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Chronic Heart Failure – Diagnosis and Management

Effective Date: October 28, 2015

Scope

This guideline provides strategies for the improved diagnosis and management of adults aged ≥ 19 years with chronic heart failure (HF) in the primary care setting.

Key Recommendations

- B-Type natriuretic peptide (BNP) **OR** N-terminal prohormone of BNP (NT-proBNP) is the biochemical test of choice for ruling-in or ruling-out the diagnosis of HF and should be considered as part of the initial evaluation of patients with dyspnea suspected of having HF. **[Amended, 2015]**
- BNP (or NT-proBNP) testing should not be used routinely for monitoring disease severity. **[New, 2015]**
- Educate the patient and family about the importance of self-monitoring to identify early decompensation at a stage where intervention may help to avoid hospitalization. Consider referral to a Heart Function Clinic or a multi-disciplinary chronic disease management clinic. **[Amended, 2015]**
- Identify who would benefit from a palliative care assessment by using the iPall – Heart Failure: Palliative Care Assessment Tool. Initiate advance care planning discussions early in the disease course. **[Amended, 2015]**
- The goals of pharmacologic management for HF patients with preserved ejection fraction (HF-pEF) are to control heart rate, blood pressure and volume status, as no medications have shown a mortality benefit in this patient group. **[New, 2015]**
- For patients with reduced ejection fraction (HF-rEF) there is robust mortality data to support the use of pharmacological and device therapies. These treatments have also been shown to improve symptom status, quality of life and decrease the risk of HF-related hospitalization. **[New, 2015]**

Definition

HF is a clinical syndrome defined by signs and symptoms suggestive of impaired cardiac output, volume overload or both. The measurement of left ventricular ejection fraction (LVEF) assists in the classification of a HF patient as having HF-pEF (EF ≥ 40%) or HF-rEF (EF < 40%). This distinction provides prognostic information and guides the clinician in identifying who will benefit from evidence-based treatment strategies. Though there is variability in reporting EF based on modality, the general cut off for treatment of HF-rEF is < 40%; however, this needs to be customized based on the individual patient.

Diagnosis

The diagnosis of HF is difficult because many of the signs and symptoms are neither sensitive nor specific. This is especially true when HF is in the early stages, when evaluating women, obese patients, the elderly or those with chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD).

To help identify those patients at-risk for HF, there is a spectrum of co-morbidities that may predict the future development of HF. These include: hypertension, diabetes, and prior myocardial infarction. A review of new HF cases in BC suggests that 80% of individuals were previously diagnosed with hypertension, 40% with diabetes, and 45% with ischemic heart disease. On average, these co-morbidities were apparent 8, 6 and 4 years before their diagnosis of HF, respectively.[2]

To confirm the diagnosis of HF, conduct a thorough medical history, physical examination and initial investigations (see Table 3). Use this information to identify potential causes for a patient's HF, any relevant co-morbid conditions or precipitating factors, and to serve as a baseline when assessing the impact of HF therapies.

Medical History & Physical Examination

Table 1. Risk factors, comorbidities, symptoms and signs for heart failure

1) Ask about and/or identify:	
Risk Factors and/or comorbidities	**Symptoms (current and past)**
• hypertension • diabetes • family history of cardiomyopathy or sudden death • sleep apnea • cardiovascular disease (e.g., valvular heart disease, coronary artery disease, atrial fibrillation) • smoking • alcohol or substance abuse (current or past) • age (> 60 years) • thyroid disease • COPD • CKD • anemia	• breathlessness • fatigue • swelling of the lower extremities • confusion • paroxysmal nocturnal dyspnea • orthopnea and paroxysmal nocturnal dyspnea • swelling and/or abdominal bloating • reduced appetite • decreased exercise capacity

2) Assess for:		
Signs of volume overload	**Signs of low cardiac output**	**Functional limitation**
• weight gain (2 kg over two days or 2.5 kg in one week) • elevated jugular venous pressure • peripheral edema • extra heart sounds • displaced apex • pulmonary crackles • educed oxygen saturation • ascites	• hypotension • tachycardia • pallor and/or cyanosis	• using the New York Heart Association (NYHA) functional classifications (Table 2)

Table 2. New York Heart Association (NYHA) functional classifications[3]

Class	Degree of Symptoms with Physical Activity and at Rest
I – mild	Asymptomatic with ordinary physical activity, no limitations on physical activity, and comfortable at rest
II – mild	Symptoms with ordinary activity, slight limitations on physical activity, and comfortable at rest
III – moderate	Symptoms with less than ordinary activity, noticeable limitations on physical activity, and comfortable at rest
IV – severe	Symptoms at rest, unable to perform any activity

Investigations

Table 3. Initial investigations to support the diagnosis and guide heart failure management

Imaging
• **Echo**: In HF patients, echo is considered the gold standard to measure LVEF and to assess for structural heart disease and diastolic function.
• **Chest radiograph**: May be considered in the context of the patient (e.g., those with co-morbid conditions).
Blood
• **BNP (or NT-proBNP)**: Considered to be the biochemical test of choice for ruling-in or ruling-out the diagnosis of HF.
• **Serum creatinine, BUN & electrolytes**: Useful to guide selection of pharmacologic therapy.
• **Thyroid stimulating hormone (TSH)**: Useful to recognize a readily reversible cause of HF.
• **Complete blood count (CBC)**: Useful for a number of reasons including diagnosis of anemia.
Other
• **Electrocardiogram (ECG) standard 12-lead**: The results are important for treatment decisions (e.g., presence of atrial fibrillation, evidence of prior infarction, bundle branch block). A normal ECG does not rule out a HF diagnosis; however a normal ECG makes HF-rEF less likely.
• **Cardiovascular disease risk assessment**: Framingham Risk Score or www.bestsciencemedicine.com/chd/calc2.html. Refer to BCGuidelines.ca – *Cardiovascular Disease – Primary Prevention*.

BNP Testing

BNP and NT-proBNP have similar clinical utility. Either biomarker can be used for diagnostic purposes, however results from the two assays are not comparable. Both tests have a high-sensitivity for the detection of HF. A low result (i.e., <100 for BNP or <300 for NT-proBNP) for either test is associated with a high negative predictive value for the clinical syndrome of HF, while elevated values (i.e., > 400 for BNP or > 450–1800, depending on age, for NT-proBNP) have a high positive predictive value for the diagnosis of HF. BNP (or NT-proBNP) testing for confirmation of a HF diagnosis is recommended if there is diagnostic uncertainty and/or there is an anticipated delay in obtaining a timely echo. At present, BNP (or NT-proBNP) testing should not be used routinely for monitoring HF disease severity. Refer to Appendix A: *Natriuretic Peptide Testing for Heart Failure in the Primary Care Setting* for further information.

LVEF Imaging

The Canadian standard is to have LVEF measured within 30 days of a HF diagnosis; however due to waitlists and regional variations in access, echo assessment of LVEF may not be feasible in all parts of BC. Within this context, LVEF measurement may also be obtained by:

- Thallium and Sestamibi (MIBI) scan – especially in those patients where ischemia may be the underlying etiology of the patient's HF; and/or
- Multi Gated Acquisition Scan (MUGA) or radionuclide angiography – especially for patients with COPD or obesity which may affect echo image quality; or in those who require precise assessment of LVEF for consideration of advanced HF therapies (e.g., defibrillator or cardiac resynchronization therapy).

Management within the Primary Care Setting

- Patients with HF benefit from an interdisciplinary approach to their care.
- For follow-up visits, consider using the patient questionnaire, assessment and information forms from the BC Heart Failure Network (website: www.bcheartfailure.ca).

1. Lifestyle Management and Self-Monitoring

HF care depends on the patient's understanding of, and participation in, optimal care. Educate the patient and their care givers about the HF Zones (see Figure 1) and lifestyle management (see Table 4). Patient educational materials are available from the BC Heart Failure Network (website: www.bcheartfailure.ca). For further assistance, refer the patient to a Heart Function Clinic or a multi-disciplinary chronic disease management clinic.

Figure 1. Heart failure zones reference guide

Table 4. Canadian-consensus based lifestyle and self-monitoring recommendations

Weight monitoring	Have the patient record their daily weight using a daily weight monitoring sheet (available at website: www.bcheartfailure.ca). A weight gain of 2 kg over two days or 2.5 kg in one week should be reported to a healthcare provider. Review recommendations for salt and fluid intake as per below.
Salt intake	Limit sodium intake to the goal of < 2000 mg per day.
Fluid intake	Limit fluid intake if patient reports symptoms of congestion, if there are signs of fluid overload, or if patient is on diuretics. The recommended total amount of fluid intake per day is 1.5–2 litres.
Alcohol	Limit alcohol consumption to no more than 1 drink per day. If the patient's HF is felt to be secondary to alcohol, alcohol must be strictly avoided. If alcohol abuse is suspected, refer to BCGuidelines.ca – *Problem Drinking* for screening and assessment information
Smoking	Stop smoking. For assistance, refer to Quitnow, website: www.quitnow.ca.
Physical activity	If stable symptoms and volume status, the goal is 30 minutes of continuous moderate exercise (e.g., you have enough breath to carry on a conversation), and weight-bearing/resistance and flexibility activities at least twice a week. Consider referral to a cardiac rehabilitation program where available. To find a program in BC, contact HealthLink BC at 8-1-1, website, www.healthlinkbc.ca (search 'cardiac rehabilitation' on the 'Find Services' box).
Immunization	Encourage an annual influenza vaccine. It is recommended that all patients receive a one-time only pneumococcal polysaccharide vaccine.
Advance care planning	Initiate advance care planning discussions early in the disease course and particularly when symptoms and/or functional status declines despite maximal medical therapy. Tools include: iPall – Heart Failure: Palliative Care Assessment Tool (available at www.bcheartfailure.ca/) and the Ministry of Health's advance care planning guide My Voice – Espressing My Wishes for Future Health Care Treatment is available at website: www.health.gov.bc.ca – under Advance Care Planning.

2. Pharmacologic Management

For all patients, review medications for intended and unintended effects (e.g., inappropriate polypharmacy, potential drug-drug interactions, and inadvertent aggravation of comorbid conditions) and consider changing or discontinuing medications as needed. Avoid the use of nonsteroidal anti-inflammatory drugs (NSAIDs, COX-2 inhibitors, not including low dose ASA), as their use may worsen the symptoms of HF. For more information on medications including dosage amounts and side effects, refer to *Appendix B: Commonly used Drugs in Heart Failure Care*.

In HF patients, EC-ASA (81 mg) and statins may be considered if there is a clear indication for secondary prevention of cardiovascular events.

2a. *Heart Failure with Preserved Ejection Fraction (EF ≥ 40%)*

For patients with HF-pEF the goals of pharmacologic management are to optimize risk factors for disease progression/decompensation, and control signs/symptoms of HF (e.g., heart rate, blood pressure, volume status). There are currently no therapies with demonstrated mortality benefit in patients with HF-pEF.

Medications to relieve symptoms:

Angiotensin Converting Enzyme Inhibitors (ACE-I) or Angiotensin II Receptor Blockers (ARB; Special Authority required)

- May be used in HF-pEF patients who have other indications for their use (e.g., hypertension and nephropathy).
- Serum creatinine may increase by up to 30% in many HF patients with initiation of an ACE-I or ARB. There is no concern if the increase stabilizes at ≤ 30%, though consider closer long-term monitoring.

Beta-blockers or Calcium Channel Blockers (CCB)

- May be used to either control heart rate or to lower blood pressure.
- No specific beta-blocker is indicated for patients with HF-pEF.
- Use a non-dihydropyridine CCB (e.g., diltiazem or verapamil) if needed to control heart rate.
- In patients with HF-pEF complicated by atrial fibrillation, who remain tachycardic despite beta-blocker therapy or CCB alone, consider the addition of digoxin.

Mineralocorticoid Receptor Antagonists (MRA; also known as aldosterone receptor antagonists)

- Spironolactone may be considered in patients with HF-pEF, increased BNP levels, serum potassium < 5.0 mmol.L, and eGFR ≥ 30 mL/min.
- Monitor serum potassium and creatinine once spironolactone has been started or change of dose at week 1, week 4 and month 4, or whenever clinically indicated.

Diuretics

- Furosemide may be used to control symptoms of volume overload. When congestion has cleared, use the lowest dose needed to maintain euvolemia.
- Use with caution as excessive diuresis may cause postural hypotension and compromise renal function.

2b. *Heart Failure with Reduced Ejection Fraction (EF < 40%)*

For patients with HF-rEF, the goals of therapy are to reduce mortality/morbidity, control signs/symptoms (e.g., heart rate, blood pressure, volume status), optimize cardiac geometry and function, and prevent HF-related hospital admissions.

Table 5. Mortality reductions based on medication for heart failure-reduced ejection fraction

Medication	ACE-I	Beta-blocker	MRA	ARB
Mortality Reduction	8%–26%	23%–65%	24%–35%	15%

Abbreviations: ACE-I = Angiotensin Converting Enzyme Inhibitors; ARB = Angiotensin II Receptor Blockers; MRA = Mineralocorticoid Receptor Antagonists (also known as aldosterone receptor antagonists).

For a therapeutic algorithm based on symptom and functional status, refer to *Associated Documents: Therapeutic Approach to Patients with Heart Failure and Reduce Ejection Fraction* from the Canadian Cardiovascular Society (CCS).

Medications to improve mortality/morbidity:

ACE-I or ARBs (Special Authority required)

- Consider initiating an ACE-I (or ARB, if ACE-I intolerant) while diuretic therapy is being optimized (e.g., while patient is wet). Start with low doses and titrate towards the target dose or the maximum dosage tolerated at one to two-week intervals.
- ARBs have not been shown to be superior to ACE-I.

- Serum creatinine may increase by up to 30% in many HF patients with initiation of an ACE-I or ARB. There is no concern if the increase stabilizes at ≤ 30%, though consider closer long-term monitoring of renal function.
- Low blood pressure is a common side effect when using an ACE-I or ARB. Consider reducing diuretic dose only if the patient experiences symptomatic hypotension AND is clinically euvolemic. Consider staggering vasoactive medications if patient is still symptomatic.

Beta-blockers

Initiate a beta-blocker once the patient is established on an ACE-I or ARB and patient is clinically euvolemic. Start with low doses and titrate towards the target dose or the maximum dosage tolerated at one to two-week intervals.

- Inform the patient that they may experience an increase in fatigue for a couple of weeks before improvement is noted.
- Carvedilol (Special Authority required) and bisoprolol are the indicated and available beta-blockers for patients with HF-rEF, as both have been shown reduce mortality and are available in Canada. Metoprolol tartrate is available in Canada, but has not been shown to reduce mortality in patients with HF.
- If patient is currently on another beta-blocker (including metoprolol), consider a therapeutic switch to carvedilol or bisoprolol.
- Reassess the dose of beta-blockers in patients with symptomatic hypotension after other potential causes of hypotension have been addressed, those with symptomatic bradycardias or resting heart rate of less than 50, and those that may have a clinical history of severe reactive airway disease.
- Patients with COPD tend to tolerate beta-blockers well. Beta-blockers have been shown to reduce mortality in meta-analyses of HF patients with COPD.

Mineralocorticoid Receptor Antagonists (MRAs; also known as aldosterone receptor antagonists)

- An MRA is recommended for those with NYHA class II – IV symptoms and an EF ≤ 35%, and with serum potassium < 5.0 mmol/L and eGFR ≥ 30 mL/min.
  - Use eplerenone (not covered by PharmaCare) for those patients with
    i. NYHA class II-III symptoms and LVEF ≤ 30%
    ii. NYHA class II-III symptoms, LVEF 30–35% and QRS duration > 130 ms on ECG
  - Use spironolactone for those patients with NYHA class III–IV symptoms.
- **Unsupervised use of a MRA may cause life-threatening hyperkalemia or renal insufficiency**. Monitor vital signs, serum creatinine and potassium at 3 and 7 days after initiating or titrating the dose and repeat as needed until potassium levels and renal function are stable. Monitoring should then be done monthly for 3 months and every 3 months thereafter. More frequent monitoring may be considered during any dehydrating illness or conditions in which renal function can worsen.

Isosorbide dinitrate and Hydralazine

- Consider the combination of isosorbide dinitrate and hydralazine as an alternative to an ACE-I or ARB, for black patients or for non-black patients unable to tolerate an ACE-I or ARB (e.g., patient with renal failure).

Medications to relieve symptoms:

Diuretics

- Use a loop diuretic (e.g., furosemide) to relieve congestive symptoms. When congestion is cleared, use the lowest dose of diuretic needed to maintain euvolemia.
- A second diuretic (e.g., metolazone) may be cautiously introduced for patients with persistent volume overload despite optimal medical therapy and maximal doses of loop diuretic as long as it is possible to closely monitor morning weight, renal function, and serum potassium.
- Higher doses of diuretics may be needed in patients with significant renal dysfunction, those with gross volume overload, or poor nutritional status.
- Patients on long term diuretic therapy may develop tolerance to diuretics necessitating higher doses in the face of fluid overload or disease decompensation.

Digoxin

- In the absence of any mortality benefit, digoxin is no longer considered a first-line therapy for HF patients even though it has been shown to relieve symptoms and reduce hospitalizations.
- It may be used in patients with sinus rhythm who continue to have moderate to severe HF symptoms despite optimally tolerated mortality driven therapy.
- It may be used in patients with atrial fibrillation who have poor control of ventricular rate despite optimal beta-blocker therapy or where beta-blockers are contraindicated.
- Pay close attention to the risk of digoxin toxicity. Monitor digoxin, potassium, and creatinine levels when changing digoxin or diuretic dosages, when adding or discontinuing drugs with potential interactions, or during a dehydrating illness.
- Use of digoxin in patients with CKD should be approached with caution unless renal function is stable and patient is symptomatically benefited.

Emerging Therapies:

Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

ARNI is a new class of medications for the treatment of HF-rEF, which both blocks angiotensin receptors and inhibits the enzyme neprilysin resulting in higher endogenous levels of vasoactive peptides (e.g., natriuretic peptides, bradykinin, and adrenomedulin). Entresto is a combination product containing sacubitril, a neprilysin inhibitor, and valsartan. In a recent landmark clinical trial4 patients treated with Entresto had a lower risk of cardiovascular death and first hospitalization compared to patients using enalapril. Entresto has recently been approved for the treatment of HF by Health Canada but at this time the cost and timelines for availability are unknown.

Ivabradine

Ivabradine is a selective sinus node inhibitor recently approved by the European Medicines Agency and the US Food and Drug Administration for HF-rEF patients with persistent functional limitations and who are in sinus rhythm with a resting heart rate of at least 75 beats per minute despite optimally tolerated beta-blocker therapy. In the SHIFT study, ivabradine significantly reduced the risk of the primary endpoint, a composite of cardiovascular death or hospital admission for worsening heart failure, by 18% compared to placebo.[5] The effects were mainly driven by decreased hospital admissions for worsening heart failure compared to placebo. At this time, ivabradine has not been approved by Health Canada and the cost is unknown.

2c. *Indications for Referrals*

To a Cardiologist/Internist for:

- Further direction on how to medically manage the patient when needed
- Persistent symptoms or signs of HF despite attempts at optimizing medical therapy
- Management of HF where valvular disease or coronary disease is a significant contributing factor

To a Heart Function Clinic for:

- Management after a recent admission or repeated admissions to hospital
- Assessment of asymptomatic left ventricular dysfunction
- Assistance with multidisciplinary HF care including education on lifestyle management skills
- Consideration for advanced therapies including PCI, surgery and implantable devices
- HF with persistent symptoms
- New diagnosis of HF

3. Device Management

Decisions about device management (e.g., implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT)) tend to be complex and require input from a cardiologist/internist/ cardiac electrophysiologist/Heart Function Clinic. Appropriate ICD utilization is associated with improved mortality, but it does not improve the patient's quality of life. By contrast, CRT is associated with improved mortality and quality of life (improved symptom status and

functional capacity).

Table 6. Mortality reductions based on device

Device	ICD	CRT
Mortality Reduction	8%–26%	23–65%

Abbreviations: ICD = implantable cardioverter defibrillator, CRT = cardiac resynchronization therapy.

ICD may be considered in patients with one of the following:

- History of hemodynamically significant sustained ventricular arrhythmia;
- Ischemic cardiomyopathy and LVEF ≤ 35% (measured at least 1 month after acute myocardial infarction, or 3 months post coronary artery revascularization); or
- Non-ischemic cardiomyopathy and LVEF ≤ 35% (measured at least 9 months after optimal medical therapy).

ICD should not be considered in patients with active NYHA Class IV symptoms.

CRT may be considered in patients with NYHA class II – IV symptoms despite maximally tolerated HF therapies, a QRS duration ≥ 130 ms, and LVEF ≤ 35%.

4. Practical Considerations for Other Clinical Conditions

A number of clinical conditions significantly influence the management of HF. Recommendations for other clinical conditions may be found using the CCS Heart Failure Compendium (type in the condition in the search box), website: www.ccs.ca/index.php/en/resources/heart-failure-compendium.

5. Palliative and End of Life Care

Identify who would benefit from a palliative care assessment by using the iPall – Heart Failure: Palliative Care Assessment Tool (available at www.bcheartfailure.ca/), which includes:

a. Ask yourself – would you be surprised if this patient died in the next 6–12 months?
b. Look for ≥ 1 general clinical indicator, which are poor/deteriorating status; multiple hospitalizations in the past 6 months; more care is needed; multiple co-morbidities causing symptoms and/or functional status decline.
c. Look closer for ≥ 2 disease related indicators, which are: NYHA class III–IV functional status; persistent symptoms despite maximal medical therapy; renal impairment; cardiac cachexia; markers of chronic inflammation/cachexia; ≥ 2 acute episodes needing intravenous (furosemide and/or inotropes) therapy in the last 6 months.

Once the decision to initiate end of life care is made, the goal of therapy is to manage pain, dyspnea, other symptoms, and quality of life. This may include providing support for the patient's family and caregivers. Consider referral to palliative care/hospice teams, if available.

- For more information, refer to BCGuidelines.ca – *Palliative Care for the Patient with Incurable Cancer or Advanced Disease* and BC Pharmacare's Palliative Care Benefits Program, website: www.health.gov.bc.ca.

References

References

1. Provincial Diagnostic Imaging Working Group. Summary report for the provincial heart failure steering committee. December 2013.
2. Ministry of Health. Descriptive statistical analysis for logistic modelling in heart failure. 2012.
3. The Criteria Committee of the New York Heart Association. (1994). *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* (9th ed.). Boston: Little, Brown & Co. pp. 253–256.
4. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371:993-1004.
5. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010 Sep 11; 376(9744):875–85.

Resources

- BC Heart Failure Network, www.bcheartfailure.ca/ – generates and shares accurate, current, and relevant HF information for health care professionals and patients in BC.
- RACE – Rapid Access to Consultative Expertise program – a telephone advice line from a selection of specialty services for general practitioners.
  - For Vancouver Coastal Health Region, www.raceconnect.ca or by telephone 604-696-2131 (Vancouver area) or 1-877-696-2131 (toll free); Monday to Friday, 8 am to 5 pm)
  - For Northern Health, www.northernpartnersincare.ca/northernrace/ or by telephone 1-877-605-7223
- BC Ministry of Health – Advance Care Planning, www.health.bc.ca. Each health authority also has an Advance Care Planning website.

Appendices

- Appendix A: Natriuretic Peptide Testing for Heart Failure in the Primary Care Setting
- Appendix B: Commonly used Drugs in Heart Failure Care

Associated Documents

The following documents accompany this guideline:

- Algorithm for Assessing and Treating Heart Failure – BC Heart Failure Network
- Therapeutic Approach to Patients with Heart Failure and Reduce Ejection Fraction – Canadian Cardiovascular Society
- Contact Information for Heart Function Clinics by Health Authority
- Heart Function Clinic Referral Form

This guideline is based on scientific evidence current as of the Effective Date.

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association, and adopted by the Medical Services Commission.

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- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

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Disclaimer

Appendix A: Natriuretic Peptide Testing for Heart Failure in the Primary Care Setting

What is BNP and NT-proBNP?

B-type natriuretic peptide (BNP) and N-terminal prohormone of BNP (NT-proBNP) are biomarkers that are measured from a simple blood test. Both tests have a high-sensitivity for the detection of HF. A low result (i.e., <100 for BNP or <300 for NT-proBNP) for either test is associated with a high negative predictive value for the clinical syndrome of HF, while elevated values (i.e., > 400 for BNP or > 450–1800, depending on age, for NT-proBNP) have a high positive predictive value for the diagnosis of HF (refer to Table 1 below). BNP (or NT-proBNP) levels can help identify symptomatic and asymptomatic left ventricular dysfunction. BNP and NT-proBNP have similar clinical utility. Either biomarker can be used for diagnostic purposes, however the results of these two assays are not comparable.

Is BNP Testing Payable by MSP?

The cost of the test is $42.56, and may be payable by Medical Services Plan (MSP) in the assessment of symptomatic patients where the diagnosis of HF remains in doubt after standard clinical assessment. Repeat testing is not payable for more than once annually unless ordered by the physician for a new clinical episode suspicious for HF or in the tertiary cardiac care outpatient setting for prognostic stratification of HF. It is also not payable for repeat testing for monitoring therapy.

What are the Indications for BNP (or NT-proBNP) Testing in the Primary Care Setting?[1]

The recommended indication for BNP (or NT-proBNP) testing in the primary care setting is:

- to confirm or exclude the diagnosis of HF. For moderately elevated BNP levels or '*HF Possible*', consider additional testing and alternative causes for elevated intracardiac filling pressures.

At this time, it is ***not recommended to routinely use BNP (or NT-proBNP) testing***:

- as a screening tool for asymptomatic patients; or
- for monitoring of disease severity.

What BNP (or NT-proBNP) Levels are Used in a Clinical Setting?

Table 1 outlines the suggested BNP and NT-proBNP concentrations that are of clinical importance in the diagnosis of HF.

Table 1. Suggested natriuretic peptide cut-off points for the diagnosis of heart failure[1]

	Cut-off points (pg/mL)					
	BNP			NT-proBNP		
	Age < 50	Age 50–75	Age > 75	Age < 50	Age 50–75	Age > 75
HF Unlikely	< 100			< 300		
HF Possible	100–400			300–450	300–900	300–1800
HF Very likely	> 400			> 450	> 900	> 1800

Routine echocardiography is not indicated for patients with '*HF Unlikely*' levels, unless they have been previously treated for HF or in whom the echo is intended to provide information regarding cardiac structures beyond ventricular function (e.g. valve disease, left ventricular hypertrophy). Consider alternative diagnoses for patients with '*HF Possible*' levels.

References

1. Canadian Agency for Drugs and Technologies in Health (CADTH). Brain Natriuretic peptide testing for Congestive heart failure: A review of the guidelines and clinical and cost-effectiveness. 2008.

Appendix B: Commonly used Drugs in Heart Failure Care[1, 2, 3]

Generic Name (trade name) (strengths and dosage form)	Adult Dosages	Cost per 30 days*	PharmaCare Coverage	Common Adverse Effects	Therapeutic Considerations & Contraindications	Drug Interactions
Angiotensin Converting Enzyme Inhibitors (ACE-I)						
ramipril Altace®, G (IR capsule: 1.25, 2.5, 5, 10 mg)	**Initial**: 1.25–2.5 mg BID **Target**: 5 mg twice BID **Max dose**: 10 mg BID	$8-12	Regular Coverage	Hypotension, hyperkalemia, dry cough, renal insufficiency, angioedema, skin rashes, taste disturbance, proteinuria, neutropenia, headache, dizziness.	Titrate dosage slowly by 50–100% every 2–4 weeks. Monitor serum creatinine and potassium 7–14 days after initiation of therapy or dose changes. **Contraindication**: Avoid in pregnancy.	Diuretics: hypotension. Potassium-sparing diuretics, potassium supplements, angiotensin receptors blockers: hyperkalemia. NSAIDs: reduced hypotensive effect, fluid retention, renal failure. Lithium: increased lithium levels and toxicity.
enalapril Vasotec®, G (IR tablet: 2.5, 5, 10, 20 mg)	**Initial**: 1.25–2.5 mg BID **Target**: 10 mg BID **Max dose**: 20 mg BID	$35	Regular Coverage			
captopril G (IR tablet: 6.25, 12.5, 25, 50, 100 mg)	**Initial**: 6.25–12.5 mg TID **Target**: 50 mg TID **Max dose**: 150 mg TID	$12–78	Regular Coverage			
lisinopril Prinivil®, Zestril®, G (IR tablet: 5, 10, 20 mg)	**Initial**: 2.5–5 mg once daily **Target**: 20–40 mg once daily **Max dose**: 80 mg once daily	$8–69	Regular Coverage			
perindopril Coversyl® (IR tablet: 2, 4, 8 mg)	**Initial**: 2 mg once daily **Target**: 8 mg once daily **Max dose**: 8 mg once daily	$17	Regular coverage			
trandolapril Mavik® (IR capsule: 0.5, 1, 2, 4 mg)	**Initial**: 0.5–1 mg once daily **Target**: 4 mg once daily **Max dose**: 4 mg once daily	$9–31	Regular coverage			

Generic Name (trade name) (strengths and dosage form)	Adult Dosages	Cost per 30 days*	PharmaCare Coverage	Common Adverse Effects	Therapeutic Considerations & Contraindications	Drug Interactions
Angiotensin Receptor Blockers (ARB)						
candesartan Atacand®, G (IR tablet: 4, 8, 16, 32 mg)	**Initial**: 4 mg once daily **Target**: 32 mg once daily	$9–10	Special Authority (IR tablet: 8, 16, 32 mg) No Coverage (IR tablet: 4 mg)	Hypotension, hyperkalemia, renal insufficiency, angioedema (rare, less frequent than with ACE-I), headache, dizziness.	Angioedema less frequent than with ACE-I. Monitor serum creatinine and potassium 7–14 days after initiation of therapy or dose changes. **Contraindication**: Avoid in pregnancy.	Diuretics: hypotension. Potassium-sparing diuretics and ACE-I: hyperkalemia. Potassium: hyperkalemia. NSAIDs: reduced hypotensive effect, fluid retention, renal failure. Lithium: increased lithium levels and toxicity.
losartan Cozaar®, G (IR tablet: 25, 50, 100 mg)	**Initial**: 12.5 mg once daily **Target**: 150 mg once daily	$5–$20	Special Authority			
valsartan Diovan®, G (IR tablet: 40, 80, 160, 320 mg)	**Initial**: 40 mg BID **Target**: 160 mg BID	$18–19	Special Authority			
Beta-Blockers						
carvedilol G (IR tablet: 3.125, 6.25, 12.5, 25 mg)	**Initial**: 3.125 mg BID **Target**: 25 mg BID if <75 kg 50 mg BID if >75 kg **Max dose**: 50 mg BID	$22–44	Special Authority	Orthostatic hypotension, worsening heart failure, worsening fluid retention, bronchospasm, dyspnea, bradycardia, malaise, fatigue, asthenia, erectile dysfunction, masking of symptoms of hypoglycemia.	Increase by 50–100% every 2 to 4 weeks. HF symptoms may get worse before they get better. More likely to cause orthostatic hypotension than bisoprolol.	Digoxin, amiodarone, diltiazem, and verapamil: brandycardia. Nondihydropyridine calcium channel blockers (e.g. verapamil and diltiazem): additive cardiodepressant effect. CYP2D6 inhibitors (e.g., SSRIs, bupropion, ritonavir, sertraline, St. John's Wort, citalopram, amiodarone): may increase carvedilol levels HF symptoms may get worse before they get better.
bisoprolol G (IR tablet: 5, 10 mg)	**Initial**: 1.25 mg once daily **Target**: 10 mg once daily **Max dose**: 20 mg once daily	$1–9	Regular Coverage			
Mineralocorticoid Receptor Antagonists (MRAs; also known as aldosterone receptor antagonists)						
spironolactone Aldactone®, G (IR tablet: 25, 100 mg)	**Initial**: 12.5 mg once daily **Target**: 25–50 mg/day (>25 mg/day rarely indicated)	$2–5	Regular Coverage	Hyperkalemia, dehydration, nausea, gynecomastia (usually reversible upon discontinuation).	Monitor serum creatinine and potassium 3 and 7 days after initiation or titrating the dose. Repeat every 1–3 months once stable. **Contraindications**: Pregnancy.	ACE-I, ARB, and potassium supplements: hyperkalemia. NSAIDS: reduced diuretic effect, worsening renal function, hyperkalemia.

Generic Name (trade name) (strengths and dosage form)	Adult Dosages	Cost per 30 days*	PharmaCare Coverage	Common Adverse Effects	Therapeutic Considerations & Contraindications	Drug Interactions
eplerenone Inspra® (IR tablet: 25, 50 mg)	**Initial**: 25 mg once daily or once every 2 days **Target**: 50 mg once daily	$43–86	No Coverage	Hyperkalemia, dehydration, dizziness, diarrhea, nausea.	Monitor serum creatinine and potassium 3 and 7 days after initiation or titrating the dose. Repeat every 1–3 months once stable. **Contraindications**: Use with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin, nefazodone): significant increases in eplerenone levels. Pregnancy.	ACE-I, ARB, and potassium supplements: hyperkalemia. NSAIDs: reduced diuretic effect, worsening renal function, hyperkalemia. Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin, nefazodone): significant increases in eplerenone levels. Strong inducers of CYP3A4 (e.g., carbamazepine, phenytoin, phenobarbital, St. John's Wort, refampicin): significant decreases in eplerenone efficacy.
Direct-Acting Vasodilators						
hydralazine G (IR tablet: 10, 25, 50 mg)	**Initial**: 10–25 mg TID **Target**: 75 mg TID to QID	$13–79	Regular Coverage	Hypotension, GI complaints, SLE-like syndrome, tachyphylaxis, may worsen oxygen demand.	Should be used in combination with isosorbide dinitrate or nitroglycerin.	
isosorbide dinitrate G (IR tablet: 10, 30 mg)	**Initial**: 10–20 mg TID **Target**: 40 mg TID to QID	$4–19	Regular Coverage	Headache, hypotension.	Should be used in combination with hydralzine.	Sildenafil, vardenafil and tadalafil: severe hypotension.
Diuretics						
furosemide Lasix®, G (IR tablet: 20, 40, 80 mg)	**Initial**: 20–40 mg/day once daily or BID **Max total daily dose**: 600 mg May be administered BID or TID for decompensated HF.	$1–107	Regular Coverage	Dehydration, hypokalemia, hypocalcemia, nausea, hypotension, azotemia, hypomagnesemia, anorexia, hyperglycemia, hyperuricemia, weakness, fatigue, rash, increased total cholesterol. Ototoxicity with high doses of furosemide.		Lithium: lithium toxicity. Digoxin: digoxin toxicity if K+ depleted. Oral corticosteroids: hypokalemia. NSAIDs: reduced diuretic effect, increased renal toxicity.
metolazone Zaroxolyn® (IR tablet: 2.5 mg)	**Initial**: 2.5 mg once daily **Max total daily dose**: 20 mg	$7–52	Regular Coverage			

Generic Name (trade name) (strengths and dosage form)	Adult Dosages	Cost per 30 days*	PharmaCare Coverage	Common Adverse Effects	Therapeutic Considerations & Contraindications	Drug Interactions
Digoxin						
digoxin Toloxin®, G (IR tablet: 0.0625, 0.125, 0.25)	0.0625–0.25 mg once daily in the evening. Lower doses may be appropriate in patients with low body mass or impaired renal function. Measure trough serum concentrations at least 8 hours after administration and adjust the dose to maintain the serum concentration between 0.6 and 1 nmol/L.	$8	Regular Coverage	Anorexia, nausea, vomiting, visual disturbances, fatigue, dizziness, confusion, delirium, cardiac arrhythmia.	May improve symptoms, exercise tolerance, and quality of life, but has not been shown to improve survival. Use only in patients with systolic HF. Electrolytes, creatinine, and digoxin serum concentrations should be obtained 5-7 days after dose adjustments.	Amiodarone, clarithyomycin, cyclosporine, erythromycin, itraconazole, propafenone, quinidine, ritonavir, tetracycline, and verapamil: increased digoxin serum levels. Antacids, cholestyramine, colestipol, neomycin, rifampin, St. John's Wort, and sulfasalazine: reduced digoxin serum levels. Amiodarone, beta-blockers, diltiazem, and verapamil: increased risk of bradycardia.

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blockers; BID = twice daily; G = generic; GI = gastrointestinal; HF = heart failure; IR = immediate-release; kg = kilogram; mg = milligram; NSAID = nonsteroidal anti-inflammatory drugs; QID = four times daily; SLE = systemic lupus erythematosus; SSRI = selective serotonin reuptake inhibitor; TID = three times daily.

Footnotes: Pricing is approximate as of May 1, 2015 and does not include dispensing fee or additional markups.

Note: Please review product monographs at hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php and regularly review current Health Canada advisories, warnings and recalls at www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index_e.html

PharmaCare Coverage Definitions: **G**: generic(s) are available; **Regular Coverage**: also known as regular benefit; does not require Special Authority. Regular benefits may be fully or partially covered.*; **Limited Coverage**: requires Special Authority for coverage. Limited Coverage benefits approved by Special Authority may be fully or partially covered.*; **RDP**: Reference Drug Program. Drugs included in the RDP are comparable agents of the same therapeutic class. Patients receive full coverage of drugs designated as the Reference Drug(s) of the therapeutic class. Other drugs in the same RDP category are covered up to the price of the Reference Drug; **No coverage**: also known as non-benefit; does not fit the above categories.

* Note: Information on which products PharmaCare covers can be obtained using the B.C. PharmaCare Formulary Search (www.health.gov.bc.ca/pharmacare/benefitslookup/). In all cases, coverage is subject to drug price limits set by PharmaCare and to the patient's PharmaCare plan rules and deductibles. See: www.health.gov.bc.ca/pharmacare/plans/index.html and www.health.gov.bc.ca/pharmacare/policy.html for further information.

References:

1. eTherapeutics+.
2. RxFiles. Heart Failure: Treatment Overview. 2014.
3. Up-To-Date. Overview of the therapy of heart failure due to systolic dysfunction.