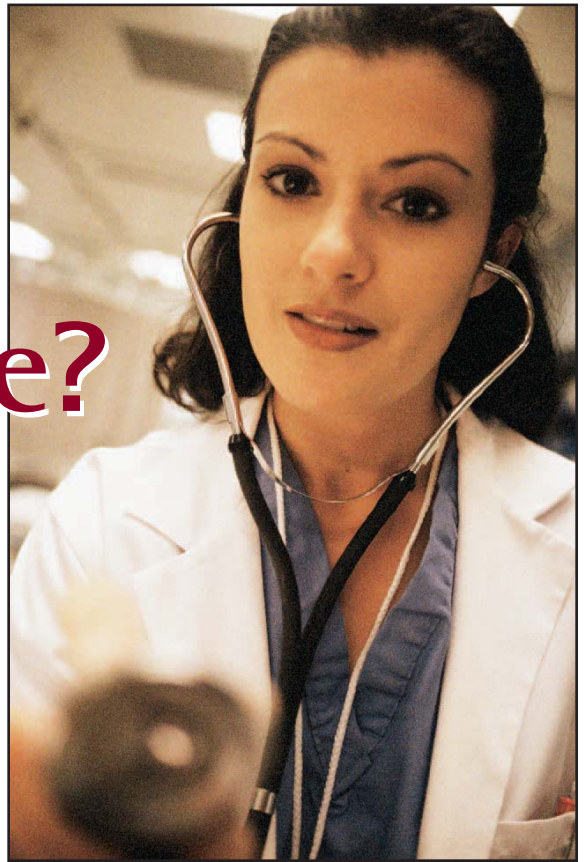# What's New in Heart Failure?

A large part of the population is at risk for congestive heart failure. With one-year mortality rates approaching 40%, it is crucial to understand the newest and best treatment applications, so this number is controlled.

By Richard Townley, MD, FRCPC; and
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The burden of disease in patients with congestive heart failure (CHF) is high. Over 350,000 Canadians are afflicted with the condition, with the one-year mortality after diagnosis ranging between 25% and 40%. This mortality significantly increases in patients over the age of 65. Heart failure remains the most common diagnosis that brings a patient to hospital for medical admission in Canada. Today, the cost of caring for heart failure in Canada exceeds $1 billion annually, with approximately 70% to 80% of these costs being due to hospitalization.[1]

Optimal therapy for this difficult patient population continues to change. There are two broad categories of CHF: systolic dysfunction, for which a great deal of evidence-based therapies exist; and diastolic with or without systolic dysfunction, for which there is a paucity of therapeutic evidence.

In this article, the authors provide an update on the diagnosis and management of patients with systolic heart failure, including:

- The role of brain natriuretic peptide (BNP) in the diagnostic work-up for CHF;
- The 12-year followup of the Studies of Left Ventricular Dysfunction, prevention arm (SOLVD-P) trial, referred to as Extended SOLVD (X-SOLVD), and the long-term benefits of angiotensin-converting enzyme (ACE) inhibitors;
- The roles of angiotensin receptor blockers (ARBs) and ß-blockers; and

In this article:

1. **How to diagnose CHF.**

2. **When to choose between an ACEI and an ARB.**

3. **When to use a beta blocker.**

- A brief summary updating the applications of implantable cardioverter defibrillator (ICD) and bi-ventricular pacing in this patient population.

Diagnosis of CHF

The diagnosis of CHF is frequently difficult to make. Heart failure is a complex clinical syndrome, resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with, or eject, blood. Coronary artery disease is the underlying cause of heart failure in approximately two-thirds of patients with left ventricular systolic dysfunction. The remainder are non-ischemic causes of systolic dysfunction and may have an identifiable cause (*i.e.,* hypertension, valvular disease, myocardial toxins or myocarditis), or they may have no discernable cause (*i.e.,* idiopathic dilated cardiomyopathy).[2]

A complete history and physical examination are the first steps in evaluating the structural abnormality or cause responsible for the development of heart failure. Although the history and physical examination provide important clues about the underlying cardiac abnormality, identification usually requires either non-invasive or invasive cardiac imaging.

One of the most useful diagnostic tests in the evaluation of patients with heart failure is the two-dimensional (2-D) echocardiogram with Doppler flow studies. Both a chest x-ray and 12-lead electrocardiogram (EKG) also provide baseline information in patients with CHF.

Recently, the measurement, or circulating levels, of BNP has become available as a means of identifying patients with evaluated left ventricular filling pressures. BNP is a neurohormone secreted mainly in the cardiac ventricles in response to volume expansion and pressure overload.[3,4]

Critical studies involving BNP in the evaluation of patients with CHF suggest four things:
1. BNP is mildly elevated in patients with asymptomatic left ventricular systolic dysfunction;
2. BNP rises with increased filling pressures;
3. BNP falls when filling pressures fall; and
4. BNP is related to prognosis.[5-9]

In a further study, BNP was able to differentiate CHF from non-CHF causes of dyspnea.[7] In addition, it showed that a single BNP level was more accurate than the National Health and Nutrition Examination Survey (NHANES) score, the Framingham Heart Study score and/or good clinical judgment.[7]

In summary, BNP is a useful addition for diagnosing CHF in selected patients where the diagnosis is not obvious. Further studies are needed before BNP is routinely used in tracking therapy and guiding prognosis. Further cost-effectiveness studies are required before BNP becomes widely implemented as part of a diagnostic and management algorithm (Figure 1).[1]

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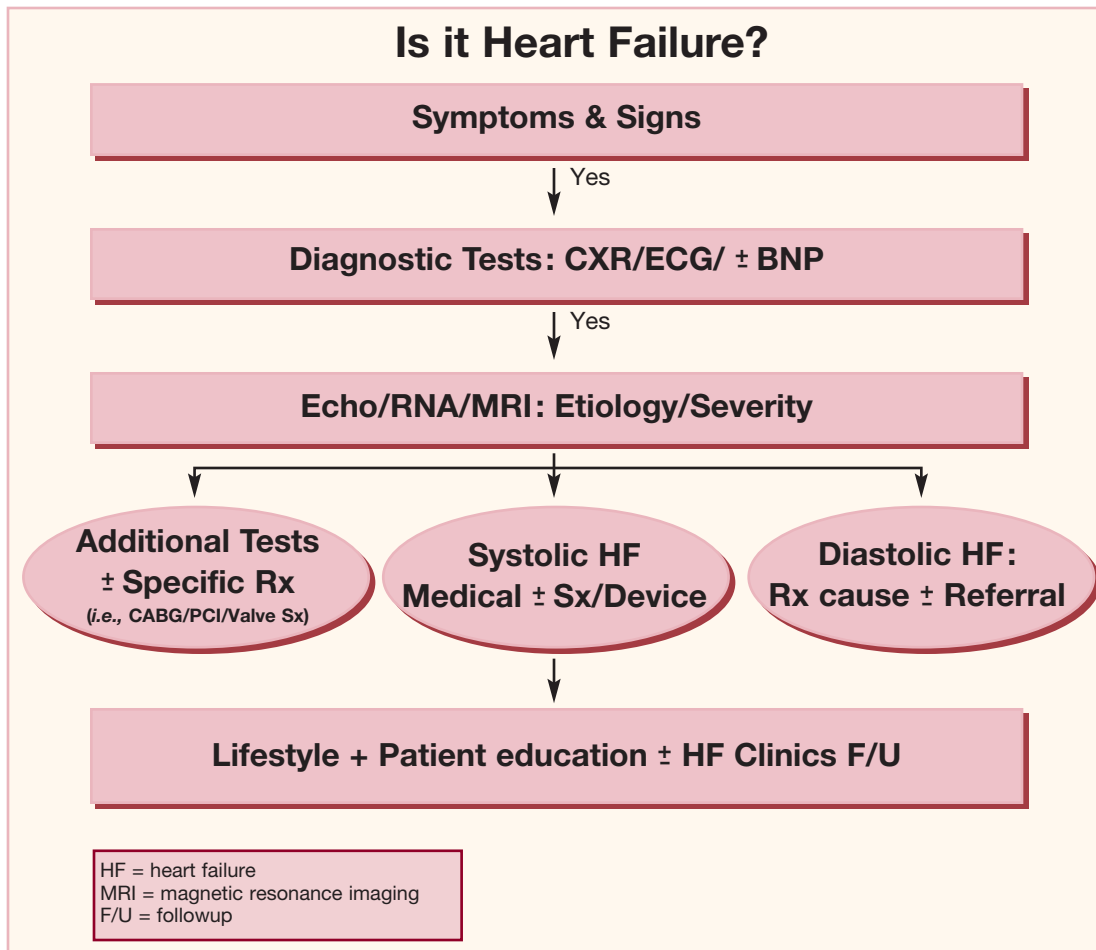
Is it Heart Failure?

Symptoms & Signs

↓ Yes

Diagnostic Tests: CXR/ECG/ ± BNP

↓ Yes

Echo/RNA/MRI: Etiology/Severity

Additional Tests ± Specific Rx (*i.e.,* CABG/PCI/Valve Sx)

Systolic HF Medical ± Sx/Device

Diastolic HF: Rx cause ± Referral

Lifestyle + Patient education ± HF Clinics F/U

HF = heart failure
MRI = magnetic resonance imaging
F/U = followup

Figure 1. Diagnostic and management algorithm for congestive heart disease.[1]

Highlights of newer CHF treatment applications

Aggressive treatment of the underlying cardiovascular disease, especially coronary artery disease, valvular disease or hypertension, should be pursued in all cases, if possible. However, specific pharmacologic therapy should be commenced to reduce morbidity and mortality.

ACE inhibitors

ACE inhibitors continue to occupy our first-line treatment for patients with symptomatic CHF and asymptomatic left ventricular sys-tolic dysfunction. Two landmark trials, the Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS) and the treat-ment arm of SOLVD (SOLVD-T), showed that ACE inhibitors reduce morbidity and mortality in all grades of CHF.[10,11] The two trials show that an ACE inhibitor was superi-or to direct-acting vasodilators.[12] Further studies show that ACE inhibitors improve survival and reduce the risk of major cardio-vascular events in patients with impaired left ventricular function (the Survival and Ventricular Enlargement [SAVE] and the Trandolapril Cardiac Evaluation [TRACE] trials) or heart failure (Acute Infarction

Ramipril Efficacy [AIRE] trial), after myocardial infarction (MI).[13]

Most recently, the X-SOLVD study was presented at the European Society of Cardiology (ESC) 2002 meeting. The aim of this trial was to establish whether the mortality benefit in SOLVD-T (enalapril) was sustained at 12-year follow-up, and whether the reduction in morbidity seen in SOLVD-P would translate to a mortality benefit during this time period. Enalapril treatment for three years in X-SOLVD extended median survival by 8.6 months. Enalapril treatment for three years in SOLVD-P extended median survival by 9.2 months.

This is an important outcome because it shows that ACE inhibitors should be initiated as early as possible in the course of heart failure. It further suggests that we should screen for asymptomatic systolic left ventricular dysfunction more aggressively.

ARBs

In large, randomized clinical trials, ACE inhibitors have been shown to reduce mortality in high-risk, post-MI patients. Selective angiotensin II receptor antagonists are an available alternative because they are known for more complete blockade of tissue in the renin-angiotensin-aldosterone system. They are also better tolerated by patients.

The recent Optimal Therapy in MI with Angiotensin II Antagonist Losartan (OPTIMAAL) study compared the ARB losartan with a proven ACE inhibitor, captopril. The primary outcome was all-cause mortality in high-risk, acute MI (AMI) patients, who also had either heart failure or new anterior wall Q-wave MI.[14]

OPTIMAAL showed a trend toward a decreased all-cause mortality in favour of captopril. There was a significantly higher incidence of cardiovascular mortality in patients randomized to losartan, and both drugs were similar when re-infarction, stroke, revascularization and all-cause hospitalization were analyzed. There was also a significantly better tolerability to losartan, with less discontinuation of the treatment due to adverse events. Most importantly, it was shown that ACE inhibitors should remain the first-line of therapy in patients after a high-risk, complicated AMI. It was concluded, therefore, that losartan should not be generally recommended in this population.

The Val-Heft investigators have evaluated whether the addition of the ARB valsartan to conventionally manage patients with heart failure would result in a clinical improvement. In patients with symptomatic heart failure and depressed left ventricular ejection fraction, the addition of valsartan did not improve mortality, but did reduce the endpoint of mortality plus non-fatal morbid events. The major benefit was associated with a reduction in hospitalizations for heart failure. There appeared to be a trend toward a negative effect with the addition of the ARB to patients who were taking an ACE inhibitor plus a ß-blocker.[15] However, this was a subgroup analysis and requires futher evaluation.

Two current studies, the Candesartan in Heart Failure Assessment in Reduction of Morbidity and Mortality (CHARM) trial and The VALsartan and MI (VALIANT) trial, will further clarify the role of ARBs in systolic and diastolic CHF, as well as in high-risk, post MI patients respectively.[16]

In summary, while ARBs are not superior to ACE inhibitors in CHF or post-MI patients, they are better tolerated (5% less discontinued). The recent OPTIMAAL trial confirms second-line therapy with these drugs. Furthermore, ARBs may have a role as addi-

tive therapy for patients with CHF already using an ACE inhibitor or a ß-blocker, or for patients who cannot tolerate ACE inhibitors. The primary goal, however, is to treat these patients with an ACE inhibitor and ß-blocker.

Inhibitors of the sympathetic nervous system

ß-Blockers

There is overwhelming evidence that ß-blockers will reduce morbidity and mortality in all grades of CHF. These findings are demonstrated by the Cardiac Insufficiency Bisoprolol (CIBIS II) study and the Metoprolol CR/XL Randomized Intervention Trial and Heart Failure (Merit-HF) trials recruiting patients with New York Heart Class (NYHC) II-III symptoms.[17-19] The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial confirmed these benefits are extended to patients with more severe CHF.[20]

The COPERNICUS trial looked at 2,289 patients with heart failure symptoms at rest or with minimal activity for greater than or equal to two months. These patients were also euvolemic and had an ejection fraction of less than 25%. There was a relative risk reduction of 35% in the primary end-point, which was all-cause mortality. There was also a 24% relative risk reduction in the secondary endpoint, which was combined death and hospitalization. The mean followup was 10.4 months.

In a subgroup analysis of COPERNICUS, carvedilol resulted in a 30% reduction in mortality in CHF patients with an extremely depressed ejection fraction of less than 15%. The take-home messages from this trial are:

- In stable patients with severe heart failure, long-term carvedilol therapy reduces the risk of death, frequency, duration and severity of hospitalizations and repeat hospitalizations;
- Carvedilol reduces the risk of progression of heart failure; and
- Carvedilol was well tolerated and did not worsen heart failure in either the initial up-titration phase or in the long-term maintenance phase.[20]

Non-pharmacologic therapy for left ventricular systolic dysfunction

Bi-ventricular pacing

Patients with CHF often have abnormal electrical activation in the myocardium reflected as a prolonged PR interval and QRS duration of the surface ECG. This electromechanical dysynchrony can lead to inefficient left ventricular function and pre-systolic mitral regurgitation. Bi-ventricular pacing the left ventricle *via* the coronary sinus may reduce these abnormalities.[21,22]

The most recent Multicenter In-Sync Randomized Clinical Evaluation (MIRACLE) study has shown bi-ventricular pacing provides long-term improvement in symptoms, ejection fraction and exercise capacity in patients with moderately severe CHF due to left ventricular dysfunction and a prolonged QRS.[23,24] There does not appear to be a mortality benefit, however, and only a third of patients will improve with pacing. In addition, it is an invasive and expensive therapy.

Long-term morbidity and mortality trials are either planned or underway, including the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) and Cardiac Resynchronization in Heart Failure (CARE-HF) trials.
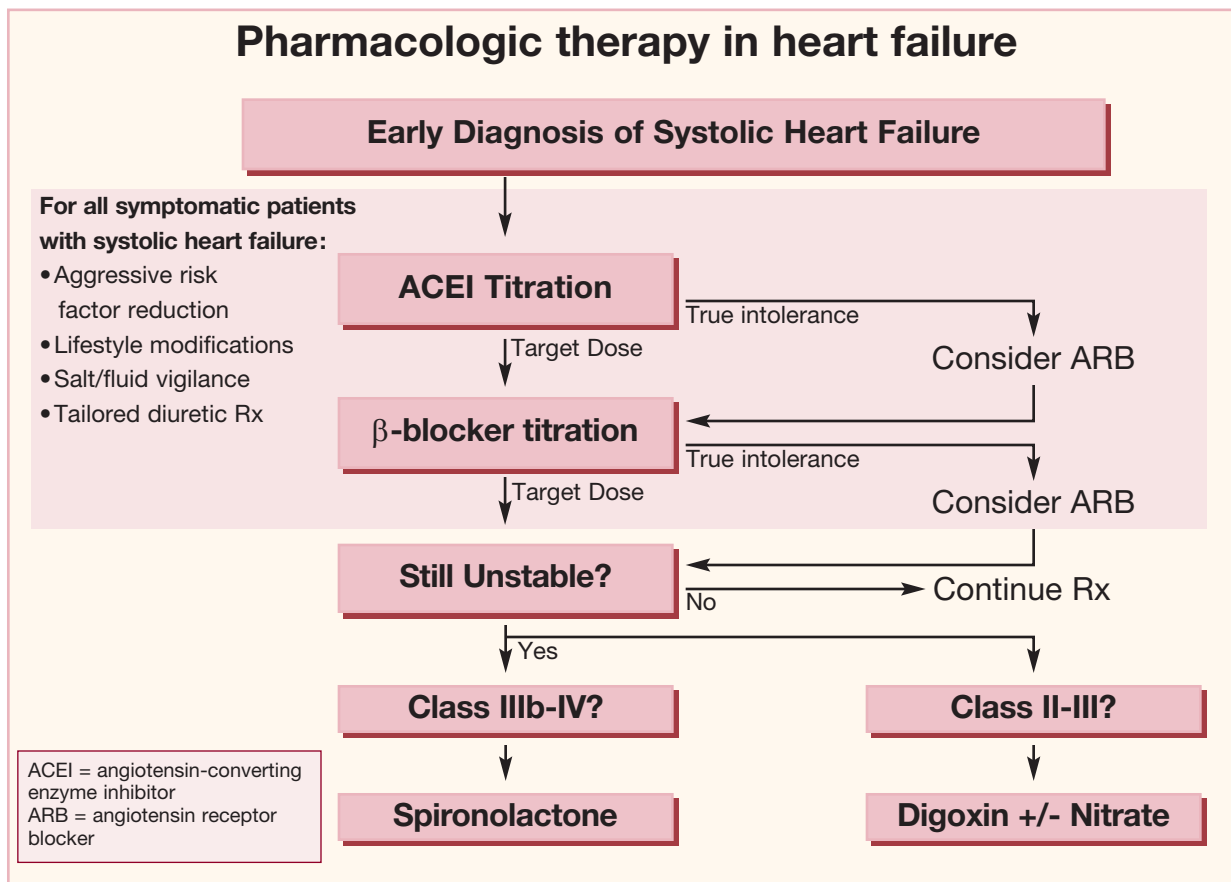
Pharmacologic therapy in heart failure

Early Diagnosis of Systolic Heart Failure

For all symptomatic patients with systolic heart failure:
- Aggressive risk factor reduction
- Lifestyle modifications
- Salt/fluid vigilance
- Tailored diuretic Rx

ACEI Titration → True intolerance → Consider ARB

Target Dose

β-blocker titration → True intolerance → Consider ARB

Target Dose

Still Unstable? → No → Continue Rx

Yes

Class IIIb-IV?

Spironolactone

Class II-III?

Digoxin +/- Nitrate

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin receptor blocker

Figure 2. Pharmacologic therapy in heart failure.[1]

ICDs

The Antiarrhythmic Versus Implantable Defibrillators (AVID) trials and the Multicenter Automatic Defibrillator Implant Trial (MADIT) demonstrated that ICDs reduce mortality in patients with a low ejection fraction and spontaneous or inducible ventricular arrhythmias.[25,26]

The most recent primary prevention trial, the MADIT-II trial, looking at patients who were at least one month out following an MI and ejection fraction of less than 30%, was stopped prematurely because of evidence suggesting the survival benefit of an ICD. This was not a heart failure trial, however, as evidenced by a very low incidence of CHF hospitalization of only 11%. Further to this, patients who were revascularized were excluded.

Thus, the role of ICDs in an era of increased revascularization is not clear. An ongoing large study, The Sudden Cardiac Death in Heart Failure Trial (SCD-HFT), will help shed further light on this difficult area. It is comparing ICD therapy with amiodarone treatment in approximately 2,500 patients with NYHC II-III symptoms and a left ventricular ejection fraction of less than 35%. The primary end-point is all-cause mortality.[25,26]

At this point, evaluation by a CHF specialist is required to carefully select patients who may benefit from either ICD or bi-ventricular pacing therapy.

Conclusion

Figures 1 and 2 summarize the current diagnostic algorithm and treatment of patients with systolic dysfunction CHF.[1] It emphasizes the key role of ACE inhibitors, ARBs and ß-block-

ers, and incorporates the use of non-pharmacologic electrophysiologic therapy for CHF.

ACE inhibitors are first-line agents for patients with CHF and/or left ventricular dysfunction, while ARBs are second-line agents if an ACE inhibitor is not tolerated. ARBs may be added onto ACE inhibitor therapy, but should not be combined with an ACE inhibitor and a ß-blocker.

ß-blockers may be used in CHF patients with NYHC II-IV symptoms. The benefit of carvedilol extends to patients with NYHC IV symptoms and/or an ejection fraction of less than 15%. ß-blockers require slow titration and patients may need an increase in their diuretic dose to maintain euvolemia during the titration phase.

In patients who are being considered for an ICD or bi-ventricular pacing, referral to a CHF specialist is necessary to select those patients who may benefit from a more invasive and expensive therapy.

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