CONGESTIVE HEART FAILURE

Pharmacological Management of Systolic Heart Failure in Older Adults

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Systolic Heart Failure: A Complex Geriatric Syndrome

Heart failure (HF) is highly prevalent, estimated to affect over 350,000 Canadians and 5 million Americans.1 The incidence and prevalence of HF increase with age.2 It is also one of the most common causes of hospitalization among older adults in developed nations and is estimated to cost over $1 billion per year in Canada.1 About half of older adults with HF have systolic dysfunction or systolic heart failure (SHF). Over the last decade, it has become increasingly clear that certain medications, specifically angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, reduce morbidity and mortality in patients with SHF.3-10 These developments led to the publication of several national guidelines in the treatment of SHF.11-13

Treatment of Older Adults with Systolic Heart Failure

Most large randomized controlled trials (RCTs) of ACE inhibitors and BBs in HF have focused on younger patients and rarely included patients > 80 years of age. However, sub-analysis of some of these studies indicates that older adults with SHF derive at least the same benefit in terms of morbidity and mortality reduction as a younger patient. Therefore, recommendation of existing HF guidelines can be applied to older adults with SHF, taking into consideration polypharmacy and multiple comorbid conditions in these patients. Generalist physicians caring for older adults with SHF might find it useful and convenient to become familiar with one or two HF guidelines and follow their recommendations.

Recommendations for pharmacological therapy for SHF with ACE inhibitors and BBs are summarized in Tables 1 and 4. ACE inhibitors should be prescribed for all eligible systolic heart failure patients. Generalist physicians, who care for most heart failure patients, are perfectly capable of prescribing these life-saving drugs to older adults with systolic heart failure and should be encouraged to do so. Greater involvement of generalist physicians in providing evidence-based therapy will translate into better quality and outcomes for older adults with heart failure.

Key words: heart failure, left ventricular systolic dysfunction, angiotensin-converting enzyme inhibitors, beta-blockers.
BBs should be prescribed to all patients with SHF who are clinically stable unless specific contraindications exist. Absolute contraindications to the use of BBs include advanced heart block and symptomatic bradycardia. Even though reactive airway disease has been mentioned as a contraindication, a recent meta-analysis demonstrated that beta-1 selective blockers such as metoprolol succinate are well tolerated by patients with reactive airway disease. Chronic obstructive pulmonary disease is not a contraindication to BB use.

There is no need to maximize the dose of an ACE inhibitor prior to initiating therapy with a BB. Digoxin should be used only in male SHF patients who are symptomatic despite therapy with ACE inhibitors, BBs and diuretics. Aldosterone antagonists should be reserved for SHF patients who are symptomatic at rest (NYHA Class IV) despite use of ACE inhibitors, BBs and diuretics, and who do not have renal dysfunction or hyperkalemia. It is important to refer patients to a cardiologist if they are considered candidates for therapy with an aldosterone antagonist.

The combination of hydralazine and a nitrate should be reserved for those patients who can tolerate neither an ACE inhibitor nor an ARB. The vast majority of SHF patients will require diuresis, often with a loop diuretic in moderate to high doses. Lastly, but not the least, it is very important to avoid several medications that are detrimental in older adults with SHF; such as non-steroidal anti-inflammatory agents, calcium channel blockers (with the exceptions ofamlodipine and felodipine) and most anti-arrhythmic agents.

### Table 1: Practical Tips for Use of ACE Inhibitors in Older Adults with Systolic Heart Failure (SHF)

| 1. | Prescribe ACE inhibitors to all older adults with SHF (left ventricular ejection fraction < 40%) unless an absolute contraindication to their use exists. |
| 2. | Continue therapy with ACE inhibitors indefinitely. |
| 3. | A history of angioedema or other allergic reaction to a previously used ACE inhibitor or a history of hereditary or idiopathic angioedema is the only absolute contraindication to the use of ACE inhibitors. |
| 4. | Avoid use of ACE inhibitors in patients with bilateral renal artery stenosis, as it might lead to acute reversible renal failure. |
| 5. | Renal dysfunction should not be considered a contraindication to start or continue therapy with ACE inhibitors. |
| 6. | Expect serum creatinine to rise after therapy with ACE inhibitors in all patients with SHF, and especially in those with high baseline serum creatinine. |
| 7. | Treat and correct hyperkalemia before initiating ACE inhibitor therapy. |
| 8. | All ACE inhibitors are likely to be beneficial, but use of those proven beneficial in clinical trials, namely captopril, enalapril, lisinopril and ramipril, is preferable. |
| 9. | There is no need to maximize the dose of ACE inhibitors to the doses used in clinical trials. |
| 10. | If patients experience cough or angioedema, switch to an angiotensin-receptor blocker (ARB). |
| 11. | If patients cannot tolerate ACE inhibitors or ARBs, consider using hydralazine and a long-acting nitrate. |
| 12. | Not using ACE inhibitors in older adults with SHF without documenting a reason for non-use is poor quality care that translates into more deaths and hospitalizations for these patients. |

### Angiotensin-converting Enzyme Inhibitors

ACE inhibitors should be prescribed to all older adults with SHF who do not have any contraindication to ACE inhibitors. These agents should form the foundation of evidence-based therapy for older adults with SHF. While there is limited data on the effectiveness of ACE inhibitors in reducing mortality and morbidity in older adults with SHF, meta-analysis of all RCTs of ACE inhibitors suggests that they are at least as effective in older adults with SHF as in younger counterparts.

Although most of the evidence regarding efficacy of ACE inhibitors in SHF is based on use of enalapril, it is believed that all ACE inhibitors will confer similar benefits. Nonetheless, current guidelines recommend use of ACE inhibitors which are proven in randomized trials in SHF to improve survival. These ACE inhibitors include captopril, enalapril, lisinopril and ramipril (Table 2). Each of these agents is eliminated via kidneys, and since older adults have decreased glomerular filtration, the response to these medications may be enhanced. Because of increased baseline serum creatinine, older adults also are likely to show a disproportionate increase in serum creatinine level in response to ACE inhibitors.

Renal dysfunction is one of the major reasons for underutilization of ACE inhibitors. In a cohort of hospitalized older adults (mean age=78.5 years; SD=7.0) with SHF (n=295) and no contraindications to ACE inhibitors, Ahmed, et al. demonstrated that use of ACE inhibitors in patients with renal dysfunction and other perceived contraindications was associated with significant short- and long-term survival benefit. Patients were considered to have perceived contraindications if they had systolic blood pressure < 90mmHg, serum creatinine level of ≥ 221μmol/L (≥ 2.5mg/dL) or serum potassium level of ≥ 5.5mmol/L on admission, or evidence of severe aortic stenosis. Patients with perceived contraindications were less likely to be discharged on ACE inhibitors.
(40% vs. 68%; p<0.001) and had poorer prognosis. Patients with perceived contraindications were twice as likely to die within one year following discharge (adjusted hazard ratio [HR]=1.66; 95% CI: 1.08–2.54). However, use of ACE inhibitors in these patients was associated with a significant 66% reduction in one-year mortality (HR=0.34; 95% CI: 0.14–0.81).

Worsening renal function after initiation of ACE inhibitors is another reason these agents are often held or discontinued. Older adults with SHF who are treated with an ACE inhibitor are likely to demonstrate some rise in serum creatinine. Older adults with SHF who also suffer from renal dysfunction are especially prone to rise in serum creatinine upon therapy with an ACE inhibitor (Figure 1). The rise of serum creatinine in response to ACE inhibitors has been compared with drop in heart rate in response to BBs, and is supported by the fact that serum creatinine levels return to normal when the ACE inhibitor is held. Patients should be advised to avoid non-steroidal anti-inflammatory drugs. Doses of diuretics may need to be adjusted if there is evidence of over-diuresis. However, lowering the dose of diuretics in the absence of over-diuresis or dehydration may result in worsening symptoms.

ACE inhibitors should be started at the lowest available doses in older adults with SHF, and doses should be increased gradually and cautiously. Older adults with SHF often cannot tolerate maximum doses of ACE inhibitors used in clinical trials, and this should not be a concern. Instead, every attempt should be made to achieve and maintain a euvolemic state so that a BB can be initiated as soon as possible. Most patients in BB trials with SHF were not receiving ACE inhibitors in maximal doses, and yet they benefited from an additional 35% reduction in risk of death. In a study of 1,532 patients with SHF (mean age 70), mortality at six months for patients receiving 5mg, 10mg and 20mg enalapril daily were 4%, 3% and 3% respectively, all of which were not statistically significant. Use of lower doses of ACE inhibitors is also less likely to be associated with rise of serum creatinine.

Older adults with SHF also are more likely to develop orthostatic hypotension and hyperkalemia in response to therapy with an ACE inhibitor. ACE inhibitors with shorter half-lives, such as captopril, are more likely to cause hypotension in response to initiation of therapy. Therefore, ACE inhibitors with longer half-lives may be more preferable in older adults with SHF. There is currently no evidence that older adults with SHF are at risk for excess mortality with ACE inhibitors. However, it is important to note that patients with SHF and renal dysfunction may have a higher risk of adverse effects with certain ACE inhibitors, particularly those with shorter half-lives.

### Table 2: Comparison of Starting and Target Doses and Pharmacokinetic Properties of ACE Inhibitors Known to Improve Survival in Randomized Controlled Trials and Commonly Used in Systolic Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Target dose</th>
<th>Half-life (in normal renal function)</th>
<th>Half-life (in renal failure)</th>
<th>Route of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>12.5mg t.i.d.</td>
<td>50mg t.i.d.</td>
<td>&lt; 2 hours</td>
<td>3.5–32 hours</td>
<td>95% in urine</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5mg o.d.</td>
<td>10mg b.i.d.</td>
<td>13 hours</td>
<td>prolonged</td>
<td>60–80% in urine with some fecal elimination</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5mg o.d.</td>
<td>20–40mg o.d.</td>
<td>12 hours</td>
<td>prolonged</td>
<td>100% urine</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5mg o.d.</td>
<td>5mg b.i.d.</td>
<td>13–17 hours</td>
<td>prolonged</td>
<td>60% urine, 40% feces</td>
</tr>
</tbody>
</table>

**Figure 1:** Projected possible rise in serum creatinine levels in patients with heart failure and impaired renal function treated with angiotensin-converting enzyme (ACE) inhibitor, based on data from subjects with normal renal function, patients with impaired renal function, and those with heart failure and normal renal function. Published with permission from Ahmed, 2002.
an increased risk for developing hypersensitivity reactions, such as angioedema and cough. Serum creatinine and potassium levels should be monitored within two weeks of initiating therapy, and periodically thereafter. A summary of practical tips for prescribing ACE inhibitors in older patients with SHF is given in Table 1.

**Beta-Blockers**

All older adults with SHF who are clinically asymptomatic and stable, have no evidence of fluid overload, are receiving an ACE inhibitor and have no contraindications to use of BBs, should be prescribed either carvedilol or metoprolol extended release (Table 3). Even though bisoprolol also has been shown to improve survival, only carvedilol and metoprolol extended release have been approved by the U.S. Federal Drug Administration for use in SHF. Furthermore, bisoprolol is eliminated renally and should be used cautiously in those with creatinine clearance < 40 mL/min, which is common in older adults. The use of and evidence for BBs in older adults with SHF has been discussed in a separate article in this issue (page 28). However, we will emphasize some key points.

Most patients in BB trials in SHF were already receiving an ACE inhibitor, but not in the high doses used in ACE inhibitor trials. Yet, use of BBs resulted in about 35% further reduction in mortality. The key message from these trials is that BBs must be initiated in all patients with SHF who are already on ACE inhibitors, and there is no need to wait before the dose of ACE inhibitor can be optimized. This is one of those clinical decisions that need not be influenced by concerns for polypharmacy, which is often a legitimate concern in geriatric practice. Like ACE inhibitor trials in SHF, BB trials in SHF also excluded older adults. However, subgroup analyses of the BB trials suggest that BBs are as effective in older adults with SHF as they are in younger adults.25,26

Carvedilol is a non-selective beta- and alpha-blocker. One of its potential adverse effects in older adults is orthostatic hypotension and dizziness. Taking carvedilol with food is likely to decrease the potential for these adverse effects. If patients still remain hypotensive, the dose of the ACE inhibitor may be temporarily reduced, the timing of BB and ACE inhibitor may be separated, or carvedilol may be switched to metoprolol succinate. Serum concentrations of carvedilol are 50% greater in older adults, but no dose reductions are recommended due to decreased pharmacodynamic responsiveness to the beta-adrenergic system. Dose should be started at 3.125 mg twice daily and titrated slowly every two weeks to maximal effective dose or maximum of 25 mg twice daily.

Metoprolol is a beta-1 selective antagonist and is associated with fewer incidences of hypotension compared to carvedilol. Metoprolol succinate is a sustained release formulation and thus can be given once daily. Food will increase the potential for adverse reactions. This is more likely in patients who are poor metabolizers of CYP2D6 substrates such as BBs. Rifampin, which induces CYP2D6, decreases levels of carvedilol by 70% and metoprolol by 40%.

If carefully started, older adults with SHF are likely to tolerate BBs well. Common adverse effects include fatigue, bradycardia, hypotension, heart block, fluid overload and shortness of breath. With basic patient education, these side effects can be managed rather efficiently. Patients should be advised to monitor daily weight, pulse and blood pressure, and advised to call if they gain 2–3 lbs in two to three days, have a pulse rate < 50 or systolic blood pressure < 90 mmHg, or if they have worsening dyspnea or fatigue. These symptoms often can be managed by adjusting the dose of ACE inhibitor or diuretic, and BBs rarely need to be discontinued. Patients should be referred to cardiologists if physicians are not familiar or comfortable in starting BBs or managing adverse effects.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Target dose</th>
<th>Route of elimination</th>
<th>Primary CYP450 enzymes</th>
<th>Plasma protein binding</th>
<th>Lipid solubility</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>3.125mg b.i.d. (with food)</td>
<td>25mg b.i.d.</td>
<td>hepatic</td>
<td>2D6</td>
<td>98% (to albumin)</td>
<td>moderate</td>
<td>7–10</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5mg o.d.</td>
<td>200mg o.d.</td>
<td>hepatic/renal</td>
<td>2D6</td>
<td>8%</td>
<td>moderate</td>
<td>3–7</td>
</tr>
</tbody>
</table>

*Table 3: Comparison of Starting and Target Doses and Pharmacokinetic Properties of Beta-blockers Approved for and Commonly Used in Systolic Heart Failure*
Angiotensin II Receptor Blockers

ARBs are recommended for patients with SHF who cannot tolerate an ACE inhibitor. Recent data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) and Valsartan in Acute myocardial Infarction (VALIANT) trials suggest that ARBs, like ACE inhibitors, are effective in reducing morbidity and mortality in patients with SHF. Since large numbers of patients were enrolled in ACE inhibitor trials in SHF and due to many years of post-trial use, it is unlikely that guideline recommendations will soon change in favour of ARBs. However, the data from these recent studies clearly indicate that SHF patients who are intolerant of ACE inhibitors and are receiving alternate therapy with an ARB are likely to receive equal survival benefit.

It is not yet apparent whether ARBs should be added to the therapy of SHF patients who are already receiving an ACE inhibitor and a BB. For instance, VALHeFT indicated that the combined use of ARB, ACE inhibitor and BB resulted in increased mortality in SHF patients. In the VALIANT trial, combined use of ARB and ACE inhibitor increased adverse effects without further reducing mortality. However, in the CHARM-Added Trial, use of an ARB (candesartan) in SHF patients already receiving an ACE inhibitor and a BB reduced mortality.

Because many SHF patients are not receiving ACE inhibitors, and many more are not receiving BBs, the issue of combined use of ARB, ACE inhibitor and BB is merely theoretical. For all practical purposes, primary care physicians caring for older adults with SHF should make every attempt to start ACE inhibitors and BBs, and may defer the decision to start an ARB to a cardiologist.

Currently, candesartan and valsartan are the only ARBs with data supporting their benefit in SHF. Candesartan is eliminated renally and dose adjustments are necessary in patients with renal impairment. While the manufacturer states that no dose adjustment is necessary in older adults, higher serum concentrations are found in older adults. Therefore, it may be necessary to titrate the initial dose of an ARB to a lower initial dose in older adults. One can start ARBs at lower doses for older adults with no dose adjustment in older adults. Therefore, it may be necessary to titrate the initial dose of an ARB to a lower initial dose in older adults. While the manufacturer states that no dose adjustment is necessary in older adults, higher serum concentrations are found in older adults. Therefore, it may be necessary to titrate the initial dose of an ARB to a lower initial dose in older adults.

Table 4: Practical Tips for Use of Beta-blockers in Older Adults with Systolic Heart Failure (SHF)

1. Prescribe BB to all asymptomatic euvolemic older adults with SHF unless an absolute contraindication to the use of BB exists.
2. Absolute contraindications to the use of BB are advanced heart block and symptomatic bradycardia.
3. Beta-1 selective blocker such as metoprolol succinate extended release may be cautiously used in patients with reactive pulmonary disease such as bronchial asthma.
4. Chronic obstructive pulmonary disease is not a contraindication.
5. Carefully examine jugular venous distension to rule out fluid overload before initiating BB or increasing its dose.
6. Become familiar with the commonly used BBs, carvedilol or and metoprolol succinate extended release.
7. Use the BB approved for use in HF.
8. Start at the lowest possible dose, and if necessary use half the starting dose for younger adults.
9. Carvedilol 0.375mg (lowest available preparation) is an elongated caplet and difficult to break in half.
10. Metoprolol succinate extended release 25mg (lowest available preparation) is a scored tablet that can be broken along the scored line without compromising the slow-release mechanism, and may be preferable for frail older adults and those with low baseline blood pressure.
11. Advise patients to monitor weight, blood pressure and pulse rate daily.
12. Educate patients and family members to take an extra dose of diuretic if they gain 1–2 kg (2–3 lbs) of weight in 2–3 days. The extra dose should be taken until the baseline weight is regained. If that is not achieved in 2–3 days, advise them to call their physicians.
13. Advise patients to call if they experience worsening dyspnea, fatigue or dizziness, or have systolic blood pressure < 90 or pulse rate < 50.
14. Re-evaluate patients every 2 weeks, and if there is no evidence of fluid overload or adverse effects, increase the dose of the BB every two weeks, with a goal of doses used in clinical trials.
15. If dyspnea worsens or fluid overload is observed after initiating or increasing the dose of BB, try increasing the dose of diuretic instead of decreasing the dose of BB.
16. If blood pressure drops, make sure carvedilol is being taken with food, adjust doses of other antihypertensive medications or separate their timing. Systolic blood pressure in the 90s may be acceptable if not associated with symptoms. Educate patients about the risk of orthostatic hypotension and advise how to avoid falls.
17. If heart rate drops and patients are symptomatic, refer to cardiologist.
18. Refer patients to cardiologist if you are not comfortable starting or maintaining BB or managing its side effects.
19. Remember BB is as important as ACE inhibitor in managing SHF.
20. With some self-education and careful patient evaluation, generalist physicians caring for older adults with SHF should be able to start BB in their SHF patients.
be sensible to reduce the starting dose of candesartan to 4mg daily and titrate slowly every two weeks to the maximal tolerated dose or to a target dose of 32mg daily.Valsartan is eliminated via biliary system as unchanged drug (83% unchanged drug in urine). Therefore, dose adjustment in renal impairment or in older adults is not necessary. The starting dose of valsartan is 80mg daily with titration to 80mg twice daily in two weeks with second titration to 160mg twice daily in two more weeks. However, dose should be adjusted in patients with mild to moderate hepatic impairment with dose not to exceed 80mg daily.Valsartan is not recommended in patients with severe hepatic impairment.

Side effects of the ARBs are similar to those observed in ACE inhibitors, with the exception of cough. Adverse effects include hypotension, hyperkalemia, and dysgeusia (which is often more pronounced in older adults). Valsartan also may increase liver transaminases, but levels return to baseline following discontinuation of therapy, thereby suggesting that valsartan does not induce irreversible hepatotoxicity.

Diuretics
Most SHF patients will need diuretics to maintain their fluid balance. The role of diuretic is very important for two reasons. First, it is essential to produce and maintain euvolemia, which is closely related to quality of life of patients with SHF. Secondly, a state of euvolemia is the prerequisite for initiation of BB therapy, which has enormous life-saving benefit. Many SHF patients require very high doses of these diuretics as some point in the disease process and some will require routine high doses.

Furosemide is the most commonly used diuretic and most clinicians find it useful to be familiar with one or two diuretics. Most patients will be euvolemic at doses between 80mg and 160mg a day. Many patients will require doses such as 240mg or higher. At this dosage, it is preferable to give furosemide twice a day, and the second dose should be given not after 3 p.m. to reduce the nocturia and sleep disturbance. The highest recommended dose of furosemide is 400mg daily. The equivalent highest doses of the other two loop diuretics torsemide and bumetanide are 200mg and 10mg daily, respectively. Many clinicians prefer to add a second diuretic, preferably a thiazide diuretic such as hydrochlorothiazide 12.5–25mg daily or metolazone 2.5–5mg daily, instead of increasing the dose of the loop diuretic beyond a moderate dose, such as furosemide 160mg daily. Combined use of a loop and a thiazide diuretic is often associated with significant electrolyte imbalance, such as hyponatremia and hypokalemia. Therefore, close monitoring is warranted. Mild hyponatremia often resolves with restricting fluid intake to < 1L a day; however, if severe, hyponatremia will require reducing the dose of the thiazide diuretic or stopping it, and appropriate increase in the dose of the loop diuretic. Hesitation on the part of clinicians to increase the dose of diuretics often results in unnecessary suffering for older adults with SHF.

Conclusion
SHF is a complex syndrome with rapidly evolving pharmacological treatment options and poor prognosis. Most SHF patients are older adults. Most SHF patients also receive care from generalist physicians. Both age and care by generalist physicians have been associated with lower rates of ACE inhibitor use. Even though there is no data on BB use in SHF, the utilization rates are likely to be even lower. Yet, these two life-saving drugs have revolutionized therapy for SHF. By familiarizing with one or two national guidelines for HF,11,12 and by careful and thorough evaluation of patients, all generalist physicians should be able to start ACE inhibitors and BBs in older adults with SHF. Physicians unfamiliar with the use of these drugs or uncomfortable using them in older adults with SHF must refer them to a cardiologist. ◆

References


