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SPECIAL ARTICLE

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The 2002/3 Canadian Cardiovascular Society consensus guideline update for the diagnosis and management of heart failure

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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 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 cardioverter defibrillators (ICDs) 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.

To facilitate the integration of the latest research evidence into clinical practice guidelines in a timely manner, while taking into account 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 experts in cardiac transplantation, arrhythmias, pharmaceutical sciences, clinical trials, guideline dissemination and professional education was carefully observed. The group has again conducted a systematic Medline search, and obtained ongoing Cochrane collaborative reviews and copies of the available American and European heart failure guidelines. The evidence was then evaluated according to the criteria in Table 1, and the consensus statements were proposed,



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debated, revised and voted on during 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. The emphasis of this update has remained on patients with chronic symptomatic heart failure.

The preparation of this guideline update was supported only by the CCS without the influence or funding from any company.

Table 1 briefly outlines the levels of evidence developed and endorsed by the Canadian Medical Association.

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 past 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 guidelines 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 past year has highlighted the continued important role of 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 (Figure 1).

Recommendations on 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 the long term (**grade A, level 1**).
- ACE inhibitors should be prescribed as soon as safely possible for all asymptomatic patients with moderate to severe left ventricular (LV) dysfunction (for example, ejection fraction [EF] less than 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 less than 40%, New York Heart Association (NYHA) functional class II to IV, unless contraindicated or not tolerated (**grade A, level 1**).
- ACE inhibitors should be prescribed for patients at risk for heart failure, even in the absence of LV dysfunction. These may include patients with previous vascular events or diabetes with one other risk factor.
- The target ACE inhibitor dose should be either the dosage regimen used (for specific ACE inhibitors where data exist) in placebo controlled mortality trials or the maximum tolerated (or recommended) dose for those ACE inhibitors for which no mortality data exist (**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 and lisinopril have been evaluated in

outcome trials of heart failure and in LV dysfunction. It is probably more important to use ACE inhibitors in higher doses than those often used in clinical practice.

- Specialist physicians treating heart failure or LV dysfunction generally prescribe ACE inhibitors to patients with serum creatinine concentration below 220 $\mu\text{mol/L}$ and potassium less than 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 on beta-adrenergic receptor blockers

- Beta-adrenergic receptor blockers are strongly recommended in all patients with NYHA class II to III heart failure and LVEF 40% or less to reduce mortality and hospitalizations, and to 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 following the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial (**grade A, level 1**). Keep in mind that the class IV heart failure patient is a moving target and the patient must be stable before considering beta-blockers.
- Beta-blockers are also recommended for patients with LV systolic dysfunction who are asymptomatic in NYHA I with LVEF less than 40%, particularly postmyocardial infarction (**grade A, level 1**).

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 B, level 2**).

Practical tips on angiotensin receptor blockers

- Contraindications and side effects to ARB therapy are similar to those for ACE inhibitors, although cough not due to pulmonary congestion is less frequent. Studies evaluating ACE/ARB combination therapy in LV dysfunction generally include patients with serum creatinine concentrations below 220 $\mu\text{mol/L}$, potassium less than 5.0 mmol/L and systolic blood pressure more than 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 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 proved to be superior. The unexpected mortality benefit of losartan over captopril observed in the Evaluation of Losartan in the Elderly (ELITE) trial (1) has 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 that ARBs are either superior or equivalent to ACE inhibitors in improving clinical outcomes, data from the more recent Valsartan Heart Failure Trial (Val-HeFT) (3) suggested the combination ARB/ACE inhibitor therapy may have a role in the treatment of heart failure.

In the Val-HeFT trial, 5010 patients with EF less than 40% and NYHA class II to IV heart failure were randomized to receive either valsartan, up to 160 mg 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 254 mg. After an average follow-up duration of 23 months, no difference was observed in the primary end point of all-cause mortality between the two groups (19.7% versus 19.4%, hazard ratio 1.02, $P=0.80$). There was a significant reduction in the valsartan group relative to the placebo group in the primary combined end point 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%, hazard ratio 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 end point of all-cause mortality between the two groups (19.7% versus 19.4%, hazard ratio 1.02, $P=0.80$).

Post hoc subgroup analyses suggested that the response to valsartan may 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 end point of mortality and morbidity in favour 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 end point 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 Valsartan in Acute Myocardial Infarction Trial (VALIANT) in postmyocardial infarction patients with low EF or heart failure has enrolled over 10,000 patients who are taking beta-blockers. One-third of these patients have been randomized to combination therapy, including captopril 50 mg tid and valsartan 80 mg 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 Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM) study (5) comparing candesartan with placebo in patients with a broad spectrum of heart failure also included a substantial

number of subjects taking 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 control groups in the pooled rates of death (odds ratio [OR] 0.96, 95% confidence interval [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 nonsignificant 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 ACE inhibitors, 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, the highest priority should be given to the initiation of ACE inhibitors and beta-blockers in all patients with systolic heart failure. 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 taking 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 scale clinical trials on the use of ARBs in patients with heart failure and preserved LV systolic function (EF greater than 40% to 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) with candesartan, which included a study arm of patients with preserved systolic function, and Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) with irbesartan. In the absence of trial data, no evidence-based recommendations can be given at this time to guide the use of ARBs in patients with diastolic heart failure. Treatment of the underlying cause such as hypertension, diabetes or ischemia remains the primary focus along with symptomatic control.

ARBs after acute myocardial infarction

Recommendations

- Current evidence does not support ARB therapy as superior or equivalent to ACE inhibitor therapy in patients with heart failure or EF less than 40% within 10 days following acute myocardial infarction. As such, ARBs are not recommended as routine therapy for patients following acute myocardial infarction (**grade B, level 2**).
- ACE inhibitors remain the drug of choice early after a myocardial infarction.

Practical tips

- Consideration may be given to the use of an ARB in patients postmyocardial

infarction with high risk features as outlined above who are truly intolerant of ACE inhibitors (for example, due to severe cough), although there are no data proving the efficacy of ARBs in this group.

Evidence and rationale

The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) is the only published randomized trial of an ARB in patients with clinical heart failure or LV 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, EF less than 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 50 mg tid or losartan 50 mg od. The study was designed to determine whether losartan was either superior (by 20% or more) or noninferior (by 5% or less) to captopril on a primary end point 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% CI 0.99 to 1.28) for losartan as compared with captopril. This also did not meet the investigators' criteria for declaration of noninferiority of losartan. Secondary outcome measures of sudden cardiac death or resuscitated cardiac arrest (relative risk 1.19, 95% CI 0.99 to 1.43), total cardiovascular deaths (relative risk 1.17, 95% CI 1.01 to 1.34) and myocardial reinfarction (relative risk 1.03, 95% CI 0.89 to 1.18) also showed no benefit of losartan over captopril. However, in retrospect the dose of losartan used in the trial may have been inadequate.

In another larger ongoing trial, VALIANT, patients with clinical heart failure or resting LV systolic dysfunction (EF less than 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 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).

ROLE OF ICDs 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 less than 30%, and are clinically stable and not in end-stage heart failure, and have otherwise a reasonable chance for long term survival, should be evaluated for an ICD (**grade B, level 2**). However, the cost effectiveness of this prophylactic therapy is unknown and would need further evaluation to clearly establish its role in practice.
- Patients with nonsustained ventricular tachycardia (VT) in the presence of coronary artery disease, prior myocardial infarction and EF of 30% to 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 nonischemic dilated cardiomyopathy, prophylactic implantation of an ICD is not recommended at this time, whether they have nonsustained VT or not. If symptomatic nonsustained VT is present, amiodarone may be considered (**grade B, level 2**). They should receive optimal pharmacological

therapy including beta-blockers, ACE inhibitors and spironolactone according to guideline recommendations.

Practical tips

- More prolonged QRS duration and the presence of atrial fibrillation increase the likelihood of benefit from ICD therapy.
- Unexplained syncope in any patient with heart failure should be considered to be possibly due to arrhythmia and mandates careful clinical evaluation.
- The precise extent of mortality benefit from prophylactic ICDs in heart failure and their cost effectiveness for this indication are not known. Additional randomized clinical trials of ICDs as primary prophylaxis are ongoing and may help to clarify these uncertainties. Given the considerable resources required to evaluate, implant and follow up 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 toward prophylactic ICDs.

Evidence and rationale

The presence of LV systolic dysfunction is associated with a high risk of sudden cardiac death, presumably from VT or ventricular 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 ICDs 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 Multicenter Automatic Defibrillator Implantation Trial (MADIT) I and Multicenter Unsustained Tachycardia Trial (MUSTT) suggested that ICDs may be indicated in patients with LVEF less than 40%, nonsustained VT on Holter monitoring and inducible VT at electrophysiological study (9,10). The Canadian Consensus Conference Guidelines on the treatment of ventricular arrhythmias have suggested the use of electrophysiological 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 four weeks prerandomization), coronary artery disease and an EF less than 30% to either the ICD or conventional medical therapy (11). Nonsustained VT or electrophysiological 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 six months had elapsed since their most recent MI, and a majority had previously received bypass surgery or coronary angioplasty. Seventy per cent 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 one, two and three years, respectively, and the number needed to treat to prevent one death over three years was approximately 11. In a subgroup analysis, patients with a QRS duration of more than 120 ms at baseline received a large benefit from ICD implantation, with a reduction in mortality from 53% to 21% at three years in this subgroup. The publication of this study (11) led to a change in guidelines for the implantation of prophylactic ICDs, with a recommendation for ICD implantation in patients meeting "MADIT II inclusion criteria" (12).

In view of the high benefit and 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 LV dysfunction. If, following consideration of all these measures, the quantitative LVEF 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 versus prophylactic ICD in patients with documented symptomatic heart failure rather than just postinfarction is still ongoing (Sudden Cardiac Death Heart Failure Trial [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 versus benefit in each patient, taking into account quality of life and resource considerations in addition to survival benefits.

In distinction to the above considerations, patients with dilated noncoronary cardiomyopathy have *not* been shown to benefit from prophylactic ICD implantation. The Cardiomyopathy Trial (CAT) 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 Amiodarone vs Implantable Defibrillator in Patients with Nonischemic Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVIRT) study, patients with dilated cardiomyopathy and EF 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 electrophysiological 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 and correction of reversible causes but who have reasonable rehabilitation potential and a mean QRS duration above 130 ms and LVEF less than 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 greater than 55 mm), mitral regurgitation and very prolonged QRS duration (greater than 150 ms), 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 dyssynchrony, 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 ventricle and LV (the latter through the coronary sinus and great cardiac vein), so-called cardiac resynchronization therapy. Several multicentre clinical trials on

cardiac resynchronization have been completed and published in the past 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, EF less than 35% and a QRS interval duration longer than 150 ms received transvenous atrioventricular 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 beats/min) and a three-month period of active (atrioventricular) pacing. The primary end point was the distance walked in 6 min. The secondary end points were the quality of life, peak VO_2 , hospitalizations related to heart failure, the patient's treatment preference and the mortality rate. During active pacing, there were significant improvements in mean distance walked in 6 min, the quality-of-life score and peak VO_2 . Hospitalizations were decreased by two-thirds. Active pacing was preferred by 85% of the patients. A 12-month follow-up of these same patients showed that the improvement in the 6 min walk test, peak VO_2 , quality of life and NYHA were maintained over this period (16). There were fewer hospitalizations for heart failure in the biventricular pacing group than in the ventricular pacing group. 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 6 min. Four hundred fifty-three patients with ischemic or nonischemic cardiomyopathy, moderate to severe symptoms of heart failure, an EF less than 35% and a QRS interval longer than 130 ms 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 with the control group, patients in the cardiac resynchronization group experienced a significant improvement in the distance walked in 6 min, functional class, quality of life, time on the treadmill during exercise testing and EF. As well, fewer patients in the resynchronization group required hospitalization for worsening heart failure ($P=0.02$). Fewer patients also required intravenous vasodilators or positive inotropic agents for worsening heart failure ($P=0.06$). In 8% 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 six 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 ongoing randomized, open-label, three-arm study of patients in NYHA class III or IV with an EF less than 35% and a QRS duration longer than 120 ms. 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, hospitalizations and cardiac morbidity, improving functional capacity, cardiac performance and quality of life, and increasing total survival. Compared with previous cardiac resynchronization trials, this trial permitted patients with a less wide QRS (120 ms or more) to be randomized, was much larger, recruiting over 2000 patients, and had a much longer follow-up of two years. This trial has just been completed, and the preliminary results are positive. However, in the absence of details in a peer reviewed publication, its true impact will have to await detailed analysis in light of available data.

B-TYPE 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 or B-type natriuretic peptide (BNP) concentration to assist with the diagnostic decision of the etiology of dyspnea and its management (**grade B, level 2**).

Practical tip

- BNP concentration 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 pretest likelihood of heart failure.
- False positive results may be seen in patients with renal disease, malignancy or extreme obesity.

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 and BNP are derived from the cardiomyocytes, whereas C-type natriuretic peptide 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 a list of clinical applications of BNP in heart failure that are either established or being evaluated:

1. Establishing the diagnosis of heart failure (20-22);
2. Stratifying short and long term prognosis (23,24);
3. Monitoring for the decompensation of heart failure and response to therapy (24-26);
4. Screening for LV dysfunction in the 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 to the discussion of the most established clinical application – that is, the diagnostic utility of BNP in patients with heart failure.

Diagnostic utility of BNP in heart failure and LV dysfunction

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 concentration was increased in patients with a final diagnosis of heart failure but not in those with primary lung disease, and BNP concentration more accurately reflected the heart failure diagnosis than LVEF (20). The availability

of a fluorescence immunoassay has allowed for the point-of-care quantitative determination of BNP in whole blood and plasma. By using this point-of-care assay, blood BNP concentrations 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 concentration 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 multicentre study, 1586 patients who visited an 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 concentrations 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%. The area under the receiver operating characteristic curve was 0.91 (95% CI 0.90 to 0.93).

Another potential use of BNP is for diagnosis in patients with heart failure and preserved systolic function. By definition, these patients have preserved systolic function (LVEF greater than 40%) or normal LVEF, and therefore heart failure cannot be easily diagnosed by simple assessment of LV systolic function. Several studies have now demonstrated increased BNP concentrations in patients with heart failure or documented diastolic dysfunction based on Doppler filling characteristics. The area under the receiver operating characteristic curve to detect diastolic dysfunction in patients with heart failure and preserved systolic function was determined to be 0.958 by the traditional radioimmunoassay and 0.92 in patients with or without symptoms by the rapid assay (31). At this point, BNP concentration by itself cannot differentiate between systolic and diastolic dysfunction, and does not substitute for a careful clinical evaluation.

It should be noted, however, that BNP concentration can increase in conditions other than heart failure. Indeed, plasma BNP concentrations increase with aging, are higher in females, and increase in renal disease, advanced pulmonary disease, with beta-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 concentration, that is, less than 50 to 80 pg/mL, the probability for heart failure as an etiology for the dyspnea is likely to be low. Therefore, BNP may be useful in patients in whom clinical decision is uncertain. An N-terminus proBNP assay is also available. The value for the N-terminal moiety is at least 100-fold higher than that of C-terminal BNP. The optimal cut-off value for this specific assay, however, 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 patients with heart failure (**grade A, level 1**).
- Multidisciplinary care should include, but not be limited to, patient education and close clinical follow-up through clinic visits, telemonitoring or telemanagement, and home visits with specialist health care professionals (**grade B, level 2**).

- Patients 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 seven 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 (36) in 1995 demonstrated the ability to reduce hospitalizations through multidisciplinary care initiated in hospital. 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 inpatient specialist care, target doses of ACE inhibitor therapy and predetermined discharge criteria. The treatment group received a multidisciplinary inpatient intervention followed by telemanagement and clinic follow-up. The treatment group had significant improvements ($P < 0.01$) in patient knowledge of heart failure, patient knowledge of diet and unplanned readmission within three months.

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 (less than six months) and lack of clarity related to the specifics of the intervention. They were also 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 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 patients may benefit the most from admission to a multidisciplinary clinic. Riegel et al (41) conducted a nonrandomized study using matched samples of heart failure inpatients. They were able to demonstrate

maximal reduction in the cost of care for patients with preadmission NYHA class II symptoms through the use of a home-based multidisciplinary intervention. Rich et al (36) found similar benefit for patients 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 and individualized pharmacological therapy, augmented with self-management support and access or referral to the full range of options of therapy for heart failure.

Future issues for consideration

- Determination of the heart failure population that 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 telemanagement directed systems;
- Determination of the implications and potential utility of the multidisciplinary setting in attaining optimum pharmacological therapy targets;
- Determination of the 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 Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) was a prospective, randomized, multicentre study sponsored by the National Institutes of Health in the United States to determine whether LV support with the HeartMate device was superior to optimal medical therapy in nontransplant-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 of any previous medical or surgical trial. Overall survival at two years was dismal, but LV assist device therapy did provide a statistically significant survival benefit at one year (52% versus 25%, $P=0.002$) and at two years (23% versus 8%, $P=0.09$). All objective physical and emotional measures were significantly higher in the LV assist device group, indicating that device therapy improved both quantity and quality of life. On the basis of the results of this landmark trial, the Food and Drug Administration in the United States has recently approved the HeartMate device as a 'destination' therapy for nontransplant-eligible patients.

Several caveats must be highlighted from this trial. First, overall survival was still poor at two years, even in the device group. Second, 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 nonfatal device malfunctions. Furthermore, a subgroup analysis demonstrates that survival benefits accrue only to patients who were in NYHA class IV on intravenous 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 years and all associated device-related complications, patients in the LV assist device 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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