disease accounting for approximately 65% followed by idiopathic dilated cardiomyopathy.

Outcomes

Based on International Society for Heart and Lung Transplantation (ISHLT) registry data for the era 1995 to 1998, the one-year and three-year rates of survival after cardiac transplantation are 82% and 74%, respectively (69). For the era 1986 to 1990 the median survival is 8.9 years and the conditional half-life for patients who have survived the first year is 11.4 years.

Ninety per cent of patients return to NYHA functional class I at year one. However, despite this only approximately 50% return to work. In general, all patients will experience some complication after transplantation. Overall, there is a 57% rehospitalization rate, a 67% incidence of hypertension and 20% incidence of diabetes at one year.

With the newer immune therapy available, rejection is a less frequent problem; however, patients still require surveillance endomyocardial biopsy. Infection remains a concern, specifically, cytomegalovirus, and Epstein Barr virus-related malignancy (70). However, the single greatest limitation to long term survival remains graft vascular disease with angiographic evidence in 42% of patients at five years (71). Recent advances have shown that there is a significant reduction in graft vascular disease and an increase in survival with routine use of HMG-CoA reductase inhibitors (72). Malignancy, especially lymphoma and skin cancer, also remains a problem for long term survivors.

Listing criteria

The minimal listing criteria for cardiac transplantation were recently reviewed by the American Society of Transplantation, as well as the Canadian Cardiac Transplant Group, and are listed below (73) (Grade C recommendation). Ideally, these criteria are designed to identify patients who are at the greatest risk and will derive the greatest benefit from transplant. Specifically:

- Advanced functional class
- Poor one-year survival – all ambulatory patients should undergo cardiopulmonary testing
 - Patients with an oxygen consumption less than 15 mL/kg/min or 55% predicted for age and

sex should be considered to have severe cardiac dysfunction and warrant further evaluation for transplantation

- Failed maximal medical therapy
- No surgical options
 - High-risk revascularization should be considered if the myocardium is viable on cardiac imaging and the target vessels are good.
- All patients should exhibit the capacity for rehabilitation after transplantation

The following comorbidities, either alone or in combination, represent relative or absolute contraindications to transplantation.

- Fixed pulmonary hypertension – all patients require screening with invasive hemodynamic monitoring. The following measurements after aggressive challenge with one or more vasodilators or inotropic agents, and a systolic BP greater than 85 mmHg should be considered relative contraindications
- Transpulmonary gradient greater than 15 mmHg; systolic pulmonary arterial pressure greater than 50 mmHg; pulmonary vascular resistance greater than 4 Wood units; pulmonary vascular resistance index greater than 6 Wood units
- Primary systemic disease that may limit the long term survival, eg, hepatic disease and pulmonary disease
- Renal insufficiency
- Creatinine level greater than 200 mmol/L
- Active infection
- Technical issues
- Psychosocial issues such as drug or alcohol abuse or documented noncompliance
- Recent malignancy of the nonbasal cell carcinoma type
- Morbid obesity (greater than 140% ideal body weight) or marked cachexia (less than 60% ideal body weight)
- Osteoporosis
- Vascular disease – cerebral or peripheral
- Diabetes mellitus with end-organ damage
- Age is not in and of itself a contraindication; however, increased age is associated with a poorer outcome after transplantation. Therefore, with increasing age there should be more aggressive screening for associated comorbidities

There should be ongoing re-evaluation of patients once they are listed for transplantation. Some patients will improve, and consideration should be made to putting them on 'hold' with repeat cardiopulmonary testing and consideration of delisting. As well, some patients develop complications while waiting and may no longer remain suitable for transplantation. (Detailed recommendations for cardiac transplantation will be available as part of the 2001 consensus conference.)

PREVENTION OF HEART FAILURE

Recommendations

- Aggressive management of cardiovascular risk factors is recommended to reduce the risk of ischemic heart disease, the main cause of heart failure. (Grade A, Level 1)
- Blood pressure lowering is of particularly benefit in patients at risk for heart failure, and effective blood pressure lowering to target recommended levels results in fewer cases of heart failure. (Grade A, Level 1)
- In patients with pre-existing disease, the use of digoxin and beta-blockers, medications shown to reduce the risk of hospitalization, should be considered as preventive measures. (Grade A, Level 1)
- In asymptomatic patients with recent infarction and moderate LV dysfunction (LVEF 40% or less) or transient heart failure, ACE inhibition therapy is strongly recommended to decrease mortality, prevent progression to overt heart failure and to reduce the risk of recurrent MI. Therapy should be started when hemodynamically stable after infarction. (Grade A, Level 1)
- In high-risk patients (age greater than 55 years and multiple risk factors) without known ventricular dysfunction or symptomatic heart failure, ACE inhibitor therapy is recommended to reduce the risk of death, MI and stroke, as well as progression to overt heart failure. (Grade A, Level 1)

Practical points

- In patients at risk, aggressive risk factors modification include the use of efficacious lipid-lowering drugs such as statins, effective high BP and diabetic control, and measures taken to encourage increasing physical activities and smoking cessation.
- Education of patients in the avoidance of acute pharmacological and nonpharmacological precipitants of acute exacerbation of heart failure should be encouraged.
- Aggressive BP lowering is particularly important in patients with additional concomitant risk factors or existing vascular complications.
- High-risk patients, or those with diabetes and vascular disease, should be considered, in addition, for ACE inhibitor therapy, unless contraindications exist.
- ACE inhibitors appear largely interchangeable, each with its own potential advantages and disadvantages. However, ramipril is the only agent on which data are available to support the use of ACE inhibitor in high-risk patients without LV dysfunction or heart failure.
- The exact therapeutic dose has not been established; however, in mortality trials, the target total daily oral dose was 20 mg for enalapril, 150 mg for captopril and 10 mg for ramipril.

Steps in the prevention of CHF can be implemented at different stages of the disease. Because the majority of CHF patients have ischemic heart disease as the underlying etiology, aggressive primary and secondary preventive steps in modifying cardiovascular risk factors are effective measures. Prevention of MI and ischemia reduces the risk of LV systolic and diastolic dysfunction and the development of symptomatic CHF. Efficacious drug therapy, particularly with statins, is available for lowering cholesterol levels. Effective strategies have been developed in controlling high BP and diabetes, and in encouraging increasing activities and smoking cessation. This issue is also addressed in another section. BP lowering is particularly important in patients with higher risk. These include patients with concomitant risk factors, particularly diabetes, or evidence of previous vascular complications, such as MI, stroke or peripheral vascular disease. The BP should be lowered to the newly recommended target levels as per Canadian Hypertension Consensus guidelines.

Education of the patients in the avoidance of acute pharmacological and nonpharmacological precipitants of CHF will help to reduce the incidence of CHF in patients with pre-existing disease.

A few medications, ACE inhibitors, digoxin and beta-blockers, have been shown to reduce the risk of hospitalization for heart failure in patients with pre-existing disease. The use of digoxin and beta-blockers in

the overall management of heart failure is addressed elsewhere, but their effect in preventing worsening of heart failure and hospitalization should be considered.

ACE inhibitor therapy has a big role in the prevention of heart failure. ACE inhibitor therapy has been shown to reduce mortality, improve quality of life (decrease hospitalization, increase exercise tolerance) and reduce the risk of MI in patients with NYHA class II to IV CHF. Patients with the lowest LVEFs and worst symptoms derive the most benefit. In asymptomatic patients with LV dysfunction, ACE inhibitors have not been shown to reduce mortality, but have been shown to prevent deterioration to overt heart failure and to prevent MI in patients with LVEF 35% or less. In the early infarct period, ACE inhibitors started three to 16 days after infarction in patients with LVEF 40% or less, or transient heart failure have been shown to decrease mortality, prevent progression to overt heart failure and reduce the risk of recurrent MI.

A recently completed trial of ramipril, the Heart Outcomes Prevention Evaluation (HOPE) trial (12), enrolled 9297 high risk patients (older than 55 years of age with evidence of vascular disease or diabetes plus one additional risk factor) without known low LVEF or heart failure to receive ramipril (2.5 to 10 mg/day) or matching placebo. After a mean follow-up of five years, the primary outcome of cardiovascular mortality, MI or stroke was significantly reduced in the ramipril group (14.0% versus 17.8% for placebo, RR 0.78, 95% CI 0.70 to 0.86, $P < 0.0001$). There were clear and significant reductions separately in cardiovascular deaths (6.1% versus 8.1%, RR 0.74, 95% CI 0.64 to 0.87, $P < 0.001$) and MI (9.9% versus 12.3%, RR 0.80, 95% CI 0.70 to 0.90, $P < 0.001$). Development of heart failure was significantly reduced (9.0% versus 11.5%, RR 0.77, $P = 0.001$). Total mortality (10.4% versus 12.2%, RR 0.84, $P = 0.005$), revascularization procedures (16.0% versus 18.3%, RR 0.85, $P = 0.002$), cardiac arrests (0.8% versus 1.3%, RR 0.62, $P = 0.02$) and diabetic complications (6.4% versus 7.6%, RR 0.84, $P = 0.03$) were also significantly reduced (12,74). This trial showed conclusively the clinical benefits of the ACE inhibitor ramipril in reducing the risk of cardiovascular events, including heart failure, in a broad range of high risk patients who are not known to have LV systolic dysfunction or heart failure.

EVOLVING NOVEL THERAPIES FOR HEART FAILURE

Recommendations

- The role of evolving therapies, such as inhibition of cytokine, endothelin, vasopressin and vasopeptidase, and synchronized biventricular pacing, will need to be evaluated through currently planned or ongoing clinical trials incorporating established therapies such as those outlined in this updated guideline. (Grade C)

To address the residual burden of mortality and morbidity despite the optimized therapy for heart failure, as outlined in this updated guideline, several novel approaches to heart failure therapy are being actively evaluated. Promising therapies include the vasopeptidase inhibitors, which block both the ACE and other metalloproteases that can increase levels of bradykinin and atrial natriuretic peptides. Preliminary data in the Inhibition of MetalloProteinase BMS-186716, omapatrilat, in a Randomized Exercise and Symptom Study with heart failure (IMPRESS) trial (75) suggested a potential benefit of vasopeptidase inhibitors in the combined end points of death, hospitalization and exercise capacity compared with ACE inhibitors. This is being evaluated in a large mortality outcome trial (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events [OVERTURE]). Similarly, cytokine inhibitors such as the soluble tumour necrosis factor receptor etanercept have been shown to improve quality of life, ventricular function and exercise capacity in patients with heart failure and depressed LVEF (Randomized Etanercept North American Strategy to Study Antagonism of Cytokine [RENAISSANCE] trial) (76). Furthermore, agents that can block the endothelin (ENDothelin Antagonist Bosentan for Lowering cardiac Events in heart failure [ENABLE] trial) and vasopressin-1 and/or 2 receptors (VITAL, AQUAVIT trials) are now also undergoing active evaluation.

Other nonpharmacological therapies are also being actively evaluated. These include the use of continuous positive airway pressure for patients with heart failure and sleep apnea or Cheyne-Stokes respiration.

Preliminary follow-up data suggested a positive benefit in clinical outcome, and this is being evaluated in an ongoing large mortality trial (Canadian Continuous Positive Airway Pressure Trial for Congestive Heart Failure Patients with Central Sleep Apnea – CANPAP) (77). Furthermore, synchronized pacing is also being evaluated as a means of improving electromechanical synchrony in the enlarged failing ventricle, and preliminary data are very encouraging for improvement in quality of life and reduction in hospitalization.

RIISING TO THE CHALLENGE OF THE HEART FAILURE EPIDEMIC

Recommendations

- There needs to be a coordinated effort among patients, physicians, allied health care workers, health care providing institutions, funding agencies, and clinical and basic researchers to work together toward a solution to stem the heart failure epidemic. (Grade C)
- There should be a public awareness program in heart failure to permit earlier recognition and treatment, as well as prevention. (Grade C)

The challenge remains large for the health care profession to stem the tide of the heart failure epidemic. As the population continues to age and comorbidities continue to rise, heart failure is increasing in its incidence and mortality despite better than ever treatment strategies being available, as evidenced by this guideline update document.

There needs to be a coordinated effort among patients, health care providers, and funding and government agencies to work together toward a solution. This will involve population surveillance, and monitoring disease burden and outcomes in Canada, joining the expertise of Health Canada, volunteer agencies, provincial databases and researchers at academic institutions. Understanding of the pathophysiology of the disease leading to innovations in therapy will require the efforts of both basic and clinical researchers, coordinating support from peer-reviewed governmental and voluntary agencies, and industry partners. Finally, the dissemination and implementation of the therapies back in the community will require the coordinated efforts of all physicians, allied health care workers, nurse practitioners in the heart failure clinics, pharmacists and, of course, most importantly, the patients. Keeping in mind the importance of prevention, as well as the challenges of cure, it is only through a coordinated effort on a nationwide basis that the tide of heart failure can be stemmed (78). There should also be a public awareness program to improve its early recognition and prevention.

We plan to update the guideline on a yearly basis under the sponsorship of the CCS to maintain its cutting-edge applicability and to improve its impact in the community. Each community should also take into account its particular facilities and demographics, and implement the guideline in the most efficient and cost effective manner to maximize its benefit on both the patient and the health care system.

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