

# **The 2001 Canadian Cardiovascular Society Guideline Update for the Management and Prevention of Congestive Heart Failure**

## Primary Panelists:

Peter Liu (Chair), Malcolm Arnold (Co-Chair). Israel Belenkie, Jonathan Howlett, Victor Huckell, Andrew Ignazewski, Marie-Helene LeBlanc, Robert McKelvie, Joel Niznick, John D. Parker, Vivek Rao, Heather Ross, Denis Roy, Stuart Smith, Bruce Sussex, Koon Teo, Ross Tsuyuki, and Michel White.

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Secondary Panelists: Don Beanlands, Vicki Bernstein, Ross Davies, Debra Issac, David Johnstone, Gordon Moe, Gary Newton, Peter Pflugfelder, Sharon Roth, Jean Rouleau, Salim Yusuf

## **Introduction & Logistics of Guideline Generation**

The Canadian Cardiovascular Society heart failure treatment consensus guidelines were previously published in 1994. The document has expertly outlined some of the fundamental treatment strategies that remain truism today. However, significant advances in understanding and treatment of heart failure have accumulated since 1994. Most notably are the use of  $\beta$ -blockers and other neurohumoral modulators and the increased adoption of Heart Failure Clinics have transformed the treatment landscape for heart failure in Canada. The currently revised guidelines incorporate these new data into 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 treating heart failure patients.

To formulate the current version of the guidelines, the individuals representing heart failure experts recommended with the CCS Council, together with individuals with expertise in cardiac transplantation, arrhythmias, pharmaceutical sciences, clinical trials, guideline dissemination and professional education were purposefully included. The group has conducted systematic Medline search, obtained copies of all the currently available U.S. and European heart failure guidelines both in print and electronic forms, and Cochrane collaborative reviews. The evidence was then evaluated according the criteria 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 finally peer reviewed through the entire CCS membership using a unique first time electronic dissemination system through both electronic mail and posting on the CCS website. We have received an unprecedented number of electronic feedback totally over 200, and have incorporated all the suggestions that are evidence based, innovative and user friendly into the new version.

The preparation of this guideline was supported only from the Canadian Cardiovascular Society without the influence 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:** Non-randomized contemporaneous controls
- **Level 4 evidence:** Non-randomized historical controls
- **Level 5 evidence:** Case series and expert opinion

## Heart Failure: A Definition

Heart failure is a pathophysiology state when 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, with the accompaniment of 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 that will impact on the lives of Canadians. This is in distinct contrast to the declining mortality of cardiovascular disease in general and acute conditions such as myocardial infarction in particular<sup>1</sup>. Currently, there are over 350,000 Canadians afflicted with the condition, and the one year mortality after diagnosis ranges between 25-40%<sup>2</sup>.

In contrast to myocardial infarction, 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 physician's office, where acute treatment is instituted. However, in contrast to the

usual perception, heart failure does not become “cured” with the relief of congestive symptoms. The disease often progresses asymptotically with continuing enlargement and adverse remodeling, leading ultimately to chronic debility and increased mortality<sup>3</sup>.

Heart failure also impacts greatly on the health care system. Heart failure remains the commonest diagnosis that brings a patient to hospital for a medical admission<sup>4</sup>. Each hospitalization averages 8 days of in patient stay in Canada, accruing a cost of over \$1 billion per year for inpatient hospital 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 to date that effective treatment strategies are now 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 HF 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 specialist, social workers, and home care providers. (Grade A)**
- **The goals of treatment are to improve patient quantity and quality of life, to reduce symptoms and hospitalizations, and to coordinate care that is patient centered and evidence based. (Grade C)**
- **Vaccination to prevent flu and pneumonia is recommended for all patients with heart failure.**
- **Increased general awareness of heart failure care in health care institutions and community should be a priority in reducing overall burden of the disease**

## Special Considerations in the Treatment of Heart Failure

### The Role of Heart Failure/Function Clinics

- Specialized patient clinics, staffed by physicians and health care professionals with an interest and expertise in heart failure, should be considered for the assessment and management of complex heart failure patients in those at higher risk. (Grade B)
- Such clinics should also be a resource for physicians, patients and their families (Grade C)
- Patients who may particularly benefit from care of a Heart Failure Clinic are those who are not responsive to treatment, experiencing deterioration while on treatment, recently seen in emergency department, requiring prompt access to care by someone with expertise in heart failure, or whose diagnosis is unclear.
- Telemonitoring of patients at high risk for deterioration by clinic nurses can provide the seamless care into the community.

### Compliance

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

### Investigations

- Basic investigations commonly required for heart failure patients include ECG, chest X-ray, routine blood work including 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 nuclear or echocardiographic techniques.
- Ischemic heart disease if suspected present should be investigated and treated as appropriate.

## Pharmacological Therapies for Systolic Heart Failure

## ***Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists***

### **Recommendations:**

#### ***Angiotensin Converting Enzyme (ACE) Inhibitors***

- ACE inhibitors should be prescribed as soon as safely possible following acute myocardial infarction for all patients (unless contraindicated or not tolerated) and continued for 6 weeks. Therapy should be continued indefinitely in those with either left ventricular ejection fraction (EF) < 40%, or who have shown clinical evidence of congestive heart failure, even if only transient. (Grade A, Level 1)
- ACE inhibitors should be prescribed as soon as safely possible for all asymptomatic patients with EF <35- 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, NYHA Functional Class II-IV, unless contraindicated or not tolerated. (Grade A, Level 1)
- The target ACE inhibitor dose should be either the dosage regimen used (for specific ACE inhibitors in whom data exists) in placebo controlled mortality trials, or the maximum tolerated (or recommended) dose for those ACE inhibitors for which no mortality data exists. (Grade A, Level 1)

#### ***Angiotensin II Receptor Antagonists (ARBs)***

- ACE inhibitors remain the therapy of choice for CHF, in preference 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)
- Angiotensin II Receptor Antagonists may be considered as adjunctive therapy when either beta blockers, or ACE inhibitors are not tolerated. It must be emphasized top priority must be given to 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/ACE inhibitor/ ARB in the management of congestive heart failure. 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 ACEi/ ARB therapy with the aim to reduce hospitalization and improve quality of life. (Grade C, Level 3)

### **Practical Tips:**

- **The literature concerning ACE inhibitors and LV dysfunction is consistent with an overall class effect. There is no evidence to suggest a 'best' ACE inhibitor, however captopril, enalapril, ramipril, lisinopril, have been evaluated for chronic CHF due to LV dysfunction. It is likely more important to use ACE inhibitors in higher doses.**
- **Studies evaluating ACE inhibitors in LV dysfunction generally include patients with serum creatinine <220 umol/L, and potassium <5.5 mmol/L and systolic BP >80-85 mmHg without a history of angioedema due to ACE inhibitors.**

## **Evidence and Rationale**

### **ACE Inhibitors and Congestive Heart Failure**

All ACE inhibitors inhibit angiotensin converting enzyme, which results in 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 leads to the ACE inhibitor cough - a dry, low grade, usually nonparoxysmal cough in the absence of ongoing venous congestion.

The CONSENSUS trial, published in 1987 was the first of several landmark trials that demonstrated ACE inhibitors significantly reduced mortality in chronic congestive heart failure (CHF) due to left ventricular systolic dysfunction (when ejection fraction is < 35-40%)<sup>5</sup>. Since then, clinical trials involving nearly 100 000 patients, randomized to 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<sup>6-9</sup>. An overview of the literature shows ACE inhibitors reduce total mortality, total hospitalizations, worsening heart failure, and recurrent myocardial infarction by 20- 25 % when used for patients with LV systolic dysfunction<sup>10</sup>. Indeed, additional observations seen in these studies have led to research of further questions. The result has been expansion of the therapeutic uses for ACE inhibitors to new indications such as chronic ischemic heart disease regardless of EF, and in diabetic renal disease<sup>11</sup> (see prevention section).

Important ancillary data from these trials has confirmed the central role of neurohormonal activation in the cause and progression of chronic CHF. Suppression of neurohormonal activation is strongly linked to improvements in hemodynamics, cardiac remodeling, symptoms and mortality benefit<sup>12</sup>. In general, patients with more advanced illness derive greater benefit than those earlier in the course of disease. There is currently no mortality data to support the use of ACE inhibitors for patients with chronic CHF and ejection fraction >

40% (CHF with preserved LV function) in the absence of another indication for ACE inhibitor therapy.

### ***Usage and Side Effects of ACE Inhibitors***

Introduction of ACE inhibitors should be done as soon as safely possible and in a step-wise fashion. Dose titration should be performed every 7-14 days or sooner if in hospital. Baseline serum electrolytes and creatinine should be documented and repeated 7 to 14 days later or before each titration. The target dose should be to equal to dosage regimens used in clinical trials, or the maximally tolerated dose.

Side effects of ACE inhibitors include cough, a *class effect* which leads to discontinuation in up to 5% of patients. It is important to remember cough can occur in up to 40% of patients with CHF and is most frequently a manifestation of uncontrolled CHF rather than ACE inhibition<sup>13</sup>. Hypotension, renal dysfunction and hyperkalemia may occur. With renal dysfunction and hypotension, over diuresis is frequently a contributing factor and 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  $> 5.0$  mmol/L (in absence of K<sup>+</sup> supplements or K<sup>+</sup> sparing diuretics), symptomatic hypotension, with systolic BP  $< 80$  mmHg, bilateral renal artery stenosis or progressive renal insufficiency. An important point regarding side effects is the frequent misconception 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 they derive at least equal benefit from ACE inhibitor therapy. The recently completed ELITE II study, randomized 3152 patients to either captopril (N= 1574) or losartan (N= 1578) and were followed for a mean 555 days<sup>14</sup>. Over 85% of these patients were  $> 65$  years of age and only 2% of patients withdrew from study medication due to renal impairment. Thus, ACE inhibitors should be strongly considered in elderly patients with baseline creatinine  $< 220$   $\mu$ mol/L and potassium  $< 5.0$   $\mu$ mol/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  $< 40\%$ . Additional comments can now be made. Previous guidelines suggested duplication of dosage regimens used in clinical trials. Recent publications show high dose ACE inhibitor therapy is superior to low doses; possibly half the benefits of ACE inhibitor therapy are related to usage of high doses.

The largest randomized trial comparing high dose to low dose ACE inhibitor therapy was the ATLAS study<sup>15</sup>. In this trial 3164 patients with chronic CHF were randomized to low dose (2.5- 5 mg daily, N= 1596) or high dose lisinopril (32.5- 35 mg daily, N= 1568). After a median 45 months follow-up, there was a 12% reduction in composite mortality/total hospitalizations in the high dose group (P= 0.002), a non-significant 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.

Table 1. Recommended initiating and target doses of commonly used ACE inhibitors based on clinical trial data

ACE Inhibitor	Initiating Dose	Target Dose
Captopril	6.25-12.5 mg t.i.d.	25-50 mg t.i.d.
Enalapril	1.25-2.5 mg b.i.d.	10 mg b.i.d.
Ramipril	1.25-2.5 mg b.i.d.	5 mg b.i.d.
Lisinopril	2.5-5 mg o.d.	20-35 mg o.d.

### Angiotensin II Receptor Antagonists (ARBs)

Angiotensin receptor antagonists (ARBs) blocks specifically the angiotensin AT1 receptor, is well tolerated with a side effect profile similar to placebo. Its efficacy in heart failure is however less clear. The enthusiasm for ARBs in heart failure was stimulated by the ELITE I trial, in which 722 patients with class II-IV heart failure were randomized to losartan 50 mg/day or captopril 50 mg t.i.d. The primary endpoint of the study was renal dysfunction, and was not different between the two arms of the study<sup>16</sup>. However, unexpectedly, the patients showed a highly significant reduction in mortality in the losartan arm (17/352 died) when compared to captopril (32/370). There was no difference in hospitalization rates. To explore this effect further, a second larger trial ELITE II (Losartan Heart Failure Survival Study) trial was conducted. Overall, 3152 patients (mean age 71.6 years) were randomized to captopril 150 mg/day or losartan 50 mg/day and followed for a mean of 555 days<sup>14</sup>. The primary endpoint was total mortality and of 1574 captopril patients, 250 died while 280 of 1578 patients died when randomized to losartan (P= 0.12). The secondary endpoint, resuscitated cardiac arrest or sustained ventricular tachycardia a trend in favor of captopril (P= 0.08) was noted. Losartan was significantly better tolerated than captopril (P= 0.001, 14.3% vs. 9.4% discontinuation rate). Thus, ELITE II failed to demonstrate superiority of losartan over captopril. This should not, however, be interpreted as equivalence of the 2 agents. On the basis of this study and the total CHF literature, ACE inhibitors remain the therapy of choice for chronic CHF due to left ventricular systolic dysfunction. For those who are ACE intolerant due to cough, ARBs may be considered. While ARBs have not been proven superior to combination hydralazine/ nitrates, it is unlikely they will be less efficacious, and very likely they will be better tolerated. However, there are no current or planned trials comparing ARBs vs. hydralazine/ nitrates in ACE intolerant patients with CHF due to LV dysfunction. Thus, optimal therapy for ACE intolerant patients has yet to be determined. One ongoing trial, the CHARM trial, has three arms, one of which is to compare candesartan versus placebo in patients with CHF due to LV systolic dysfunction (N= 1700) who are intolerant to ACE inhibitors<sup>17</sup>. 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 vs. hydralazine/ nitrates will be possible in this study. The results are expected in 2002.

There may be a rationale for combination ACE/ARB therapy. Although both agents cause similar hemodynamic changes, each effects its changes through a different mechanism<sup>18</sup>. When ARBs are used in combination with ACE inhibitors, further improvements in hemodynamic and exercise variables occur<sup>19</sup>. Indeed, in the RESOLVD Pilot study involving over 700 patients with CHF, the combination of ACE/ARB therapy (enalapril + candesartan) was associated with attenuation of left ventricular remodeling and improvements in neurohormonal activation when compared with either agent alone<sup>20</sup>. Preliminary but yet unpublished data from the much larger VAL-HEFT study (Valsartan Heart Failure Study) enrolled 5010 patients with chronic, stable mild to moderate CHF on ACE inhibitor therapy, and randomized them to either additional ARB (valsartan up to 160 mg po bid, n= 2511) or placebo (n= 2499). There were two primary endpoints- 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 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 endpoint (723 or 28.8% in valsartan arm, vs. 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 reduction in morbidity when ARB is added to ACE inhibitors.

Additionally, 7% (366) of randomized patients were not on ACE inhibitors at study entry. In this group, there was a 44% reduction in the composite primary endpoint in the valsartan arm. Another pre-specified subgroup analysis involved beta blockade treatment. The valsartan arm demonstrated a significant reduction of the primary composite endpoint in those patients without beta blocker therapy. In the approximately 1500 patients on beta blocker at study randomization there was a slight and non-significant trend toward increase in the composite primary endpoint 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, the CHARM combination arm (N= 2500) has a similar design as VAL-HEFT but with significant differences<sup>17</sup>. This trial has high dose candesartan (up to 32 mg. po od) as the intervention with a follow up of two years. Baseline characteristics of the CHARM vs. 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 neurohormonal blockade including inhibition ACE, beta receptors, aldosterone and angiotensin II.

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

As previously mentioned, patients with CHF with preserved left ventricular function (EF > 40%) currently have no proven therapy for reduction of mortality. If there is no other reason for prescription of ACE inhibitors, no available evidence suggests their use. One ongoing trial, the PEP-CHF trial, randomized 1000 elderly patients with diastolic heart failure to perindopril 4 mg od or placebo. Results will be available in 2002. The final arm of the CHARM trial (N= 3000) involves the randomization of patients with diastolic heart failure to either candesartan or placebo. The use of concomitant ACE inhibitor therapy (if indicated) has been allowed in the CHARM trial.

## ***β-Adrenergic Receptor Blockers in Congestive Heart Failure***

### **Recommendations:**

- **Beta-adrenergic receptor blockers are strongly recommended in all patients with NYHA class II - III heart failure, and left ventricular ejection fraction  $\leq$  .40 to reduce mortality, hospitalizations, improve cardiac function and quality of life, unless contraindicated (Grade A, Level 1).**
- **Beta-blockers are now also indicated in patients with stable class IV heart failure patients following the COPERNICUS trial (Grade A, Level 1). Keeping 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 I with LVEF < 40% post myocardial infarction (Grade B).**

### **Practical Tips:**

- **Beta-blockers should be initiated with low doses (e.g. 3.125-6.25 mg carvedilol b.i.d., 1.25 mg of bisoprolol o.d., or 6.25-12.5 mg metoprolol b.i.d.) and the doses should be increased slowly at intervals of 2 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 (<60/min). Diabetes is not a contraindication.**
- **Patients should be assessed clinically for worsening of 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 2-12 weeks. Objective improvement in cardiac function may not be fully achieved for up to 1 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 there is substantial difficulty in management of the failure with vasodilators and diuretics.**
- **Acute congestive failure 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.**

## Evidence for Beta-Blockers

The most dramatic changes from the previous guideline 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 now definitive evidence for the use of beta blockers has emerged in the last 4 years to transform the treatment of heart failure. The benefits of beta blockers for heart failure are demonstrated in both ischemic and non-ischemic forms of heart failure, and include reduction in mortality (20-65%; most studies showed a reduction of ~33% with one study using carvedilol demonstrating a 65% reduction), progression of failure and rehospitalizations (~25%)<sup>21-29</sup>. There is also improvement in symptoms and feeling of well-being but only equivocal changes in measured exercise capacity<sup>30</sup>. LV end-diastolic and end-systolic volumes are consistently decreased and ejection fraction is increased, sometimes remarkably<sup>31,32</sup>. The benefits appear to be similar across different demographics including age (up to 80 years in the clinical trials)<sup>33</sup>.

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 COPERNICUS using carvedilol have shown a significant benefit, while BEST trial using bucindolol have failed to show a benefit. It is important to emphasize the patients who were enrolled in COPERNICUS 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.* These included patients who were in the intense care unit and who were on IV inotropes or vasodilators. A brief summary of some of the representative major clinical trials is outlined below in the table. Please keep in mind that all the patients are on background therapy of ACE inhibitors and diuretics.

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	Total N	Placebo Mortality (per year)	Treated Mortality (per year)	Number Needed to Rx (NNT)/ 1Year
U.S. Carvedilol <sup>26</sup>	Carvedilol	II-III	1,094	9%	3%	16
CIBIS II <sup>24</sup>	Bisoprolol	II-III	2,647	11.0%	7.2%	26
MERIT <sup>23</sup>	Metoprolol XL	II-III	3,991	13.2%	8.8%	23
BEST <sup>34</sup>	Bucindolol	III-IV	2,708	16.8%	15.1%	59
COPERNICUS <sup>35</sup>	Carvedilol	III-IV	2,289	18.5%	11.4%	14

The pathophysiological pathways contributing to morbidity and mortality in congestive heart failure include those mediated by the beta-receptors which 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 from those which 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 blocker (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 if efficacy will be shown to be different with the different agents<sup>36,37</sup>. The trial results with metoprolol, bucindolol and carvedilol suggest that important differences may exist. A large randomized clinical trial designed to compare carvedilol to metoprolol is still in progress. Until the results are available, metoprolol, bisoprolol and carvedilol can all be considered for clinical use in heart failure in Canada. There are limited data on the differences between long- versus short-acting metoprolol, even though it is the former that was used in the MERIT trial<sup>38</sup>. 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 having 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.

The most optimal target doses are not clear at this time. Maximum doses are usually up to 50 mg carvedilol b.i.d. and up to 200 mg metoprolol CR/XL o.d. although many patients will only tolerate lower doses. Benefits are evident even at low doses of carvedilol so that doses lower than target should be maintained when the higher ones cannot be achieved. However, achieving higher tolerated doses if possible is still desirable as there is a suggestion of a dose-response relationship of beta-blockers on improvement in LV ejection fraction.

Adverse effects most often seen during dose titration include worsening of failure, hypotension and bradycardia. Non-specific symptoms due to the beta-blockade are also common. Optimal use of vasodilators and diuretics prior to implementation of the beta-blocker

will minimize these occurrences. If failure increases, increasing the vasodilators if the blood pressure and symptoms permit and/or diuretics will usually be effective in controlling the failure. Consideration of 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 intensification of medical regimen may be needed.

## **Aldosterone Antagonism in Heart Failure**

### **Recommendations:**

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

### **Practical Tip:**

- **The patient should have baseline creatinine <200 mg/L, and potassium <5.0 mEq/L before initiation. The average maintenance dose of spironolactone is low at 25 mg per day. The patient must be followed within 5 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 RALES trial)**

The RALES trial (Randomized ALdactone Evaluation Study)<sup>39</sup> enrolled 1,663 patients with class III/IV heart failure with left ventricular ejection fraction <35%, serum creatinine <2.5 mg/dL and a serum potassium level <5 mmol/L, who were already on an ACE inhibitor as tolerated, diuretics and/or digoxin. The patients were randomized to spironolactone (25 mg o.d., N=822) or placebo (N=841), and clinical events were followed, with total mortality being the primary endpoint. The average dose of spironolactone ultimately used was 27 mg per day.

The RALES trial was terminated prematurely after 2 years of follow up, due to 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 2 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/year. 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. Since previous studies have suggested that ACE inhibitors do not adequately suppress aldosterone production, the patient is still at risk for its adverse remodeling influences<sup>40-42</sup>. Since the dose of spironolactone used is relatively low, it also suggests that the mechanism of ventricular remodeling and fibrosis, promoted by aldosterone, to be 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 post 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 usage may be considered in select patients with intractable heart failure or temporary deterioration after optimization of standard therapy. (Grade B, Level 2)**

### **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, e.g. significant loss of body mass, deterioration of renal function or at risk of drug interactions, particularly with amiodarone.**
- **Digoxin levels should be measured immediately pre-dose or 6 hours or more post dose, after steady state is reached 3 to 4 half lives after a dose adjustment. While therapeutic digoxin levels range up to 2.0 µg/L or higher, lower levels at around 1.0 µg/L appear safer than higher levels.**

Since the CCS Consensus Conference on Heart Failure was published in 1995, additional data have become available<sup>43</sup>, particularly the results of the Digitalis Investigation Group (DIG) mortality trial<sup>44</sup>. The results of the few new trials of non-glycosides 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, improving the left ventricular ejection fraction, and will result in clinical deterioration when discontinued. The largest prospective randomized long term trial of digoxin, the Digitalis Investigation Group (DIG) mortality trial, was completed and published in 1997. In 6,800 patients with left ventricular ejection fraction of 45% or less, with 3397 patients randomized to digoxin and 3403 patients to placebo, mortality was unaffected (34.8% with digoxin and 35.1% with placebo; risk ratio 0.99, 95% confidence interval 0.91 to 1.07, P=0.08), after 37 months of follow-up. Treatment was in addition to diuretics and angiotensin converting enzyme inhibitors. There was a trend toward a decrease in risk of death attributed to worsening heart failure in the digoxin group (risk ratio 0.88, 95% confidence interval 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% vs 24.7%, risk ratio 0.72, 95% confidence interval 0.66 to 0.79, P<0.001). In the ancillary trial of 988 patients with preserved left ventricular 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 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, 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, 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 at risk of drug interactions. To be interpretable, the blood taken for measurement should be taken following standard guidelines, i.e., prior to the next dose, or 6 hours or more post dose and after steady state is reached 3 to 4 half lives after a dose adjustment. In the setting of heart failure, maintaining digoxin levels at around 1.0 µg/L or below appears safer and lowers the risk of toxicity.

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

	ACEI/ ARBs	Amiodarone	$\beta$ blockers	Digoxin	Loop diuretics	Potassi
ACEI/ARBs						
amiodarone	—					
$\beta$ blockers	[ $\downarrow$ BP]	$\uparrow$ effect of $\beta$ blocker				
digoxin	—	$\uparrow$ serum digoxin levels ~2 fold	[ $\downarrow$ HR, $\downarrow$ AV conduction], carvedilol may $\uparrow$ dig levels ~25%			
loop diuretics	[ $\downarrow$ BP]	—	[ $\downarrow$ BP]	hypokalemia $\uparrow$ digoxin effect		
potassium	$\uparrow$ K <sup>+</sup>	—	—	—	—	
spironolactone	[ $\downarrow$ BP], $\uparrow$ K <sup>+</sup>	—	[ $\downarrow$ BP]	may $\uparrow$ digoxin levels	[ $\downarrow$ BP, dehydration]	$\uparrow$ K
warfarin	—	$\uparrow$ warfarin effect	—	—	—	—

Possible drug interactions with moderate to major impact are listed. Individual patient responses may vary.

[ ] indicates additive pharmacologic effect, e.g., additive hypotensive effects [ $\downarrow$ BP]

Adapted from: Tatro DS, Ed. Drug Interaction Facts. Facts and Comparisons, Wolters Kluwer Co, St. Louis.

## 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 to arrhythmias (Grade A, Level 1).
- Patients in 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 (Grade B, Level 2).
- In the setting of recent onset atrial fibrillation, consideration of cardioversion may be clinically indicated (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 LVEF less than 35%, should be considered for an ICD therapy (Grade A, Level I).

- **Patients who have had previous MI with LV dysfunction (EF 35% or less) and asymptomatic spontaneous nonsustained VT who would be suitable candidates for an ICD should undergo an invasive EP study to determine the inducibility of VT or ventricular fibrillation. If sustained VT or ventricular fibrillation are induced, the patient should be considered for an ICD (Grade B, Level II).**
- **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 agents of choice (Grade B, Level II).**

Heart failure and arrhythmias are both common conditions, and owing to common risk factors shared by both, they often co-exist 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 protecting the injured heart and correction of neurohumoral activation with angiotensin modulators and beta blockers. These effective pharmacological treatments do show the reduction in both overall mortality and sudden deaths in the large randomized trials<sup>5,23,24</sup>. 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 in heart failure can lead to sudden and rapid deterioration of symptoms. Restoration of sinus rhythm electively accompanied by appropriate anticoagulation or urgently guided by transesophageal echo, is often effective in reversing the symptoms and should be considered where it is clinically appropriate<sup>45</sup>. Amiodarone is more effective than other class I antiarrhythmic agents in maintaining sinus rhythm after effective cardioversion<sup>46</sup>, and metoprolol CR/XL has also been shown to be more effective than placebo in maintaining sinus rhythm<sup>47</sup>, although the efficacy of these therapies in the specific setting of heart failure is currently unknown. In patients where the ongoing risk of atrial fibrillation is still present, including intermittent episodes, the patient should receive full anticoagulation to maintain INR in the range of 2.0-3.0<sup>48</sup>.

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 the 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 resting heart rate, with little influence on the exercise heart rate. Unlike individuals without left ventricular dysfunction, atrial fibrillation in patients with heart failure needs constant review and the complex situation may need referral to an electrophysiology expert, for additional considerations including AV nodal ablation therapy.

### ***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 has been reviewed in the 2000 CCS consensus conference on "Prevention of sudden death from ventricular arrhythmias"<sup>49</sup>, and 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 2 relevant studies, CIDS<sup>50</sup> and AVID<sup>51</sup>. These studies included patients whose VT episode caused cardiac arrest or syncope, and those in whom LVEF was less than 35%, and were randomized to receive either an ICD (implantable cardiac defibrillator) or amiodarone as the primary intended treatment. Meta-analysis of the ICD trials indicated a 27% reduction in mortality with the ICD when compared to 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 on amiodarone was 12.3%, and this was reduced to 8.7% with the ICD. The benefit of 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 accounting for the efficacy of the ICD observed. Therefore, the recommendation of the consensus conference for management of resuscitated VF or VT or symptomatic VT in the presence of LVEF less than 35% was to consider ICD as the first line treatment.

In the setting of primary prevention following symptomatic ventricular arrhythmias, the evidence is more controversial. Two studies to date have included patients with LV dysfunction and asymptomatic nonsustained VT – MADIT<sup>52</sup> and MUSTT<sup>53</sup>. Both studies have demonstrated improved survival with a treatment strategy that included the use of the ICD. Both studies included patients with severely depressed EF (the average EF 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 criteria in MADIT. Therefore the consensus recommendation currently cautiously suggests that patients who have had previous MI with LV dysfunction (EF 35% or less) and asymptomatic spontaneous nonsustained VT who would be suitable candidates for an ICD should undergo an invasive EP 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 primary prevention, such as MADIT II and SCD-HeFT, randomizing patients with heart failure or LV dysfunction to ICD or best conventional therapy.

## **Lifestyle Modifications**

### **Recommendations:**

- **All heart failure patients should be counseled 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, counseling regarding smoking cessation and advice regarding physical activity. (Grade C, level 3)**
- **Effective lifestyle modification requires time, specific expertise and is best conducted as a focused discussion session with planned follow-up**

A history of hypertension or coronary artery disease are often the cause for the development of heart failure. Risk factors including smoking, diabetes mellitus, and hyperlipidemia have been recognized as being in part 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<sup>54</sup>. Thus risk factors in heart failure patients should be addressed and aggressively treated. Sodium and water retention leading to an expansion of extra cellular fluid volume has been well described in the heart failure syndrome. When normal subjects reduce salt consumption from an average of 10 gm per day to 5 gm per day, (1 gm salt = 0.4 gm or 17.1 mmol of Sodium) the extracellular fluid volume has been observed to decrease by 1.0 - 1.5 litres<sup>55</sup>. 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<sup>56</sup>. Therefore it would seem reasonable to have patients with an alcohol-induced cardiomyopathy abstain from alcohol while patients with heart failure due to other etiologies may use small quantities of alcohol.

## **Exercise Training in Heart Failure**

### **Recommendations**

- **Regular physical activity is recommended for all heart failure patients**

- **Stable NYHA-FC I-III heart failure patients 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 prior to 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 has accumulated which challenges this recommendation and in fact limiting physical activity may not only be unnecessary but also undesirable because it could lead to further disability<sup>57</sup>.

Studies have not demonstrated a relationship between left ventricular ejection fraction and peak exercise performance. This finding suggests the reduction in exercise capacity may be more importantly influenced by factors other than poor ventricular function. Heart failure patients have been found to have reduced skeletal muscle strength, skeletal muscle atrophy, impaired muscle blood flow, as well as abnormalities in skeletal muscle metabolism, biochemistry and histology<sup>57</sup>.

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 decrease in sympathetic nervous system activation, improvement in exercise performance and clinical status<sup>57,58</sup>. 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 would suggest exercise training may decrease clinical events<sup>58</sup>.

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, and therefore either resistance exercise training or interval exercise training should be part of the program<sup>59</sup>.

## **Revascularization & 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 ejection**

**fraction (LVEF < 35%) or a history of congestive heart failure is not a contraindication to surgery. (Grade B, Level 2)**

- **Patients with chronic coronary artery disease who are asymptomatic (i.e. 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 2)**
- **Partial ventriculotomy (e.g. Batista or Dor procedure) is not recommended unless future follow up suggest benefit (grade C, level 3).**
- **Patients with idiopathic dilated cardiomyopathy and severe mitral regurgitation and class 3 to 4 symptoms may be considered for mitral valve reconstructive surgery prior to listing for cardiac transplantation (grade C, level 3)**

Survival for patients with ischemic cardiomyopathy and poor left function is poor. Patients with an ejection fraction < 25 % have a 1 year mortality of 25% and a 5 year mortality of 60%. Surgical revascularization should be considered as a treatment option in the management of patients with ischemic left ventricular dysfunction and CHF. As a result of their low ejection fractions, many of these patients, formerly thought to be best treated medically, can undergo safe (perioperative mortality rate 5% - 10%) and effective revascularization with excellent medium term results. Factors that may affect outcome of surgical revascularization include the presence of viable myocardium, bypassable coronary vessels, left ventricular dilatation, elevated left ventricular 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 been done for patients with LVEF < 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 3-5 year survival with CABG (68% - 80%) compared to historical controls treated medically (28%-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. Despite the obvious limitations of these studies, it is reasonable to consider CABG for appropriate patients.

Heart failure patients with evidence of clinical ischemia (e.g. 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 coronary artery bypass surgery.

### ***Coronary Artery Bypass Surgery for Impaired LV Function without Angina***

The ultimate goal of coronary artery bypass surgery in patients with impaired LV function without angina is to improve survival. At present, there are no controlled studies available on the effect of revascularization in this population of patients. Previous randomized trials of coronary artery bypass surgery excluded patients with heart failure symptoms (NYHA > II). Coronary Artery Surgery Study (CASS) Registry compared the survival of patients with predominant symptoms of heart failure treated medically and surgically showed an equally poor 5 year survival rate of 23% in both groups. In addition, the perioperative mortality rate was in the range of 15-20%. However, there are now, numerous retrospective studies regarding revascularization of patients with ischemic cardiomyopathy demonstrating improved medium term survival (50 – 80% 5 Year Survival) with improvements in LV ejection fraction 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 coronary artery bypass surgery 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 left ventricular 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 ejection fraction, 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-hour reinjection imaging; and positron emission tomography (PET) with [<sup>18</sup> F] 2-fluoro-2-deoxy-D-glucose (FDG). There should be demonstration of substantial regions of myocardial viability that would benefit from revascularization. Such areas must be perfused by bypassable coronary arteries.

Patients who should be considered for investigations with view to possible coronary artery bypass surgery include a) patients with a history of myocardial infarction but no current angina and b) patients with neither angina nor a past history of myocardial infarction but have cardiovascular risk factors.

### ***Percutaneous Transluminal Coronary Angioplasty (PTCA) for LV Dysfunction and Angina***

Percutaneous transluminal angioplasty (PTCA) with / without stenting in patients with multi-vessel coronary disease and heart failure has not been shown to improve prognosis or surrogate endpoints such as LV ejection fraction, heart failure symptoms or exercise tolerance. Patients with LV dysfunction and heart failure should be considered for coronary artery bypass surgery. PTCA with/without stenting should be reserved for patients on maximum medical therapy, who are ineligible for surgery but who require further intervention for symptomatic control of their angina.

### ***Partial left ventriculectomy***

This technique has been pioneered by Batista<sup>60</sup> and has been proposed to 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, Batista surgery involved resection of LV muscle, and also 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<sup>60</sup> showed a significant clinical improvement over one year in some patients. These observations were limited by a difficult and on a somewhat unreliable follow-up. The Cleveland Clinic experience reported a 58% freedom from death, relisting for cardiac transplantations, or need for LVAD support in patients who had undergone the Batista procedure<sup>61</sup>. This survival was much less than the 82 one-year survival in similar patients with a cardiomyopathy. Among the survivors, LV ejection fraction and peak oxygen uptake increased, but LV diameter failed to improve. Accordingly, the Batista procedure is not recommended until more studies allow either better identification of candidate patients or there is more encouraging follow up data.

### ***Mitral valve reconstruction***

Earlier studies reported that the development of heart failure post-mitral valve replacement with normal preoperative left ventricular ejection fraction was above 30% at 10 years<sup>62</sup>. However, outcome improved when mitral valve replacement was performed with cordal preservation<sup>63</sup>. More recently, mitral valve reconstruction by remodeling ring annuloplasty without mitral valve replacement was reported in patients with idiopathic dilated cardiomyopathy with severe mitral regurgitation and class 3 to 4 symptoms<sup>64</sup>. Longer term follow-up (24 months) study<sup>64</sup> showed beneficial reverse remodeling, increase left ventricular ejection fraction and stroke volume, and improvement in functional class. Based on this data, it is recommended that patients with idiopathic dilated cardiomyopathy and severe mitral regurgitation with or without incidental coronary artery disease, and with class 3 to 4 symptoms undergo such reconstructive surgery prior listing for cardiac transplantation. More work needs to be done and 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<sup>64</sup>.

### ***Left Ventricular Assist Devices***

After maximal medical therapy for congestive heart failure, 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 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:

1. Emergency cardiac assist systems to treat acute circulatory insufficiency.

2. Temporary cardiac assist systems that could support the circulation for days to months, providing time for recovery or for eventual transplantation.
3. Permanent cardiac assist systems that could treat the patient for the remainder of their life.
4. Total artificial hearts that could permanently replace the native heart.

At present, all four of these objectives have been achieved with clinical success, although the total artificial heart is still being utilized as a bridge to transplant<sup>65</sup>. Currently available circulatory support devices with FDA approval include the centrifugal Biomedicus Pump (Medtronic, Inc.), the ABIOMED BVS 5000 (ABIOMED Inc), the Thoratec ventricular assist device (Thoratec Labs), the TCI HeartMate pneumatic and vented electric devices (ThermoCardiosystems Inc) and the Novacor LVAS (WorldHeart Corp). 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 post-cardiotomy shock. The Thoratec, HeartMate and Novacor systems are all designed for prolonged support (>30 days) in patients awaiting transplantation. The TCI HeartMate device is currently under investigation for potential destination therapy in the REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure)<sup>66</sup>. Further improvements in device design should allow for smaller, totally implantable devices capable of long term (>5 years) support.

## Cardiac Transplantation

### Recommendations:

- **Patients with class IV heart failure with anticipated poor one-year survival, who has failed medical therapy and exhausted all surgical options, but has an opportunity for rehabilitation, may be referred to a cardiac transplantation center 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 transplanted as status 4 recipients (IABP or mechanical assist device supported) is increasing. Waiting times continue to increase and the mortality while waiting is substantial at 25-30% per year. The commonest indication for transplant in Canada remains coronary artery disease accounting for  $\approx$ 65% followed by IDCM.

## **Outcomes**

Based on ISHLT registry data for the era 1995→1998 there is a 82% one year and 74% three year survival<sup>67</sup>. For the era 1986 → 1990 the median survival is 8.9 years and conditional half-life for patients who have survived the first year is 11.4 years.

Ninety percent of patients return to FC I at year one. However despite this only  $\cong$  50% return to work. In general all patients will experience some complication after transplant. Overall there is a 57% re-hospitalization rate at one year, 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 CMV, and EBV related malignancy<sup>68</sup>. However the single greatest limitation to long-term survival remains graft vascular disease with angiographic evidence in 42% of patients at 5 years<sup>69</sup>. 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<sup>70</sup>. Malignancy also remains a problem for long-term survivors, especially lymphoma and skin cancer.

## **Listing criteria**

The minimal listing criteria for transplant were recently reviewed by the American Society of Transplantation as well as the Canadian Cardiac Transplant Group and are listed below<sup>71</sup>. (Grade C Recommendation). Ideally these criteria are designed to identify those patients who are at the greatest risk and will derive the greatest benefit from transplant. Specifically:

- Advanced functional class
- Poor 1-year survival – All ambulatory patients should undergo cardiopulmonary testing
  - A  $VO_2 < 15$  ml/kg/min or 55% predicted for age and gender 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
    - Viable myocardium on cardiac imaging
    - Good target vessels
- All patients should exhibit the capacity for rehabilitation after transplantation
- **Absence of contraindications** – this is a list of comorbidities that 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 vasodilator or inotropic agent and a systolic BP  $> 85$  mmHg should be considered relative contraindications
  - Transpulmonary gradient  $> 15$ ; systolic PAP  $> 50$  mmHg; PVR  $> 4$  wood units; PVRI  $> 6$
  - Primary systemic disease – that may limit the long-term survival e.g.,

- Hepatic
- Pulmonary disease
- Renal insufficiency
- Creatinine > 200  $\mu\text{mol/l}$
- Active infection
- Technical issues
- Psychosocial issues
  - Drug or ETOH abuse
  - Documented non-compliance
- Recent malignancy – of the non basal cell carcinoma type
- Morbid obesity (> 140% ideal body weight) or marked cachexia (< 60% ideal body weight)
- Osteoporosis
- Vascular disease – Cerebral or Peripheral
- Diabetes Mellitus – with end organ damage
- Age is not in and of itself a contra-indication however increased age is associated with a poorer outcome after transplant. Therefore, with increasing age there should be more aggressive screening for associated comorbidities

There should be ongoing re-evaluation of patients once listed for transplant. Some patients will improve and consideration should be made to putting them on 'hold' with repeat cardiopulmonary testing and consideration of de-listing. As well some patients will develop complications while waiting and may no longer remain suitable for transplantation.

## Prevention of Heart Failure

**Recommendations for prevention of CHF are:**

- **Aggressive management of cardiovascular risk factors is recommended in order to reduce the risk for ischemic heart disease, the main cause of heart failure. (Grade A, Level 1)**
- **In patients with preexisting 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 left ventricular 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 myocardial infarction. Therapy should be started when hemodynamically stable postinfarction. (Grade A, Level 1)**

- **In high risk patients (age>55 yrs and multiple risk factors) without known low LVEF or symptomatic heart failure, ACE inhibitor therapy is recommended to reduce risk of death, myocardial infarction 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 blood pressure and diabetic control and measures taken to encourage increasing physical activities and smoking cessation.**
- **Education of patients in the avoidance of acute pharmacologic and non-pharmacologic precipitants of acute exacerbation of heart failure should be encouraged.**
- **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 date to support ACE inhibitor use in high risk patients without left ventricular 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. Since a large 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 myocardial infarction and ischemia reduces the risk of left ventricular systolic and diastolic dysfunction and the development of symptomatic CHF. Efficacious drug therapy, particularly with statins, is available in lowering cholesterol levels. Effective strategies have been developed in controlling high blood pressure and diabetes, and in encouraging increasing activities and smoking cessation. This issue is also addressed in another section.

Education of the patients in the avoidance of acute pharmacologic and non-pharmacologic precipitants of CHF will help in reducing 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 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 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 myocardial infarction in patients with NYHA class II to IV CHF. Patients with lowest ejection fractions and worst symptoms derive the most benefit. In asymptomatic patients with left ventricular dysfunction, ACE inhibitors have not been shown to reduce mortality, but have been shown to prevent deterioration to overt heart failure and to prevent myocardial infarction in patients with LVEF 35% or less. In the early infarct period, ACE inhibitors started three to 16 days postinfarction in patients with LVEF 40% or less, or transient heart failure have been shown to decrease mortality, prevent progression to overt heart failure and to reduce the risk of recurrent myocardial infarction.

A recently completed trial of ramipril, the Heart Outcomes Prevention Evaluation (HOPE) trial enrolled 9,297 high risk patients (>55 years with evidence of vascular disease or diabetes plus one additional risk factor) without known low EF or heart failure to receive ramipril (2.5mg to 10 mg/day) or matching placebo. After a mean follow-up of 5 years, the primary outcome of cardiovascular mortality, myocardial infarction or stroke was significantly reduced in the ramipril group (14.0% vs 17.8% for placebo, relative risk, RR, 0.78, 95% confidence interval 0.70 to 0.86,  $p<0.0001$ ). There were clear and significant reductions separately in CV deaths (6.1% vs 8.1%, RR 0.74, 95% CI 0.64 to 0.87  $p<0.001$ ), myocardial infarction (9.9% vs 12.3%, RR 0.80, 95% CI 0.70 to 0.90,  $p<0.001$ ). Development of heart failure was significantly reduced (9.0% vs 11.5%, RR 0.77,  $p<0.001$ ). Total mortality (10.4% vs 12.2%, RR 0.84,  $p<0.005$ ), revascularization procedures (16.0% vs 18.3%, RR 0.85,  $p<0.002$ ), cardiac arrests (0.8% vs 1.3%, RR 0.62,  $p=0.02$ ) and diabetic complications (6.4% vs 7.6%, RR 0.84,  $p<0.03$ ) were also significantly reduced<sup>11,72</sup>. This trial showed conclusively the clinical benefits of the ACE inhibitor, ramipril, in reducing risk of cardiovascular events, including heart failure, in a broad range of high risk patients who are not known to have left ventricular systolic dysfunction or heart failure.

## **Evolving Novel Therapies for Heart Failure**

### **Recommendations:**

- **The role of evolving therapies, such as inhibition of cytokine, endothelin, vasopressin, vasopeptidase, and synchronized biventricular pacing will need to be evaluated through currently planned or ongoing clinical trials incorporating established therapies as those outlined in this updated guidelines (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 blocks both the angiotensin converting enzyme and other metalloproteases that can increase levels of bradykinin and atrial natriuretic peptides. Preliminary data in the IMPRESS trial suggested a potential benefit in combined endpoints of deaths, hospitalization and exercise capacity when compared to ACE inhibitors<sup>73</sup>. This is being evaluated in a large mortality

outcome trial (OVERTURE) Similarly, cytokine inhibitors such as the soluble tumour necrosis factor receptor, etanercept, has been shown to improve quality of life, ventricular function and exercise capacity in patients with heart failure and depressed ejection fraction (RENAISSANCE trial)<sup>74</sup>. Furthermore, agents which can block the endothelin (ENABLE) and vasopressin-1 and/or 2 receptors (VITAL, AQUAVIT) are now also undergoing active evaluation.

Other non-pharmacological 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 (CANPAP)<sup>75</sup>. 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..

## **Rising to Challenge of the Heart Failure Epidemic**

### **Recommendations:**

- **There needs to be a coordinated effort amongst patients, physicians, allied health care workers, health care providing institutions, funding agencies, and clinical and basic researchers to work together towards 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 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 available, as evidenced by this guideline update document.

There needs to be a coordinated effort amongst patients, health care providers and funding and government agencies to work together towards 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, voluntary agency and industry partners. Finally, the dissemination and implementation of the therapies back to the community will require coordinated efforts of all the physicians, allied health care workers, the nurse-practitioner 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 nation wide basis that we can stem the tide of heart failure<sup>76</sup>. There should also be a public awareness program to improve its early recognition and prevention.

We plan to update the guidelines on a yearly basis under the sponsorship of CCS to maintain its cutting edge applicability, and improve on its impact in the community. Each

community should also take into account their particular facilities and demographics, and implement the guidelines in a most efficient and cost-effective manner to maximize its benefit on both the patient and the health care system.

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