

# Beta-blockers for the management of chronic heart failure: A summary of the evidence

## INTRODUCTION

Chronic heart failure continues to be a significant health problem causing progressively worsening symptoms, decreased quality of life, hospitalization and death.<sup>1-3</sup> Patients diagnosed with chronic heart failure have some degree of cardiac dysfunction when objective diagnostic procedures are used (ejection fraction <40%, grade II-IV left ventricular dysfunction or dilation on imaging).<sup>1</sup> This disease is further classified based on symptoms according to the New York Heart Association (NYHA) classification system, as outlined in table 1.<sup>1</sup> Although significant improvements have been made in the chronic management of heart failure, further efforts are needed to optimize patient outcomes.

Once contraindicated in patients with heart failure, beta-blockers are now recommended in most clinical guidelines for the long-term management of this disease.<sup>1-3</sup> Although beta-blockers have been used for many years in the management of hypertension, angina, arrhythmias, and myocardial infarctions, their use to treat heart failure is a recent phenomenon. Support for the use beta-blockers as a treatment for heart failure has emerged slowly.<sup>4</sup> Traditional theories suggested that chronic heart failure was solely due to impaired systolic function, and that any medication with a negative

### Bottom Line

- In patients with chronic heart failure, the beta-blockers carvedilol, metoprolol and bisoprolol have been shown to significantly reduce the risk of death compared with placebo.
- Potential risks of beta-blocker therapy in patients with heart failure include worsening of the heart failure symptoms (e.g., onset of or increase in shortness of breath, dyspnea/fatigue on exertion or at rest, weight gain, edema or swelling), bradycardia, hypotension, depression, sexual dysfunction, and fatigue.
- To improve tolerability, beta-blockers should be initiated at very low doses and titrated slowly.
- Further evidence is required to determine if there is a clinically important difference in outcomes between carvedilol, metoprolol, and bisoprolol.

inotropic effect was contraindicated.<sup>4</sup> However, as the understanding of the pathophysiology of heart failure has evolved, so has the rationale for the use of beta-blockers. The current theory is that chronic heart failure is caused by an impairment in left ventricular function, which leads to activation of the sympathetic nervous system and the renin-angiotensin aldosterone system in an effort to support the failing heart.<sup>5</sup> However, these compensatory responses exert further stress on the ventricle and play a fundamental role in the progression of the disease.<sup>5</sup> Therefore, it was theorized that breaking the cycle of neurohormonal activation with a beta-blocker might have a positive impact on the long-term outcome of the disease.

Several large randomized trials have examined the impact of beta-blockers on clinically relevant outcomes in patients with chronic heart failure. This article summarizes and interprets these key trials.

**Stacey MacAulay, BScPharm, PharmD,  
Derek Jorgenson, BSP, PharmD,**

*Stacey MacAulay is an Evidence-Based Pharmacy Consultant with the Evidence-Based Prescribing Initiative at the London Health Sciences Centre in London, Ontario. She is also the coordinator of the Clinical Forum series. Derek Jorgenson is a Clinical Pharmacy Specialist in ambulatory care at the University Health Network in Toronto. He works in a large family practice clinic as well as a cardiac risk reduction clinic at the Toronto Western Hospital.*

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**Table 1.** New York Heart Association (NYHA) symptom classification for chronic heart failure<sup>1</sup>

<b>Class I</b>
No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause undue fatigue or dyspnea.
<b>Class II</b>
Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
<b>Class III</b>
Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
<b>Class IV</b>
Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

## EFFICACY

### Background

Several beta-blockers have been evaluated in randomized, controlled trials for the chronic management of heart failure.<sup>6-11</sup> Among these, carvedilol, metoprolol and bisoprolol have improved survival compared with placebo.<sup>6-8,10</sup> Carvedilol is a nonselective  $\beta_1$ - and  $\beta_2$ -receptor blocker with  $\alpha_1$ -receptor blocking activity.<sup>12,13</sup> Carvedilol also exhibits antioxidant activity and antiendothelin effects, which theoretically may lead to positive outcomes in heart failure patients.<sup>12-15</sup> In contrast to carvedilol, both metoprolol and bisoprolol are  $\beta_1$ -selective adrenergic receptor blockers.<sup>8,9</sup>

### Evidence

Key trials evaluating beta-blocker therapy in the management of chronic heart failure are summarized in table 2.

### Carvedilol

Several trials have evaluated carvedilol in patients with heart failure. Two key studies that measured outcomes related to cardiovascular morbidity and mortality are the US Carvedilol Heart Failure Study and the COPERNICUS Trial.<sup>6,7</sup>

The US Carvedilol Heart Failure Study was a random-

ized, double blind trial that enrolled 1094 patients with symptomatic heart failure (NYHA class II-IV), despite treatment with diuretics and ACE-inhibitors. Concurrent treatment with digoxin, hydralazine, or nitrates was permitted, but not required. Patients had a left ventricular ejection fraction (LVEF) of  $\leq 35\%$  at time of enrollment. Patients were randomly assigned to receive carvedilol 12.5 mg twice daily (titrated up to 50 mg twice daily, as tolerated) or placebo in addition to their usual medication. The objectives of this study were to measure all-cause mortality and hospitalization. The patients in both groups were similar at the start of the trial with respect to age (mean 58 years), LVEF (mean 23%), NYHA class (53% Class II, 44% Class III, 3% Class IV), comorbidities, and concomitant medication use. The trial was stopped prematurely, after a median follow-up of 6.5 months, when the benefits of carvedilol were clear. A statistically significant reduction in overall mortality (7.8% placebo, 3.2% carvedilol; absolute risk reduction [ARR] 4.6%; number needed to treat [NNT] 22;  $p < 0.001$ ) and hospitalizations (19.6% placebo, 14.1% carvedilol; ARR 5.5%; NNT 19;  $p < 0.05$ ) was observed in the carvedilol group. Patients in the carvedilol group received an average daily dose of 45 mg. Overall, 7.8% of the placebo group and 5.7% of the carvedilol group discontinued therapy before the end of the trial due to adverse effects.<sup>6</sup>

COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study Group) was a randomized, double blind trial that enrolled 2289 patients with severe heart failure, defined as dyspnea or fatigue at rest or on minimal exertion, and a LVEF of  $<25\%$ , despite treatment with a diuretic and an ACE-inhibitor or angiotensin II-receptor blocker. Concurrent treatment with digoxin, hydralazine, nitrates, spironolactone, or amiodarone was permitted, but not required. Patients were randomized to receive either carvedilol 3.125 mg twice daily (titrated to a target dose of 25 mg twice daily, as tolerated) or placebo. Endpoints of the trial were all-cause mortality and the combined risk of death or hospitalization. Patients in both groups were similar at the start of the trial with respect to age (mean 63 years), LVEF (mean 20%), NYHA class (100% Class IV), comorbidities, and concomitant medication use. The trial was stopped prematurely, after a mean of 10 months follow-up, when the beneficial effects of carvedilol were clear. Treatment with carvedilol was associated with a statistically significant reduction in all-cause mortality (16.8% placebo, 11.2% carvedilol; ARR 5.6%; NNT 18;  $p < 0.01$ ) and in the combined endpoint of death or hospitalization (44.7% placebo, 36.8% carvedilol; ARR 7.9%; NNT 13;  $p < 0.001$ ). Patients received an average daily dose of 37 mg of carvedilol. Despite a slow dose titration, 14.8% of patients receiving carvedilol withdrew before the end of the trial, compared with 18.5% in the placebo group.<sup>7</sup>

**Table 2.** Summary of the key trials of beta-blockers in patients with heart failure

STUDY	TREATMENTS	DURATION OF FOLLOW-UP	NO. OF PATIENTS	NYHA CLASS AT BASELINE (%)	MORTALITY	ARR	NNT	P-VALUE
<b>Carvedilol</b>								
US Carvedilol Heart Failure Study (1996) <sup>6</sup>	Carvedilol (target 50 mg bid) vs placebo	6.5 months	1094	II 53% III 44 % IV 3 %	Carvedilol 3.2% Placebo 7.8%	4.6%	22	<0.001
COPERNICUS (2001) <sup>7</sup>	Carvedilol (target 25 mg bid) vs placebo	10 months	2289	IV 100 %	Carvedilol 11.2% Placebo 16.8%	5.6 %	18	<0.01
<b>Metoprolol</b>								
MERIT-HF (1999) <sup>8</sup>	Metoprolol CR/XL (target 200 mg qd) vs placebo	12 months	3991	II 41% III 55 % IV 4 %	Metoprolol 7.3% Placebo 10.8%	3.5 %	29	<0.05
<b>Bisoprolol</b>								
CIBIS (1994) <sup>9</sup>	Bisoprolol (target 5 mg qd) vs placebo	1.9 years	641	III 95% IV 5%	Bisoprolol 16.6% Placebo 20.9%	NS	N/A	0.22 (NS)
CIBIS-II (1999) <sup>10</sup>	Bisoprolol (target 10 mg qd) vs placebo	1.3 years	2647	III 83% IV 17%	Bisoprolol 11.8% Placebo 17.3%	5.5 %	19	<0.0001

ARR = absolute risk reduction; bid = twice daily; CIBIS = Cardiac Insufficiency Bisoprolol Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Study Group; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NNT = number needed to treat; NS = Not Significant; N/A = Not Applicable; NYHA = New York Heart Association; qd = once daily.

## Metoprolol

The MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) trial was a randomized, double blind trial that enrolled 3991 patients with symptomatic heart failure (NYHA class II-IV) and a LVEF of  $\leq 40\%$ . For the majority of patients, concomitant medication included a diuretic and an ACE-inhibitor or angiotensin II-receptor blocker, with or without digoxin. Patients were randomly assigned to receive metoprolol controlled release/extended release (CR/XL) 12.5-25 mg once daily (titrated to a target dose of 200 mg once daily, as tolerated) or placebo and followed for a mean of one year. The primary endpoint of this trial was all-cause mortality. Patients were similar at the start of the trial with respect to age (mean 64 years), LVEF (mean 28%), NYHA Class (41% Class II, 55% Class III, 4% Class IV), comorbidities, and concomitant medication use. This trial was stopped early because of a significant decrease in the risk of death with metoprolol (10.8% placebo, 7.3% metoprolol; ARR 3.5%; NNT 29;  $p < 0.05$ ). Patients in the metoprolol CR/XL group received an average daily dose of 159 mg. Metoprolol CR/XL was permanently discontinued early in 13.9% of patients, compared with a discontinuation rate of 15.3% in the placebo group.<sup>8</sup>

## Bisoprolol

The CIBIS (Cardiac Insufficiency Bisoprolol Study) study was also a randomized, double blind study, which enrolled 641 patients with NYHA class III or IV heart failure and a LVEF  $< 40\%$ . The majority of patients received a diuretic and an ACE-inhibitor, with or without digoxin. Patients were randomized to receive bisoprolol 1.25 mg daily (titrated to a target dose of 5 mg daily, as tolerated) or placebo for a mean of 1.9 years. The primary endpoint of this trial was all-cause mortality. Patients were similar at the start of the trial with respect to age (mean 60 years), LVEF (mean 26%), NYHA class (95% Class III, 5% Class IV), and concomitant medication use. However, more patients in the bisoprolol group had a history of myocardial infarction, and a higher diastolic blood pressure. In contrast to the larger CIBIS-II trial, the CIBIS trial did not show a significant reduction in mortality with bisoprolol (placebo 20.9%, bisoprolol 16.6%;  $p = 0.22$ ). During the study, 51% of patients receiving bisoprolol achieved the target dose of 5 mg daily. Study treatment was discontinued early in 23% of patients receiving bisoprolol and 26% of patients receiving placebo.<sup>9</sup>

The CIBIS-II study was a randomized, double blind trial that enrolled 2647 patients with NYHA class III or

IV with a LVEF  $\leq$  35%. Concomitant medication for the majority of patients included a diuretic and an ACE-inhibitor, with or without digoxin. Patients were randomly assigned to either bisoprolol 1.25 mg daily (titrated to a target dose of 10 mg daily, as tolerated) or placebo. Endpoints in this trial included all-cause mortality and hospitalizations. Patients were similar at the start of the trial with respect to age (mean 61 years), LVEF (mean 28%), NYHA class (83% class III, 17% class IV), and concomitant medication use. This trial was stopped early (mean follow-up of 1.3 years) because of a significant reduction in mortality with bisoprolol compared with placebo (placebo 17.3%, bisoprolol 11.8%; ARR 5.5%; NNT 19;  $p < 0.0001$ ). Bisoprolol was also associated with a significant reduction in hospitalizations compared with placebo (placebo 38.9%, bisoprolol 33.2%, ARR 5.7%, NNT 18,  $p < 0.001$ ). During the trial, 43% of patients receiving bisoprolol achieved the target dose of 10 mg daily.<sup>10</sup>

### Carvedilol versus Metoprolol

Several small trials have directly compared carvedilol and metoprolol (no published studies were identified that compared bisoprolol with another beta-blocker).<sup>16-18</sup> These trials are limited by their small sample size, short duration of follow-up, use of surrogate endpoints, and/or open-label design. However, a more recent and better-designed trial by Metra and colleagues adds some initial insight into the comparative efficacy of carvedilol and metoprolol.<sup>19</sup> This randomized, double blind trial enrolled 150 patients with NYHA class II-IV symptoms and a LVEF  $\leq$  35%. The majority of patients were using a diuretic and an ACE-inhibitor, with or without digoxin. Patients were randomly assigned to carvedilol 3.125 mg twice daily (titrated to a target dose of 25 mg twice daily, as tolerated) or metoprolol 5 mg twice daily (titrated to a target dose of 50 mg twice daily, as tolerated) and followed for a mean of 14 months. Patients were similar at the start of the trial with respect to age (mean 57 years), LVEF (mean 21%), NYHA class (31% class II, 60% class III, 9% class IV), concomitant medication use, and comorbidities. The main endpoint of this trial was the change in LVEF. During the trial, the LVEF increased significantly from baseline in both the carvedilol and metoprolol groups; however, this increase was significantly greater among the patients receiving carvedilol (carvedilol 10.8%, metoprolol 7.2%;  $p < 0.05$ ). Mortality was not assessed in this trial. Mean doses achieved were 44 mg/day and 115 mg/day for carvedilol and metoprolol, respectively.<sup>19</sup>

### Interpretation and application of evidence

The trials summarized above indicate that carvedilol, metoprolol and bisoprolol significantly reduce the risk of death in patients with chronic heart failure compared

**Figure 1.** Sample monitoring plan for beta-blocker use in the chronic management of heart failure

<b>Patient name:</b> _____ <b>NYHA class:</b> _____ <b>LVEF:</b> _____ <b>Beta-blocker &amp; dose:</b> _____ <b>Date of 1<sup>st</sup> fill:</b> _____ <b>Date of callback(s) or Rx refill(s):</b> _____  <b>Comments:</b> _____   
<p><b>CHECKLIST FOR MONITORING PARAMETERS</b></p> <p><b>Efficacy</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Dose of beta-blocker is maximized</li> <li><input type="checkbox"/> Patient is adherent with beta-blocker therapy</li> </ul> <p><b>Safety</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Worsening heart failure (e.g.: onset of or increase in shortness of breath, dyspnea/fatigue on exertion or at rest, weight gain, edema or swelling)</li> <li><input type="checkbox"/> Bradycardia</li> <li><input type="checkbox"/> Hypotension</li> <li><input type="checkbox"/> Excessive fatigue</li> <li><input type="checkbox"/> Sexual dysfunction</li> <li><input type="checkbox"/> Symptoms of depression</li> <li><input type="checkbox"/> Other</li> </ul>

with placebo. The magnitude of this benefit is clinically meaningful, with an ARR in the range of 3.5-5.6% and a corresponding NNT ranging between 18 and 29. This suggests that only 18 to 29 patients would have to be treated with one of these beta-blockers rather than placebo for approximately six months to 1.9 years to prevent one additional death. In addition to improved survival, beta-blockers were generally associated with a reduction in hospitalizations compared with placebo. The benefits of beta-blockers were seen primarily in patients with NYHA class II-IV for carvedilol, NYHA class II-III for metoprolol, and NYHA class III-IV for bisoprolol. For the most part, this benefit was demonstrated in patients using concomitant diuretics and ACE-inhibitors, with or without digoxin.<sup>6-10</sup>

This body of evidence is very compelling and the benefit of beta-blocker therapy in the chronic management of heart failure is clear. The only key trial that failed to show a mortality benefit, CIBIS with bisoprolol, may have been too small and, therefore, underpowered to achieve statistical significance for this endpoint.<sup>9</sup> The

evidence to date indicates that, unless contraindicated, most heart failure patients should receive a beta-blocker as part of their heart failure regimen.<sup>2,3</sup> However, there are some limitations and unanswered questions.

- *Do all beta-blockers provide a benefit in the chronic management of heart failure?*

Only carvedilol, metoprolol and bisoprolol have been shown to reduce mortality in heart failure patients. Prescribing other beta-blockers is not recommended and has the potential to cause harm. Administration of bucindolol in patients with NYHA class III-IV heart failure was found to be no more effective at reducing mortality than placebo in the BEST Trial, suggesting that there may not be a class effect of beta-blockers in heart failure.<sup>11</sup> Although other beta-blockers such as atenolol may be used in clinical practice, it is important to remember that there is no evidence to support this practice.

- *Which beta-blocker should be used for the chronic management of heart failure?*

Unfortunately, there have been no head-to-head morbidity and mortality trials published comparing the various beta-blockers in chronic heart failure. However, there is an ongoing study (COMET Trial) that is comparing carvedilol with an immediate release formulation of metoprolol, with the objective of identifying any differences in morbidity or mortality between the two agents.<sup>20</sup> The results of this highly anticipated trial are expected to be presented in late 2003. In the meantime, surrogate endpoint data may be used to make an assessment. The study by Metra and colleagues showed that carvedilol was superior to metoprolol in terms of increasing the LVEF.<sup>19</sup> These results have also been duplicated in a recent meta-analysis by Packer and colleagues.<sup>21</sup> However, this evidence is preliminary and must be viewed with caution because an improvement in ejection fraction (a surrogate endpoint) may not translate into an improved survival rate. In summary, it remains unknown at this time which beta-blocker is best for the chronic management of heart failure.

- *What dose of beta-blocker should be used?*

The optimal dose of each beta-blocker is unknown.<sup>3</sup> The target doses used in the trials summarized above were: carvedilol 25-50 mg twice daily, metoprolol CR/XL 200 mg/day, and bisoprolol 5-10 mg/day.<sup>5,9</sup> However, these doses may not always be tolerated in practice, and little is known about the effects of lower doses of beta-blockers, which many patients inevitably receive. There is one prospective, randomized, dose-ranging study that compared three different doses of carvedilol (6.25, 12.5, 25 mg twice daily) with placebo in patients with mild to moderate heart failure.<sup>22</sup> The investigators found dose-

related improvements in LVEF and survival with carvedilol. However, mortality was not a predefined endpoint in the trial and the sample size in this study was very small; therefore, definitive conclusions cannot be drawn about the optimal dose of carvedilol.<sup>22</sup> Also, in a post-hoc, subgroup analysis of the MERIT-HF trial, patients who did not tolerate doses of metoprolol above 100 mg/day may still have derived a survival benefit from the metoprolol.<sup>23</sup> The Canadian Cardiovascular Society Consensus Guidelines recommend that the doses used in the key trials be targeted, but that lower doses be maintained when higher doses are not tolerated.<sup>3</sup>

- *Do all beta-blockers provide a benefit regardless of baseline disease severity?*

There may be some differences between the various beta-blockers when looking at effects in specific patient subgroups. Of particular interest is the group with the most severe disease (NYHA class IV). COPERNICUS (carvedilol versus placebo) is the only key study that enrolled a significant proportion of patients with NYHA class IV heart failure;<sup>7</sup> therefore, carvedilol may be preferred in such patients.

The other group of patients underrepresented in the key beta-blocker trials is those with the mildest disease (NYHA class I). All trials summarized here, with the exception of COPERNICUS, enrolled primarily patients with NYHA class II or III heart failure. There are two small trials not summarized above, that compared carvedilol with placebo, and may shed some light on this issue.<sup>24, 25</sup> The ANZ (Australia/New Zealand) Trial was a randomized, double blind trial that compared the effects of 19 months of treatment with carvedilol or placebo in 415 patients with heart failure. The carvedilol group, of which almost 30% had NYHA class I disease, had a lower risk of hospitalization (of borderline significance), but no significant reduction in death compared to placebo.<sup>24</sup> The CAPRICORN trial found a reduction in mortality using carvedilol in patients who had a myocardial infarction within three to 21 days of randomization. Patients were included if they had a LVEF  $\leq$  40%, but did not necessarily have symptomatic heart failure. Unfortunately, the authors did not report how many of the 1959 patients actually had heart failure; therefore, it is also unknown how many had NYHA class I heart failure.<sup>25</sup> The Canadian Cardiovascular Society Consensus Guidelines recommend beta-blocker therapy for patients with left ventricular systolic dysfunction that have NYHA class I heart failure with a LVEF  $<$ 40%, especially after a myocardial infarction.<sup>3</sup>

- *Is the formulation of metoprolol used in MERIT-HF important?*

The formulation that was used in the MERIT-HF trial,

metoprolol succinate CR/XL, is not available in Canada.<sup>8</sup> The pharmacokinetic and pharmacodynamic properties of immediate release metoprolol tartrate do not appear to be equivalent to that of metoprolol succinate CR/XL.<sup>26,27</sup> Since there are no published trials evaluating the mortality effects of immediate release metoprolol tartrate in heart failure, it is unknown if this formulation will result in the same benefits provided by metoprolol succinate CR/XL in the MERIT-HF trial.<sup>8</sup> This uncertainty may be resolved when the results of the COMET trial become available, which is evaluating an immediate release metoprolol formulation.<sup>20</sup>

- *What beta-blockers are officially indicated in Canada for the chronic management of heart failure?*

Despite the evidence for metoprolol and bisoprolol, carvedilol is the only beta-blocker that is officially indicated for the management of chronic heart failure in Canada.

## SAFETY AND TOLERABILITY

### Evidence

In the clinical trials described above, beta-blocker therapy was associated with a risk of adverse events, including bradycardia, worsening of heart failure, hypotension, dizziness and fatigue.<sup>6-10</sup> These side effects can have a significant impact on patient medication adherence.

### Interpretation and application of evidence

The risk of adverse events with beta-blockers must be balanced with their proven benefit in reducing the risk of mortality and hospitalization. Considering the significant benefits that beta-blockers have demonstrated in clinical trials, it is imperative that pharmacists be involved in implementing strategies directed at improving patient compliance, minimizing the risk of adverse effects, and optimizing the dose of the beta-blocker. Some examples of these strategies include:

### Start low and go slow

The overall tolerability of a beta-blocker may be improved if it is initiated at a very low dose, and titrated very slowly, especially in patients with more severe disease. The Canadian Cardiovascular Society Consensus Guidelines recommend starting with 3.125-6.25 mg of carvedilol twice daily, 6.25-12.5 mg of metoprolol twice daily, or 1.25 mg of bisoprolol once daily, and increasing the dose slowly at intervals of two weeks or more. Close follow-up during the titration phase is vital to encourage medication adherence and to monitor for signs of decompensating heart failure (e.g., onset of, or increase in shortness of breath, dyspnea/fatigue on exertion or at rest, edema/swelling, or weight gain). As well,

beta-blockers should not be instituted during a period of acute decompensation in patients with heart failure.

## Patient Counseling

The long-term management of heart failure is a therapeutic area where effective pharmacist-patient communication may have a significant impact on adherence and patient outcomes. Patients should be advised about potential adverse effects and to seek medical attention if they occur. It is particularly important for patients to be taught to recognize the signs of decompensating or worsening heart failure, which may result from the initiation of a beta-blocker, or from an increase in dose of a beta-blocker (see figure 1).

It should be reinforced with patients that they are taking a medication that may actually make them feel worse (i.e., they may experience adverse effects), but that may significantly reduce their risk of death and hospitalization in the future. When explaining this to patients, it may be helpful to use an analogy with investing: "contributing to an RRSP is painful now, but may pay big dividends in the future." Patients who understand this issue may be less likely to discontinue the beta-blocker prematurely.

## Monitoring

Pharmacists should actively participate in the monitoring and follow-up of patients who are started on a beta-blocker to ensure that the strategies mentioned above are effectively implemented. A very important period for pharmacist follow-up is soon after the initiation of the beta-blocker and after a dose increase. This is when adverse effects are most likely to occur and when patients may become nonadherent. However, long-term follow-up is also important to ensure that tolerability, adherence, and dose targets are achieved. Specific monitoring and follow-up plans will vary depending upon the patient's condition and pharmacist's practice site. For example, an intervention such as a telephone callback program can be integrated into most practice sites (figure 1). One suggested monitoring plan might include follow-up by telephone weekly for the first month after initiation of the beta-blocker using the template in figure 1. Subsequent follow-up monitoring can be modified based upon factors such as patient tolerability and adherence.

## CONCLUSION

Several large, randomized trials have consistently demonstrated a significant reduction in mortality with beta-blocker therapy in patients with chronic heart failure.<sup>6,8,10</sup> These trials, as well as current guidelines,<sup>1-3</sup> suggest that beta-blockers are an integral component of the treatment armamentarium for patients with heart failure. Despite the strength of this evidence, it appears

that many patients with documented chronic heart failure are not receiving beta-blockers. Recent estimates from the United States and Europe suggest that only 34 to 40.9% of patients with a documented LVEF of <40% are receiving beta-blockers.<sup>28,29</sup> Identification of patients who may benefit from beta-blocker therapy represents a key role for pharmacists. Systematic screening of pharmacy computer databases for eligible patients not receiving therapy, or ensuring beta-blockers are initiated before hospital discharge, are examples of strategies that may be effective. Pharmacists can also educate patients and their families about the appropriate use of these agents and engage in a monitoring plan designed to ensure effective and safe use of beta-blockers in patients with chronic heart failure.

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**Corresponding author:** Stacey MacAulay, London Health Sciences Centre, Room S 121, 375 South Street, London, ON, N6A 4G5, stacey.macaulay@lpsc.on.ca