The 2002/3 Canadian Cardiovascular Society Consensus Guideline Update for the Diagnosis and Management of Heart Failure

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Introduction

The Canadian medical community in general, and the Canadian Cardiovascular Society (CCS) in particular, have played a major role in promoting evidence based clinical practice in Canada. The Heart Failure Guideline Consensus Panel of the CCS published one of the first national guidelines on the clinical evidence for the diagnosis and treatment of heart failure in 1994 and published a comprehensive update in the Canadian Journal of Cardiology in December of 2001.

However, since then, additional provocative but well conducted clinical trial evidence has emerged in the diagnosis and therapy for heart failure. For example, while the evidence is strong in its own right, devices such as automatic implantable defibrillators (AICDs) and point of care brain natriuretic peptide measurements have been approved for clinical use in Canada, yet their specific role in clinical practice has not been clearly defined.

In order to facilitate the integration of the latest research evidence into clinical practice guidelines in a timely manner, while taking into account of the specific attributes of the Canadian health care system, the CCS Council has granted permission for the consensus panel to conduct a regular but timely update of specific topics in heart failure. This is not meant to replace the previous versions of CCS guidelines, but only to provide consensus evaluations for topics of new and immediate interest within the medical community. While the scope of the update is limited, the same due diligence with respect to the inclusion of individuals with expertise in cardiac transplantation, arrhythmias, pharmaceutical sciences, clinical trials, guideline dissemination and professional education were carefully observed. The group has again conducted a systematic Medline search, obtained ongoing Cochrane collaborative reviews and copies of the currently available U.S. and European heart failure guidelines. The evidence was then evaluated according to the criteria below, and the consensus statements were proposed, debated, revised and voted on using conference calls and face to face meetings. The document was peer reviewed through the entire CCS membership using an established successful electronic dissemination system. Suggestions were then evaluated by the panel and incorporated into the final document. Emphasis of this update has remained on patients with chronic symptomatic heart failure.

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Levels of Evidence

These levels of evidence are those developed and endorsed by the Canadian Medical Association, and are briefly outlined here.

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

Emphasis of the Importance of Angiotensin Converting Enzyme Inhibitors and Beta Blockers in Heart Failure

The major and dramatic change in the treatment of heart failure in the last half decade has been the overwhelming clinical evidence of the benefit of angiotensin converting enzyme (ACE) inhibitors in combination with carefully titrated doses of beta blockers in the treatment of all patients with chronic systolic heart failure. The previous update of the guideline in 2001 carefully documented the major impact of this combination in decreasing mortality and improving quality of life. The publication of new trials in the last year has highlighted the continued important role for ACE inhibitors. The impact of beta-blockers extends across the entire symptomatic spectrum of systolic heart failure, and most major clinical trials involving beta blockers have been stopped early because of overwhelming benefit. The careful but deliberate addition of beta blockade to ACE inhibitors in stable patients with systolic heart failure, often in the context of a heart failure/function clinic, has transformed the natural history of the disease.

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 at least 6 weeks. Therapy should be continued indefinitely in those with either left ventricular ejection fraction (EF)< 40%, or who have shown clinical evidence of, even if only transient, congestive heart failure. (Grade A, Level 1)**
- **ACE inhibitors should be prescribed as soon as safely possible for all asymptomatic patients with moderate to severe left ventricular dysfunction (e.g. EF <35%), unless contraindicated or not tolerated. (Grade A, Level 1)**
- **ACE inhibitors should be prescribed for all patients with symptomatic congestive heart failure and EF <40%, 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 where 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)**

Practical Tips on ACE Inhibitors:

- **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 in outcome trials of heart failure and in LV dysfunction. It is likely more important to use ACE inhibitors in higher doses than are often used in clinical practice.**
- **Specialist physicians treating HF or LV dysfunction generally prescribe ACE inhibitors to patients with serum creatinine <220 umol/L and potassium <5.5 mmol/L without postural hypotension or a history of angioedema due to ACE inhibitors.**
- **Introduction of ACE inhibitors in graduated doses when the patient is either normovolemic or slightly volume overloaded will avoid the unnecessary hypotension or renal dysfunction seen in hypovolemic patients.**

Recommendations:

β-Adrenergic Receptor Blockers

- **Beta-adrenergic receptor blockers are *strongly* recommended in all patients with NYHA class II - III heart failure, and left ventricular ejection fraction ≤ 40% to reduce mortality, hospitalizations, improve cardiac function and quality of life, unless contraindicated (Grade A, Level 1).**
- **Beta-blockers are 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 also recommended for patients with LV systolic dysfunction who are asymptomatic in NYHA I with LVEF<40%, particularly post myocardial infarction (Grade A).**

Angiotensin Receptor Blockers in Heart Failure and Myocardial Infarction

Angiotensin Receptor Blockers in Heart Failure

Recommendations:

- **Current evidence has shown angiotensin receptor blockers (ARBs) to be neither superior nor equivalent to ACE inhibitors in the treatment of heart failure due to LV systolic dysfunction. As such, ACE inhibitors remain the first therapy of choice. (Grade A, Level 1)**
- **ARBs may be considered, as alternatives to ACE inhibitors in cases where ACE inhibitors clearly cannot be tolerated. (Grade B, Level 2)**
- **ARBs may be considered as adjunctive therapy to ACE inhibitors when beta-blockers are either contraindicated, or not tolerated after careful attempts at initiation. (Grade A, Level 1)**

Practical Tips:

- **Contraindications and side-effects to ARB therapy are similar to those for ACE inhibitors though cough not due to pulmonary congestion is less frequent. Studies evaluating ACE/ARB combination therapy in LV dysfunction generally include patients with serum creatinine <220 umol/L, and potassium <5.0 mmol/L and systolic BP >90 mmHg.**
- **The risk of angioedema with ARBs is not known, but case reports have been published. Clinical judgment should be used when considering ARBs in patients who have a history of angioedema related to ACE inhibitors.**
- **Current evidence does not support routine concurrent use of triple therapy with beta-blockers, ACE inhibitors and ARBs for patients with systolic heart failure. However, patients with advanced symptoms who are on maximal therapy and who have adequate renal function and blood pressure may be referred for consideration of combination therapy with ACE inhibitors and ARBs. This should be initiated by a clinician experienced in the management of heart failure.**

Evidence and Rationale

Despite the theoretical superiority of angiotensin receptor blocker (ARB) over an ACE inhibitor in counteracting the deleterious effects of the renin-angiotensin-aldosterone system, the clinical efficacy of ARBs in reducing mortality and morbidity in patients with heart failure has not been proven to be superior. The unexpected mortality benefit of losartan over captopril observed in the ELITE (Evaluation of Losartan in the Elderly) trial[1] had been refuted by the much larger ELITE II trial[2] which showed no difference in all-cause mortality between heart failure patients randomized to losartan and those randomized to captopril. Although ELITE II and other trials predating it had not shown either superiority or equivalency of ARBs as compared with ACE inhibitors in improving clinical outcomes, data from the more recent Val-HeFT (Valsartan Heart

Failure Trial) study[3] suggested there might be a role for the combination ARB/ACE inhibitor therapy for the treatment of heart failure.

In the Val-HeFT trial, 5010 patients with ejection fraction <40% and NYHA Class II to IV heart failure were randomized to receive either valsartan, up to 160mg BID, or placebo. Background ACE inhibitors and beta-blockers were given in 93% and 35% of the cohort respectively. The mean dose of valsartan achieved was 254mg. After an average follow-up duration of 23 months, no difference was observed in the primary endpoint of all-cause mortality between the two groups (19.7% versus 19.4%, HR 1.02, P=0.80). There was a significant reduction favoring the valsartan group as compared with placebo in the primary combined endpoint of mortality and morbidity, the latter of which was defined as cardiac arrest with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs without hospitalization (28.8% versus 32.1%, HR 0.87, P=0.009). The benefit of valsartan was largely attributed to a 24% risk reduction in hospitalizations for worsening heart failure (P<0.001). No difference was observed in the primary endpoint of all-cause mortality between the two groups (19.7% versus 19.4%, HR 1.02, P=0.80).

Subgroup analyses suggested that the response to valsartan might be influenced by the number of neurohormonal inhibitors given as background therapy. In the subgroup of 366 patients who were not treated with ACE inhibitors at baseline (with or without concomitant beta-blockers), there was a 33% risk reduction in mortality (P=0.02) and a 44% risk reduction in the combined endpoint of mortality and morbidity in favor of the valsartan group (P<0.001)[4]. On the contrary, in the subgroup of 1610 patients who were treated with both ACE inhibitors and beta-blockers at baseline, valsartan had an adverse effect on mortality (P=0.009) and was associated with a trend toward an increase in the combined endpoint of mortality and morbidity (P=0.10). At present, it remains unclear whether the adverse effects of valsartan observed in this subgroup are real or due to a play of chance.

However, the ongoing VALIANT study in post myocardial infarction patients with low EF or heart failure has enrolled over 10,000 patients who are on beta blockers. One third of these patients have been randomized to combination therapy, including captopril 50 mg tid and valsartan 80 bid. The Data and Safety Monitoring Committee has not stopped or altered this trial prematurely, and the results are expected later in 2003. The ongoing CHARM (Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity) study[5] comparing candesartan with placebo in patients with a broad spectrum of heart failure also included a substantial number of subjects on both ACE inhibitors and beta-blockers. These two trials should help to clarify any potential interaction between ARBs and other neurohormonal inhibitors, and are expected to be reported in 2003.

A meta-analysis of 17 trials involving 12,469 patients in which five ARBs were studied (losartan, candesartan, valsartan, irbesartan, and eprosartan) had concluded that ARBs were not superior to ACE inhibitors in reducing adverse clinical outcomes in patients with heart failure and LV systolic dysfunction[6]. Overall, there was no difference between ARBs and controls in the pooled rates of death (OR 0.96, 95% CI 0.75 to 1.23) or hospitalization for heart failure (OR 0.86, 95% CI 0.69 to 1.06). Stratified analysis, however, showed a non-significant trend in benefit toward ARBs over placebo in reducing mortality (OR 0.68, 95% CI: 0.38 to 1.22) and

hospitalization (OR 0.67, 95% CI: 0.29 to 1.51) when ARBs were given in the absence of ACE inhibitor therapy. ARBs, when compared directly with ACEIs, were not superior in reducing either mortality (OR 1.09, 95% CI: 0.92 to 1.29) or hospitalization (OR 0.95, 95% CI: 0.80 to 1.13). In contrast, the combination therapy of ARBs and ACE inhibitors was superior to ACE inhibitors alone in reducing hospitalization (OR 0.74, 95% CI: 0.64 to 0.86) but not mortality (OR 1.04, 95% CI: 0.91 to 1.20). It should be noted that the results of this meta-analysis were largely driven by the results of ELITE II and Val-HeFT. The stratified analyses on hospitalization outcomes were also based on only a small number of trials, thus limiting the power of the meta-analysis to detect smaller but potential clinically meaningful benefits of ARBs.

The preponderance of evidence supports ACE inhibitors as the therapy of choice over ARBs in patients with heart failure and LV systolic dysfunction. Additionally, highest priority should be given to the initiation of ACE inhibitors and beta-blockers in all systolic heart failure patients. Caution is also warranted when considering combination of ARBs and ACE inhibitors in patients already receiving beta-blockers. In patients with mild to moderate heart failure who are on ***either*** ACE inhibitors or beta-blockers but cannot tolerate both, the addition of ARBs as adjunctive therapy should be considered.

At present, there are no published morbidity and mortality data from large-scaled clinical trials on the use of ARBs in patients with heart failure and preserved LV systolic function (ejection fraction >40-45%), also referred to by some as diastolic heart failure. Clarification of the role of ARBs in diastolic heart failure must await the results from two ongoing randomized placebo-controlled studies— CHARM[5] (Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity) with candesartan, that included a study arm of patients with preserved systolic function, and I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) with irbesartan. In the absence of trial data, no evidence based recommendations can be given to guide the use of ARBs in patients with diastolic heart failure at this time. Treatment of the underlying cause such as hypertension, diabetes or ischemia remains the primary focus along with symptomatic control.

Angiotensin Receptor Blockers Post Acute Myocardial Infarction

Recommendations:

- **Current evidence does not support angiotensin receptor blocker therapy as superior, or equivalent to ACE inhibitor therapy in patients with heart failure or EF<40% within 10 days following acute myocardial infarction. As such, they are not recommended as routine therapy for patients following acute myocardial infarction (Grade A, Level 1)**
- **ACE inhibitors remain the drug of choice early after a myocardial infarction**

Practical Tips:

- **Consideration may be given to the use of an angiotensin receptor blocker in those patients post myocardial infarction with high risk features as outlined**

above, who are truly intolerant of ACE inhibitors (e.g. due to severe cough), although there are no data proving their efficacy in this group.

Evidence and Rationale

The OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) is the only published randomized trial of an ARB in patients with clinical heart failure or left ventricular systolic dysfunction following acute myocardial infarction[7]. In this multicentre, randomized, controlled trial, 5477 high risk patients (with confirmed myocardial infarction and either symptoms of heart failure in the acute phase, ejection fraction <35%, reinfarction, or Q-wave anterior infarction) 50 years of age or older were randomized within 10 days of their qualifying event to receive captopril 50mg tid or losartan 50mg od. The study was designed to determine if losartan was either superior (by 20% or more) or non-inferior (by 5% or less) to captopril on a primary endpoint of all cause mortality.

Over an average of 2.7 years of follow-up, the relative risk for all-cause mortality was 1.13 (95% confidence interval 0.99-1.28) for losartan as compared with captopril. This also did not meet the investigators' criteria for declaration of non-inferiority of losartan. Secondary outcome measures of sudden cardiac death or resuscitated cardiac arrest (relative risk 1.19, 95% confidence interval 0.99-1.43), total cardiovascular deaths (relative risk 1.17, 95% confidence interval 1.01-1.34), and myocardial reinfarction (relative risk 1.03, 95% confidence interval of 0.89-1.18) also showed no benefit of losartan over captopril.

Another larger ongoing trial, the Valsartan in Acute Myocardial Infarction Trial (VALIANT), randomized patients with clinical heart failure or resting LV systolic dysfunction (EF <40%) will be randomized to valsartan 160 mg po bid, captopril 50 mg po tid or valsartan 80 mg po bid plus captopril 50 mg po tid. This trial includes over 14,500 patients after recent myocardial infarction[8] and will be reported in mid 2003.

It is currently unknown whether ARBs are superior to placebo in these patients. Similarly, there are no data of the effects of ARBs in patients following myocardial infarction who do not have evidence of significant LV systolic dysfunction or clinical heart failure (even if transient).

The Role of ICD in Heart Failure and LV Dysfunction

Recommendations

- **Patients with documented coronary artery disease and prior myocardial infarction, who are already receiving evidence-based optimal pharmacological therapy for heart failure, have an EF<30%, and are clinically stable and not in end stage heart failure, and have otherwise a reasonable chance for long term survival, should be considered for evaluation and risk stratification for an implantable cardioverter defibrillator (ICD). (Grade B Level 2). However, the**

cost-effectiveness of this prophylactic therapy is currently unknown, and would need further evaluation to clearly establish its role in practice.

- **Patients with non-sustained ventricular tachycardia (VT) in the presence of coronary artery disease, prior myocardial infarction, and EF of 30-40%, should be considered for electrophysiological study. If VT is inducible at electrophysiological study, they should be considered for an ICD (Grade B Level 2).**
- **In patients with non-ischemic dilated cardiomyopathy, prophylactic implantation of an ICD is not recommended at this time, whether they have nonsustained ventricular tachycardia or not. If symptomatic nonsustained ventricular tachycardia is present, amiodarone may be considered. (Grade B, level 2). They should receive optimal pharmacological therapy including beta blockers, ACE inhibitors, and possibly spironolactone as per guideline recommendations.**

Practical Tips

The more prolonged QRS duration, and the presence of atrial fibrillation increased the the likelihood of benefit from prophylactic ICD therapy.

Unexpected syncope in any patient with heart failure should be considered as possibly due to arrhythmia and mandates careful clinical evaluation.

The precise extent of mortality benefit from prophylactic ICD's in heart failure and their cost effectiveness for this indication are not known. Additional randomized clinical trials of ICD's as primary prophylaxis are ongoing and may help to clarify these uncertainties. Given the considerable resources required to evaluate, implant, and follow these patients, caregivers and health policy planners need to carefully assess the incompletely understood benefits of ICD in certain subgroups, when considering the amount of resources to be devoted towards prophylactic ICD's.

Evidence and Rationale

The presence of left ventricular systolic dysfunction is associated with a high risk of sudden cardiac death, presumably from ventricular tachycardia or fibrillation. Although optimal pharmacological therapy with beta blockers, ACE inhibitors, statins as appropriate, and spironolactone if required, reduces all cause and possibly sudden death mortality, death rates in such patients remain high.

Based on the premise that implanted cardioverter defibrillators can prevent sudden arrhythmic death if it is destined to occur, a number of trials have examined the potential benefit from the prophylactic implantation of cardioverter defibrillators in such patients.

In brief, the MADIT I and MUSTT studies suggested that ICD's may be indicated in patients with LVEF < 40%, nonsustained ventricular tachycardia on holter monitoring, and inducible VT at electrophysiological study[9,10]. The Canadian Consensus Conference Guidelines

on the treatment of ventricular arrhythmias have suggested EP studies and consideration of ICD implantation in such patients.

A recent large study, the MADIT II study, randomized 1232 patients with a history of prior myocardial infarction (more than 4 weeks pre-randomization), coronary artery disease, and an ejection fraction of < 30%, to either the ICD or conventional medical therapy[11]. Nonsustained VT or electrophysiologic studies were not required for study inclusion. The majority of patients in this study had NYHA class I or II functional status, and the mean age was 65 years. In the majority of patients, more than 6 months had elapsed since their most recent MI, and a majority had previously received bypass surgery or coronary angioplasty. Seventy percent of patients received ACE inhibitors and 70% received beta blockers at baseline. There was an aggregate 31% reduction in the risk of death from any cause over an average follow-up of 20 months; the absolute reduction in all cause mortality was 1%, 6%, and 9% at 1, 2, and 3 years respectively, and the number needed to treat to prevent one death over 3 years was approximately 11. In a subgroup analysis, patients with a QRS duration of more than 120 msec at baseline received a large benefit from ICD implantation, with the mortality reduction from 53% to 21% at 3 years in this subgroup. The publication of this study[11] led to a change in guidelines for the implantation of prophylactic ICD's, with a recommendation for ICD implantation in patients meeting "MADIT II inclusion criteria"[12].

In view of the high benefit and/or lower cost of beta blockers, ACE inhibitors, statins, spironolactone, and revascularization where indicated, these therapies should be considered and applied where indicated to all patients with coronary artery disease and moderate to severe left ventricular dysfunction. If, following consideration of all these measures, the quantitative LV ejection fraction is less than 30%, patients should be considered for prophylactic ICD implantation, even in the absence of arrhythmia related symptoms or heart failure symptoms. A detailed cost efficacy analysis of the MADIT II study has not yet been published, and the cost effectiveness of ICD implantation in these patients is not yet known.

A large randomized trial of medical therapy vs. prophylactic ICD in patients with documented symptomatic heart failure rather than just post-infarction is still ongoing (SCD-HEFT), and the follow-up period has just been extended. Therefore, in the absence of a confirmatory trial for prophylactic ICD in the classic heart failure population, one should carefully consider the risk vs. benefit in each individual patient, taking into account quality of life and resource considerations in addition to survival benefits.

In distinction to the above considerations, patients with dilated, non-coronary cardiomyopathy have ***not*** been shown to benefit from prophylactic ICD implantation. The CAT trial randomized patients to ICD implantation versus standard medical therapy, in the presence of a dilated cardiomyopathy. No benefit could be shown for defibrillator implantation[13]. In the AMIOVIRT study, patients with dilated cardiomyopathy and ejection fraction less than 40% were randomized to oral amiodarone versus the implanted defibrillator. The trial was stopped early for futility, and the mortality curves in the amiodarone versus the ICD groups were nearly superimposable. There are ongoing trials further assessing the benefit of prophylactic ICD in patients with dilated cardiomyopathy. For the moment, there is no evidence that prophylactic ICD implantation prolongs life in such patients. No large and blinded individual trial has shown reduction of sudden death from amiodarone, but meta analysis suggests that amiodarone may possibly be of benefit in reducing sudden and all cause mortality in patients with cardiomyopathy at risk for sudden death[14]. Neither holter monitoring nor electrophysiologic studies have been

clearly shown to be of prognostic benefit or to help assess the efficacy of therapy in patients with dilated cardiomyopathy.

Resynchronization Therapy in Heart Failure

Recommendations:

- **Patients with heart failure who are still severely symptomatic despite optimal medical therapy but have reasonable rehabilitation potential, and also have mean QRS duration > 130 mseconds and LV ejection fraction <35%, may be considered for evaluation of resynchronization therapy for symptomatic improvement. (Grade B, Level 2)**

Practical Tip:

- **Patients with marked LV chamber enlargement (LV end-diastolic diameter > 55 mm), mitral regurgitation, very prolonged QRS duration (<150 msec) and patients with severe symptoms or high diuretic requirements may be particularly good candidates**

Evidence and Rationale

Ventricular conduction abnormality is frequent in heart failure. The electrical conduction delay leads to cardiac contractile dysynchrony, which may further compromise ventricular function and hasten the progression of heart failure. To restore contractile synchrony, one may install pacemaker leads in both the right and left ventricle (the latter through coronary sinus and great cardiac vein), so called cardiac resynchronization therapy (CRT). Several multi-center clinical trials on cardiac resynchronization have been completed and published in the last few years. These trials have assessed the effect of cardiac resynchronization on functional capacity, quality of life and hospitalizations for heart failure but not on survival.

One such trial is the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial[15]. In this study, 67 patients with severe heart failure NYHA class III, ejection fraction < 35% and a duration of the QRS interval of > 150 msec received transvenous atriobiventricular pacemakers. This was a single-blind, randomized, controlled crossover study comparing the responses of the patients during two periods: a three-month period of inactive pacing (ventricular inhibited pacing at a basic rate of 40 bpm) and a three-month period of active (atriobiventricular) pacing. The primary end point was the distance walked in six minutes; the secondary end points were the quality of life, peak VO2, hospitalizations related to heart failure, the patients' treatment preference and the mortality rate. During active pacing, there were significant improvements in mean distance walked in six minutes, the quality-of-life score and peak VO2. Hospitalizations were decreased by two thirds. Active pacing was preferred by 85 percent of the patients. A 12

month follow-up of these same patients showed that the improvement in the 6- minute walk test, peak VO2, quality of life and NYHA were maintained over this period[16]. No conclusions could be drawn with respect to survival.

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial was done in a randomized double-blinded design[17] to evaluate the effect of cardiac resynchronization on the NYHA functional class, quality of life, and the distance walked in six minutes. Four hundred fifty-three patients with ischemic or non-ischemic cardiomyopathy, moderate-to-severe symptoms of heart failure, an ejection fraction of <35% and a QRS interval of >130 msec were randomly assigned to a cardiac-resynchronization group or to a control group for six months, while conventional therapy for heart failure was maintained. When compared to the control group, patients in the cardiac resynchronization group experienced a significant improvement in the distance walked in six minutes, functional class, quality of life, time on the treadmill during exercise testing and ejection fraction. As well, fewer patients in the resynchronization group required hospitalization or intravenous medications for the treatment of heart failure. In 8 percent of patients, implantation of the device was unsuccessful and overall complications were low. These included refractory hypotension, bradycardia, asystole and perforation of the coronary sinus requiring pericardiocentesis.

One of the main limitations of this study was the short-term follow-up of only 6 months. The ability of these devices to maintain long-term clinical benefits remains undetermined as is their effect on survival. When considering survival, the potential benefits of cardiac defibrillators must be addressed. The Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial[18] is an on-going randomized, open-label, 3-arm study of patients in NYHA class III or IV with an ejection fraction < 35% and a QRS duration of >120 msecs. The study objectives are to determine whether optimal medical therapy used with ventricular resynchronization therapy alone or ventricular resynchronization therapy combined with a cardioverter-defibrillator is better than optimal medical therapy alone in reducing combined all-cause mortality and hospitalizations; reducing cardiac morbidity; improving functional capacity, cardiac performance, and quality of life; and increasing total survival. Compared to previous cardiac resynchronization trials, this trial will permit patients with a less wide QRS (≥ 120 msecs) to be randomized, it will be much larger recruiting over 2000 patients and have a much longer follow-up of 2 years. This trial has just been completed, and the preliminary results are positive. However, in the absence of details in a peer review publication, its true impact will have to await detailed analysis in light of currently available data.

Brain Natriuretic Peptide in the Diagnosis of Heart Failure

Recommendations:

- **Patients who present with dyspnea with unclear but suspected cardiac etiologies may be considered to have venous blood taken for the measurement of brain natriuretic peptide (BNP) level to assist with the**

diagnostic decision and therefore appropriate management of the dyspnea. (Grade A Level 1 Evidence)

Practical Tip:

- **BNP level is *not* a stand-alone test for heart failure and must be used in conjunction with careful clinical evaluation, and in patients with an intermediate pre-test likelihood of heart failure**
- **Falsely positive results may be seen in patients with renal disease, malignancy, extreme obesity or with chronic administration of beta-blockers**

Evidence and Rationale

The clinical utility of BNP in the management of heart failure

The natriuretic peptide family consists of a group of structurally similar but genetically distinct peptides that exert diverse cardiovascular, renal, and neurohormonal effects. Atrial natriuretic peptide (ANP) and brain or B type natriuretic peptide (BNP) are derived from the cardiomyocytes whereas C type natriuretic peptide (CNP) is derived from the endothelial cells. BNP, derived mainly from the mammalian ventricle, is the natriuretic peptide at the most advanced stage of development for clinical application in patients with heart failure[19]. The following is list of clinical applications of BNP in heart failure that are either established or are currently under evaluation:

1. Establishing the diagnosis of heart failure[20-22]
2. Short and long term prognostic stratification[23,24]
3. Monitoring for the decompensation of heart failure and response to therapy[24-26]
4. Screening for left ventricular dysfunction in general population[27,28]
5. Therapy for acute heart failure (nesiritide)[29,30]

Applications 2 to 4 are still under evaluation. Nesiritide (recombinant human BNP) is not available in Canada. This update will be limited the discussion to the most established clinical application i.e. the diagnostic utility of BNP in patients with heart failure.

Diagnostic utility of BNP in heart failure and left ventricular dysfunction

Currently the most established clinical application of BNP is for the detection of cardiac etiologies for dyspnea in patients who present to an urgent care facility setting with dyspnea and in whom the diagnosis is not readily apparent after clinical evaluation. A frequent problem in these patients is to distinguish between dyspnea from primary pulmonary versus cardiac disorders. In a prospective study of 52 elderly patients presenting with acute dyspnea, admission plasma BNP level was elevated in patients with a final diagnosis of heart failure but not in those with primary lung disease, and BNP level more accurately reflected the heart failure diagnosis

than left ventricular (LV) ejection fraction (LVEF)[20]. The availability of a fluorescence immunoassay has allowed for the point-of-care quantitative determination of BNP in whole blood and plasma. Using this point-of-care assay, blood BNP levels were measured from 250 patients who presented to urgent-care departments with dyspnea[21]. The gold standard for the diagnosis of heart failure was based on retrospective review of all clinical data by consensus opinion of two cardiologists blinded to the BNP results. At a blood level of 80 pg/ml, BNP was an accurate predictor of the presence of heart failure (95%), and values below 80 pg/ml had negative predictive value of 98%. The same rapid assay of BNP has also recently been shown to help differentiate pulmonary from cardiac etiologies in patients who presented to the emergency department with dyspnea.[16] The largest study of the diagnostic utility of BNP to date is the Breathing Not Properly Multinational Study (BNP study)[22]. In this multicenter study, 1586 patients who visited emergency department with acute dyspnea had BNP determined using the rapid assay. Clinical diagnosis of heart failure was adjudicated by two cardiologists blinded to the BNP results. BNP levels by themselves were more accurate than any historical, physical examination or laboratory findings in identifying heart failure as the cause of dyspnea. Using a cut-off of 100 pg/ml, the diagnostic accuracy was 83.4%. Using a cut-off of 50 pg/ml, the negative predictive value was 96%. Area under the receiver-operating-characteristic (ROC) curve was 0.91 (95% confidence interval, 0.90-0.93).

Another potential use of BNP is for the diagnosis of patients with heart failure and preserved systolic function. By definition, these patients have preserved systolic function (LVEF>40) or normal LVEF, and therefore heart failure cannot be easily diagnosed by simple assessment of LV systolic function. Several studies have now demonstrated elevated BNP levels in patients with heart failure or documented diastolic dysfunction based on Doppler filling characteristics. Area under the ROC curve to detect diastolic dysfunction in patients with heat failure and preserved systolic function was 0.958 using the traditional radioimmunoassay, and 0.92 in patients with or without symptoms using the rapid assay[31]. At this point, BNP level by itself cannot differentiate between systolic and diastolic dysfunction.

It should be noted, however, that BNP level can increase in conditions other than heart failure. Indeed, plasma BNP levels increase with aging, levels are higher in female, and increase in renal disease, advanced pulmonary disease, with β-blockade therapy and in other cardiac conditions. Notwithstanding these false positives, in a patient who presents to an urgent care setting and who has a low BNP level i.e. less than 50 to 80 pg/ml, the probability for heart failure as an etiology for the dyspnea is likely to be low. N-terminus proBNP assay is also available. The value for the N-terminal moiety is at least 100 fold higher than the value of C-terminal BNP. The optimal cut-off value for this specific assay remains to be determined.

Role of Multidisciplinary Heart Failure/Function Clinics

Recommendations:

- **Specialized hospital based clinics, staffed by physicians, nurses and other health care professionals with expertise in heart failure, should be considered for assessment and management of higher risk individuals with heart failure (Grade B, Level 2)**
- **Multidisciplinary care should include, but not be limited to patient education, and close clinical follow-up through clinic visits and/or telemonitoring or telemanagement and home visits with specialist health care professionals. (Grade B, Level 2)**
- **Individuals with heart failure who have been recently hospitalized with heart failure may receive maximum benefit from a multidisciplinary heart failure/function clinic setting (Grade B, Level 2)**
- **Heart failure/function clinics may also provide opportunities for exploration of a full range of treatment options for heart failure, including pharmacological, interventional, electrophysiological and surgical therapeutic options. (Grade C, Level 5)**

Practical Tips:

- **Telephone calls by experienced nurses to check on the progress of patients with heart failure is often the key intervention that may prevent recurrent hospitalization**
- **Teaching patients to weigh themselves daily and adjust their own diuretics is a key strategy to maintain clinical stability**
- **In Canada, there are recommendations on how to set up a multidisciplinary heart failure/function clinic available at www.cchfcn.org, website of the Canadian Congestive Heart Failure Clinics Network**

Evidence and Rationale

Over the past 7 years, evidence has been accumulating in favour of the role of heart failure/function clinics[32-35]. Several small, randomized controlled trials of multidisciplinary care have demonstrated benefit. Rich, et al. in 1995 demonstrated the ability to reduce hospitalizations through multidisciplinary care initiated in hopsital[36]. Stewart, et al[37] and Blue, et al[38], both of whom demonstrated reduction in unplanned readmission through a multidisciplinary home-based intervention, supported this work. Cline, et al.[39] demonstrated similar benefit through the use of multidisciplinary outpatient heart failure clinics following discharge from hospital. Most recently, McDonald et al.[40] have released the results of a randomized control trial of multidisciplinary care in which both control and treatment groups received in-patient specialist care, target doses of ACE Inhibitor therapy and pre-determined discharge criteria. The treatment group received a multidisciplinary in-patient intervention followed by telemanagement and clinic follow-up. The treatment gropu had significant improvements ($p<0.01$) in patient knowledge of heart failure, patient knowledge of diet, and

unplanned readmission within 3 months found for the treatment group.

Although the results of the reported trials are supportive of heart failure/function clinics these studies have a number of limitations. Some of the limitations common to these trials were a relatively short duration of follow-up ($\leq$ 6 months), lack of clarity related to the specifics of the intervention, and they were performed in the pre-beta blocker era. Although the latter may be a potential limitation[38], the presence of the nurse clinician in the clinic has the potential to facilitate up titration of beta blocker therapy. Another important limitation to these studies has been selective recruitment of patients thus limiting the generalizability of these studies to date[36,38,39].

Among the reported studies there have been some similarities in the type of intervention used, these included patient education, telemanagement and home and/or clinic visits with health care professionals specialized in heart failure care. Successful programs have uniformly used nurse clinicians with many programs including dietitians, pharmacists and social workers.

Given the high prevalence of heart failure and that at present there is only limited access to this specialized type of heart failure program some studies have examined which individuals may benefit the most from admission to a multidisciplinary clinic. Riegel et al.[41] conducted a non-randomized study using matched samples of heart failure in-patients. They were able to demonstrate maximal reduction in the cost of care for individuals with pre-admission NYHA Class II symptoms through the use of a home-based multidisciplinary intervention. Rich et al.[1] found similar benefit for individuals who were at high risk for readmission. This study suggests potential benefit to patients with complex heart failure.

Heart failure/function clinics of this nature operating in Canada offer specialized, multidisciplinary care directed at providing evidence-based medical therapy, individualized pharmacological therapy, augmented with self-management support, and access/referral to the full range of options of therapy for heart failure.

Future issues for consideration include:

- determination of the heart failure population, which may derive maximal benefit from multidisciplinary heart failure/function clinics,
- determination of the comparative health and financial benefits of different types of delivery of multidisciplinary care, including home based, clinic based, and/or telemanagement directed.
- Implications and potential utility of the multidisciplinary setting in attaining optimum pharmacologic therapy targets, and
- Implications and potential utility of BNP testing and other point of care assays in the heart function/failure clinic setting in the selection of patients, titration of medical therapy and assessment of disease progression.

Update in Surgical Therapy for Heart Failure

The most significant trial in surgical therapy for heart failure was published in November 2001[42]. The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial was a prospective, randomized, multi centre study sponsored by the NIH to determine if left ventricular support with the HeartMate device was superior to optimal medical therapy in non-transplant eligible end stage heart failure patients. All objective screening data support the finding that this trial enrolled, by far, the sickest group of heart failure patients than any previous medical or surgical trial. Overall survival at two years was dismal, but LVAD therapy did provide a statistically significant survival benefit at one year (52% vs 25%, p=0.002) and at two years (23% vs 8%, p=0.09). All objective physical and emotional measures were significantly higher in the LVAD group, indicating that device therapy improved both quantity and quality of life. Based on the results of this landmark trial, the FDA has recently approved the HeartMate device as a "destination" therapy for non-transplant eligible patients.

Several caveats must be highlighted from this trial. Firstly, overall survival was still poor at two years, even in the device group. Secondly, the device group suffered from 2.35 times the number of adverse events as the medical group. These adverse events were primarily septic in nature or related to non-fatal device malfunctions. Furthermore, a careful subgroup analysis by Stevenson et al demonstrates that survival benefits accrue only to those patients who were in NYHA class IV on IV inotropes. No benefit was observed in patients who were hemodynamically stable on oral medication.

Despite the above shortcomings, the REMATCH trial provided valuable information. Even with a first generation device, an average recipient age of 68 and all associated device-related complications, patients in the LVAD group displayed improvement over their medical counterparts over the short term. Clearly with careful patient selection and future improvement in device technology, the overall survival in this high risk cohort of patients may be further improved.

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