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Dr. Grace Chua is a community cardiologist at Mackenzie Health in Richmond Hill and Vaughan, Ontario. Her medical and cardiology training included a fellowship in Adult Echocardiography as well as Clinical Epidemiology at the University of Toronto. She was the Chief of the Division of Cardiology at Mackenzie Health from 2003-2017 and was the initiating force in the development of the hospital's rapid access cardiology clinic and heart function service. Currently, her passions lie in clinical education and knowledge translation, particularly in the field of heart failure, as well as prevention of cardiometabolic disease. She has been involved in the development and delivery of many educational programs in different formats, both locally and nationally.

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THE FAMILY PHYSICIAN'S UNIQUE ROLE IN HEART FAILURE MANAGEMENT

Introduction

Heart failure (HF) is an epidemic with a prognosis that is worse than some cancers. Prevention, early diagnosis, coordination, and implementation of guideline-directed medical therapy (GDMT) are imperative to stem this tsunami wave. The family physician stands in a unique, critical, and first-line position to be able to offer all 3. Their understanding and implementation of these roles are crucial for success in the battle against HF. This review offers a perspective on the role of family physicians in managing HF.

Definitions and Classifications

The universal definition of HF was recently established as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and is corroborated by elevated natriuretic peptide (NP) levels and/or objective evidence of pulmonary or systemic congestion. The stages of HF are as follows. **Stage A**, which describes patients at risk for HF but without current or prior signs of HF and without structural or biomarker evidence of heart disease. **Stage B**, or pre-HF, describes those with structural heart disease or abnormal cardiac function or elevated NP levels but without current or prior symptoms or signs of HF. **Stage C** describes patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality. **Stage D**, or advanced HF, describes patients with severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT, requiring advance therapies such as consideration for transplant, mechanical circulatory support, or palliative care. In addition, a revised classification of HF based on left ventricular ejection fractions (LVEF) was proposed. This includes HF with reduced ejection fraction (HFrEF), defined as HF with an LVEF of <= 40%; HF with mildly reduced ejection fraction (HFmrEF), defined as HF with an LVEF of 41–49%; HF with preserved ejection fraction (HFpEF), defined as HF with an LVEF of >= 50%; and HF with improved ejection fraction (HFimpEF), defined as HF with a baseline LVEF of <40% with a >=10% point increase from baseline LVEF, and a second measurement of LVEF of >40%[1] (**Figure 1**). The stages and classifications of HF emphasize that it is a dynamic condition that can cross a spectrum of stages and LVEF. The idea of a stable HF patient does not exist and should be avoided. Every effort should be made to ensure that patients receive the best possible therapy to improve symptoms, quality of life, prognosis, and to prevent worsening HF (WHF), even when symptoms are well controlled.

Risk Factors, Prognosis and Burden of Disease

As of 2019, it is estimated that 56.2 million people worldwide are living with HF. The prevalence ranges from 1–3% of the overall population, with a 29.4% increase observed from 2010 to 2019, varying by country. Incidence rates are 2–3 cases/1000 person years in Europe and North America.[2] In Canada, the 2021–2022 prevalence rate for patients aged 40 years or older was 3.9%, with the highest rate of 17.8% observed in

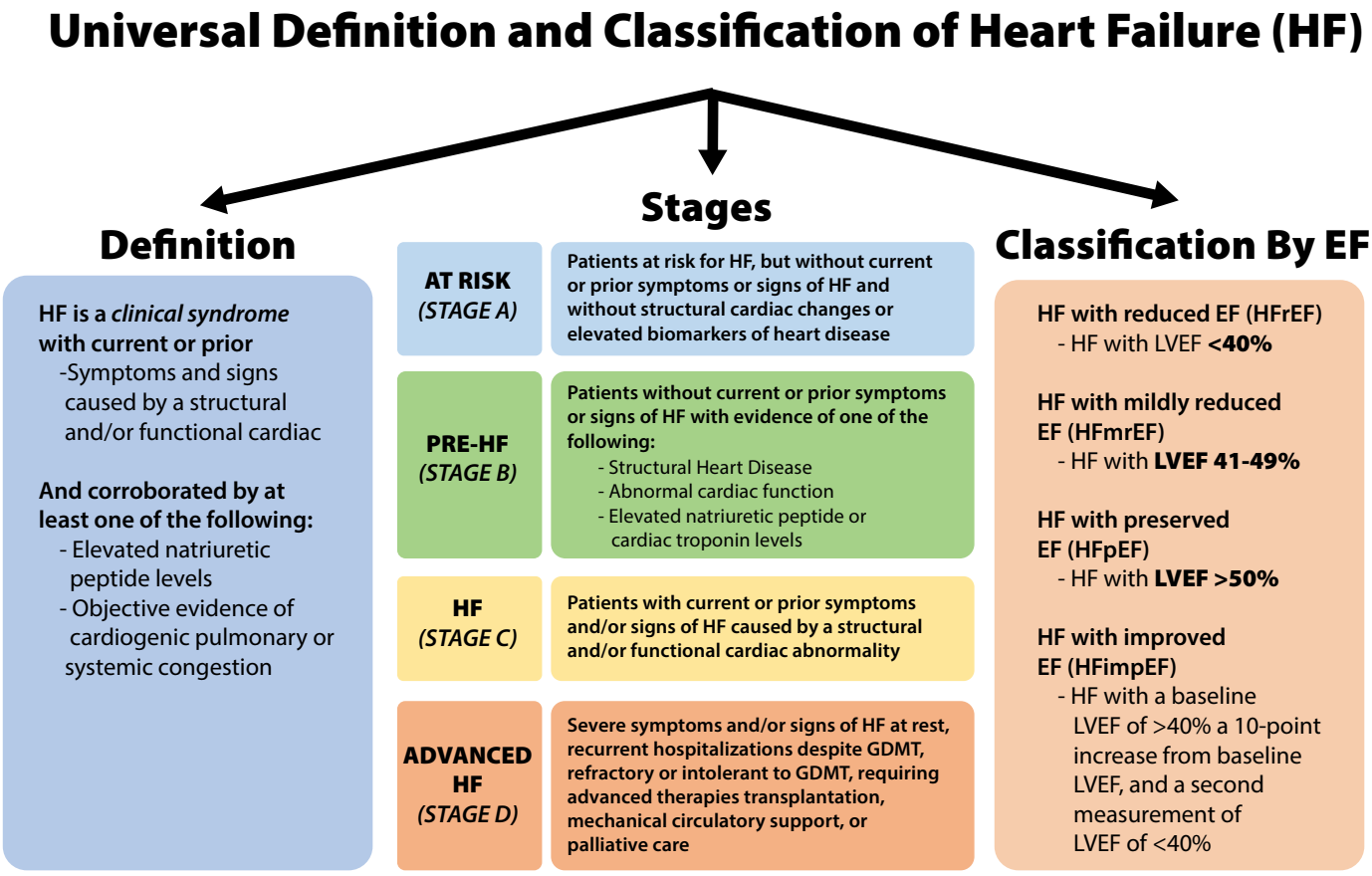

Figure 1. Universal Definition and Classification of HF. Definition, Stages and Classification by ejection fraction of HF allows for standardization in language and communication. It also emphasizes that HF is not a static disease but exists in a continuum. There is no such thing as a "stable" heart failure patient; *adapted from Gibson G, Blumer V, Mentz RJ, Lala A. Universal Definition and Classification of Heart Failure: A Step in the Right Direction from Failure to Function. American College of Cardiology July 13, 2021 https://www.acc.org/Latest-in-Cardiology/Articles/2021/07/12/12/31/Universal-Definition-and-Classification-of-Heart-Failure.*

patients aged 80 years or older. The incidence rate of HF is 511 per 100,000 persons, again differing by age. It is highest in patients over 80 years old, at 2,983 per 100,000 persons, and 799 per 100,000 in patients aged 65–79 years old.[3] Currently, more than 787,000 Canadians are living with HF, with >111,000 Canadians diagnosed annually. Despite improvements in evidence-based HF therapies, the 30-day readmission rate for HF remains at 21%, with a median hospital length of stay of 7 days. It is estimated that HF will cost Canada more than $2.8 billion a year by 2030.[4-6]

A 2019 meta-analysis looking at patients in Europe and North America report a 5-year survival rate of 57% for all types of HF. The survival rate was higher for those under 65 years, at 79%, while it was 50% for those over 75 years.[7] Hospitalization portends a poorer prognosis as evidenced by a study looking at a cohort of patients from 2005-2009, which showed a 5-year mortality rate of 75%, with no difference observed across both HFrEF and HFpEF patients.[8] Data from Ontario in 2007 showed that 10% of patients died within 30 days of hospitalization for HF.[9] Survival rates significantly decrease after each HF hospitalization, ranging from 2.4 years after the first hospitalization to 0.6 years after the fourth hospitalization. This data highlights the urgency to start patients on GDMT as quickly as possible to prevent hospitalizations and improve their prognosis.[10]

HF is the end-stage manifestation of many forms of heart disease. Thus, risk factors for HF involve traditional factors such as advancing age, hypertension, hyperlipidemia, smoking, excess alcohol intake, and a sedentary lifestyle. In addition, other disease processes such as ischemic heart disease, arrhythmia, obesity, diabetes, and chronic kidney disease (CKD) contribute to HF risk. Emerging mechanisms, owing to the discovery of new therapeutics, include inflammation and fibrosis, genetics (hypertrophic cardiomyopathy) and cardiac amyloidosis. With the increasing prevalence of obesity, diabetes, metabolic syndrome, and cardiovascular disease, HF cases continue to rise, reaching epidemic proportions.

Prevention and Diagnosis

Prevention and diagnosis of HF starts with a very high index of suspicion (**Figure 2**). Close attention should

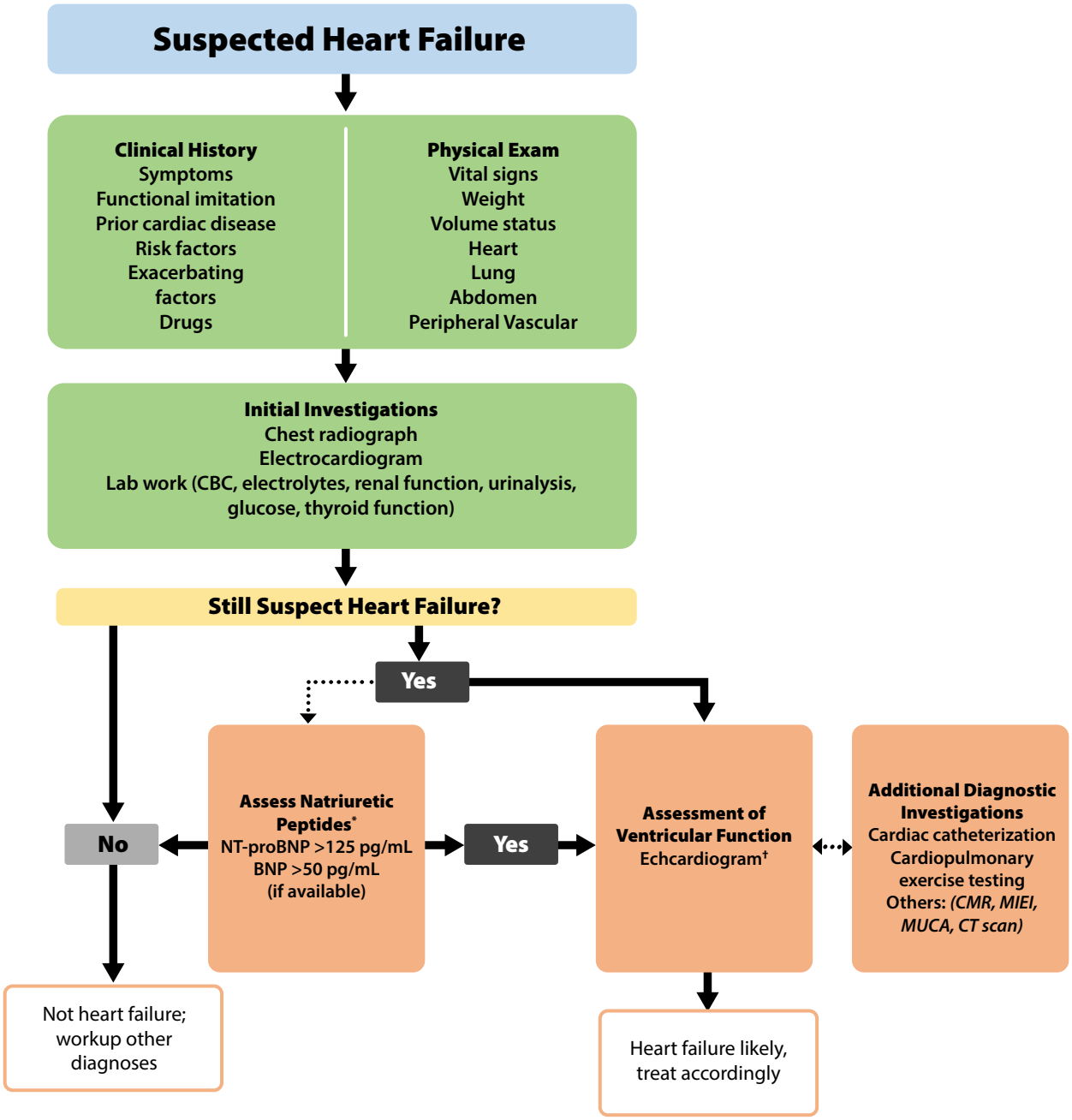

Figure 2. Suggested algorithm for diagnosis of HF in the ambulatory care setting; *as per Canadian Cardiovascular Society. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Mrioslaw R, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, Leblanc M-H, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can Journal of Cardiology 33 (2017):1342-1433.*

Algorithm for the diagnosis of the heart failure in the ambulatory care setting. For patients with heart failure, a history, physical exam, and initial investigations should be supplemented with natriuretic peptides and/or imaging tests.

*Natriuretic peptides are not available in all jurisdictions in Canada.

†Includes systolic as well as diastolic parameters (eg, numeric left ventricular ejection fraction, transmitral and pulmonary venous flow patterns, or mitral annulus velocities); a preserved ejection function on a routine echocardiogram does not rule out the clinical syndrome of heart failure and therefore clinical judgement is required if other indicators point to heart failure as a diagnosis. A lower BNP cutoff for suspecting heart failure in the ambulatory settings facilitates earlier implementation of guideline-directed care.

Abbreviations: BNP: B-type natriuretic peptide, **CBC:** complete blood count, **CMR:** cardiac magnetic resonance, **CT:** computed tomography, **MUGA:** multigated acquisition, **CMR:** cardiovascular magnetic resonance

be paid to high-risk patients who have a history of hypertension, longstanding diabetes, cardiometabolic syndrome, obesity, CKD, or a previous history of cardiovascular disease (coronary/peripheral artery disease, valvular heart disease, cardiac arrhythmias). A constellation of typical symptoms such as dyspnea, fatigue, weakness, functional limitation, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, along with less typical symptoms such as nocturnal cough, decreased appetite, palpitations, chest pain, nocturia/oliguria, dizziness, syncope, delirium, and confusion should trigger alarm bells to investigate further. When taking a patient's history, ask quantifying questions, such as (Do you get short of breath after walking from the parking lot to the office?) rather than questions that give a yes/no response (Are you short of breath?). A thorough physical examination should be conducted, which focuses on signs such as tachycardia, irregular pulse, tachypnea, an elevated jugular venous pressure (JVP) and hepatojugular reflux, a third heart sound, cardiac murmur, peripheral edema, rales, pleural effusion, hepatomegaly, and ascites. Weight can either increase acutely if there is edema, or decrease in advanced HF due to cachexia. Initial investigations should include an electrocardiogram (ECG), chest X-ray (CXR), and lab work including a complete blood count (CBC), electrolytes, estimated Glomerular Filtration Rate (eGFR), urinalysis, glucose levels, thyroid function, and urinary albumin-creatinine ratio. CKD, particularly albuminuria, is associated with incident HF and signals worse outcomes in patient with existing HF.[11-13]

Role of Natriuretic Peptides

Since an elevated NP level is included in the universal definition of HF, measuring and understanding the role of NP is crucial. NPs (B-type natriuretic peptide (BNP), N-terminal pro B-type natriuretic peptide (NT-proBNP), midregional pro A-type natriuretic peptide [MR-proANP]) are biomarkers triggered by end-diastolic wall stress, increased intracardiac filling pressures, and volumes. Elevated plasma concentrations of these biomarkers strongly correlate with the presence and severity of cardiac stress and HF. Physical findings such as rales, elevated JVP, and peripheral edema, as well as ECG and CXR have limited sensitivity of only 50–60%. NPs are highly accurate at differentiating HF from other causes of dyspnea. **NPs should be measured in all patients presenting with symptoms suggestive of new-onset or worsening HF, as their use facilitates both early diagnosis and the early exclusion of HF**.[14] However, due to confounding factors (**Table 1**), the diagnosis of HF cannot be made solely by elevated NP levels, and should be considered in conjunction with other clinical factors. Diagnostic levels of NPs vary depending on whether the patient has acute HF (with very high filling pressures) or chronic HF (with a mild increase in filling pressures at rest). NT-proBNP levels are more affected by increasing age, resulting in different cut-off levels by age compared to BNP (**Table 2**). In an ambulatory care setting, a BNP level <50 pg/mL and an NT-proBNP level < 125 pg/mL lowers the likelihood of HF, particularly in HFrEF where NP levels tend to be higher than in HFpEF. Obesity, which is often associated with HFpEF, falsely lowers NP levels, secondary to a decreased release of NP by adipose tissue. In these circumstances, NP levels below the cut-off do not definitively rule out HF. It has been suggested that cut-off levels should be lowered by up to 50% in obese patients, with a linear correlation indicating that a higher BMI corresponds to lower cut-off concentrations.[15] Results should always be interpreted with knowledge of renal function and BMI, which are the 2 most significant confounders of NP levels.

NP has also been found to be useful in screening for the prevention of incident HF (Stage B) in asymptomatic patients. NP levels may be elevated early in the disease process before the onset of symptoms. Several randomized controlled trials (RCTs) have shown the utility of using elevated NP levels to guide more intensified therapy, including increased use of cardiovascular investigations, renin angiotensin-aldosterone system inhibitors (RAASi), and beta-blockers. This approach has been shown to reduce outcomes such as new-onset HF, major adverse cardiovascular events, hospitalizations, and death in patients with cardiovascular risk factors.[16,17] Other uses of NP include assessing an increase of symptoms in established HF patients. To be effective, the NP level at a stable, dry state needs to be available. A clinically relevant change is suggested by an increase of at least 30% to 50%.[14,18] Another use is observing pre-discharge NP levels in acute HF patients. There should be a drop of at least 30% from the admission NP level.[18] The discharge NP level is the best predictor of prognosis in acute HF patients, including risks of death and re-hospitalization.[14] Persistently elevated NP levels that do not decrease with HF treatment indicate a high-risk patient with a poorer prognosis and a higher risk of WHF events that require closer monitoring and intensification of therapy. Therapies for HF such as RAASi, mineralocorticoid receptor antagonists (MRA), beta-blockers, diuretics, Sodium-Glucose Co-Transporter-2 inhibitors (SGLT2i), and cardiac resynchronization therapy (CRT), all chronically reduce NP levels, leading to left ventricular (LV) remodelling and better outcomes. Exceptions include the early titration of beta-blockers, which can transiently raise NP levels, as well as the use of sacubitril/valsartan, which increases BNP levels but lowers NT-proBNP levels. NT-proBNP is a more accurate reflection of clinical status and should be used in patients taking sacubitril/valsartan. The use of NP to guide HF therapy is controversial, with some studies showing benefit, and others not.[19,20] The difference lies in HF care. In studies with very aggressive usual care with intensive GDMT, NP-guided therapy may not be as effective in improving outcomes. (**Table 3**)

Causes of elevated NP levels other than primary HF
Non cardiac cause:
Advanced age (NTproBNP affected more than BNP)
Kidney disease
Severe anemia
Severe metabolic disease (thyrotoxicosis, DKA, severe burns)
Pulmonary disease (COPD, pneumonia, pulmonary embolism)
Critical illness (shock, sepsis)
Liver disease
Stroke
Medications (use of Sacubitril/Valsartan increases BNP but not NTproBNP)
Cardiac cause:
Acute coronary syndrome/myocardial infarction
Myocarditis
Valvular heart disease
Cardiac contusion/infiltration (malignancy, infiltrative disease such as amyloid)
Inherited disorders (congenital heart disease, hypertrophic cardiomyopathy)
Pericardial disease
Cardioversion/ICD shock
Atrial or ventricular arrhythmia (AF can increase levels by 3 fold)
Pulmonary hypertension, right heart failure
Invasive or surgical procedures on the heart
Causes of lower NP levels:
Obesity or elevated BMI (weight loss produces an increase in NP levels)
Certain pericardial disease (with pericardial effusion, NPs may rise after pericardiocentesis)

Table 1. Factors other than primary HF that can increase or lower NP levels. Attention should be paid to clinical factors when looking at NP levels; *adapted from reference 1, Bozkurt B, et al. European Journal of Heart Failure (2021) 23, 352-380.*

Role of Echocardiography

When HF is suspected, transthoracic two-dimensional and Doppler echocardiogram (TTE) is the first choice for initial imaging. TTE assesses chamber size, systolic and diastolic function of both the left and right ventricles, valvular status, wall thickness, LV mass, LVEF, and pericardial disease, which helps in diagnosis. If imaging is suboptimal, contrast echocardiography, or radionuclide angiography can be used. Other modalities, such as cardiac CT, MRI, and cardiac catheterization, can assist in diagnosis and in determining the etiology of HF. It is also important to classify patients into HFrEF, HFmrEF ,and HFpEF to start and prioritize therapy. The suggested timing of when to assess LVEF with TTE and other modalities is summarized in **Table 4**.

Once HF has been diagnosed and classified, its etiology should be determined. While the different etiologies are beyond the scope of this article, they are listed in **Figure 3**, and referring the patient to a cardiac specialist may be appropriate for further work-up and management.

Treatment of Heart Failure

Lifestyle, diet, exercise, self-care, and risk factor modification are important components of both prevention and treatment of HF, though these topics will not be discussed in this article. The treatment of HF is based on classification by LVEF. The evidence that forms the current treatment guidelines is discussed elsewhere and is beyond the scope of this review. For HFrEF, all societal guidelines uniformly recommend starting with the use of 4 pillars, including RAASi (ACEI/ARB/Angiotensin Receptor Neprilysin Inhibitor (ARNI), prioritizing ARNI), beta-blockers, mineralocorticoid receptor antagonist (MRA), and SGLT2i.[21-23] There are many suggested sequencing techniques for initiating the 4 pillars, although none have been proven to be superior.[24,25] High readmission and event rates in HFrEF patients, especially within 30 days post admission, and the efficacy of quadruple therapy (showing a 73% reduction of death over 2 years),[26] as well as large absolute reductions in mortality and hospitalization within days to weeks, emphasize the need to implement all 4 agents as quickly as possible (recommended range 4 weeks to 6 months). Some overarching principles include: **1)** Attempt to start low doses of as many pillars as possible (within the

	Natriuretic peptide cut points for the diagnosis of HF			
	Age, years	HF is unlikely	HF is possible but other diagnosis need to be considered	HF is very likely
Acute setting				
BNP	All	<100 pg/mL	100–400 pg/mL	>400 pg/mL
NT-proBNP	<50	<300 pg/mL	300–450 pg/mL	>450 pg/mL
	50–75	<300 pg/mL	450–900 pg/mL	>900 pg/mL
	>75	<300 pg/mL	900–1800 pg/mL	>1800 pg/mL
Ambulatory care setting				
BNP	All	<50 pg/mL		
NT-proBNP	All	<125 pg/mL		

Table 2. Cut off NP levels for the diagnosis of HF; *adapted from Ezekowtiz JA, et al., 2017. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Mrioslaw R, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, Leblanc M-H, Masoudi FA, Ross, HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can Journal of Cardiology 33 (2017):1342-1433.*

Abbreviations: BNP: B-type natriuretic peptide, **HF:** heart failure, **NT-proBNP:** N-terminal propeptide BNP

Uses of Natriuretic Peptides in Heart Failure:
1) Diagnosis of HF (acute and chronic, HFrEF and HFpEF, but does not diagnose etiology)
2) Prevention of new-onset HF symptoms in asymptomatic, high-risk patients or patients with asymptomatic LV dysfunction
3) Differentiating new symptoms in patients with established HF (cardiac or non-cardiac). Must compare with baseline NP levels when patient is euvolemic
4) Pre-discharge NP levels in acute HF patients to look at prognosis
5) Prognosis in high-risk patients, identifying those requiring more intense follow-up and therapy
6) Guiding HF therapy—controversial, usually in patients not receiving intensive follow-up and therapy

Table 3. Uses of natriuretic peptides in heart failure: *courtesy of Grace L. Chua, MD, FRCPC, FACC.*

limits of heart rate [HR], blood pressure [BP], volume status, renal function and potassium levels) before up-titrating doses, **2)** Some pillars can improve the tolerance, adherence, and persistence of other pillars. For example, SGLT2i can lower potassium levels, allowing the initiation of MRA. Compared to ACEI/ARB, ARNIs decrease hyperkalemia and improve renal function, SGLT2i and ARNIs may increase diuresis, allowing for the lowering or discontinuation of diuretics. **3)** When BP or renal function limits the adjustment of GDMT, look for potential therapies that do not confer prognostic benefits, such as diuretics, and calcium channel blockers to discontinue. **4)** Rapid sequencing is safe as long as there is early follow-up (within 1–2 weeks) of making a change. During follow-up, assess volume status, HR, BP, potassium levels, and renal function before making further changes. In fact, in-hospital initiation has been found to be safe and effective.[27-29] The STRONG-HF trial demonstrated the proof in concept for rapid up-titration of medications with close follow-up in acute HF. The high intensity care group showed an 8.1% reduction in 180-day HF readmission and all-cause death with a hazard ratio of 0.66 [95% CI 0.50–0.86, p=0.0021].[30] Once GDMT has been optimized, there should be an assessment of the need for second line therapies depending on clinical circumstances. An ECG and TTE should be obtained after 3 months to assess LVEF, the presence of significant functional mitral regurgitation, QRS duration, and rhythm to determine if device therapy is required. (**Figure 4**) This assessment should be conducted in conjunction with a cardiologist specializing in HF management.

The evidence for HFpEF is not as robust. The European Society of Cardiology (ESC) guidelines suggest using SGLT2i, diuretics for fluid retention, treatment of the etiology, and both CV and non-CV comorbidities such as hypertension, CAD, AF, diabetes, obesity, sleep apnea, CKD, anemia, and chronic obstructive pulmonary disease (COPD).[31] SGLT2is have irrefutable class 1 evidence for HF treatment across the spectrum of LVEF. Other therapies, such as MRA, ARB, and ARNI have less definitive data for treating HFpEF and carry a lower class 2b recommendation in the American guidelines.[23] LVEF exists

Suggested timing for measurement of LVEF, according to clinical scenario			
Clinical scenario	**Timing of measurement**	**Modality of measurement**	**Comments**
New-onset HF	Immediately or within 2 weeks for baseline assessment	ECHO (preferred when available); or CMRI	Report should include numeric EF or small range of EF and diastolic function evaluation
After titration of triple therapy for HFrEF, or consideration of ICD/CRT implantation	3 months after completion of titration	ECHO or CMRI (preferably the same, modality and laboratory test as initial test)	LVEF after medical therapy might increase, obviating device therapy
Stable HF	Approximately every 1–3 years, and possibly less frequently if EF is persistently >40%	ECHO or CMRI	Clinical rationale is to identify improving (better prognosis) or worsening ventricular function (worse prognosis, need for additional therapy such as ICD/CRT)
After significant clinical event (i.e., after some HF hospitalization)	Within 30 days, during hospitalization if possible; not necesary when repeated admissions occur without need to identify a cause	ECHO or CMRI	Frequently helpful information such as EF, degree of valvular dysfunction, and RSVP

Table 4. Suggested timing for measurement of LVEF; *adapted from Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Mrioslaw R, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, Leblanc M-H, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can Journal of Cardiology 33 (2017): 1342-1433 .*

Nuclear, computed tomography, or other measures are appropriate and acceptable in certain circumstances taking into account, radiation, cost, and information gained.

Abbreviations: CMRI: caridac magnetic resonance imaging, **CRT:** cardiac resynchronization therapy, **ECHO:** echocardiogram, **EF:** ejection fraction, **HF:** heart failure, **HFrEF:** heart failure with reduced EF, **ICD:** implantable cardioverter-defibrillator, **LVEF:** left ventricular EF, **RVSP:** night ventricular systolic pressure.

on a spectrum, and evidence for the 4 pillars of treatment becomes stronger with lower ejection fractions, making them recommended for HFmrEF. Patients with HFimpEF should still be considered at risk for WHF, and treatment should not be withdrawn unless the sole etiology for HF and LV dysfunction has been eliminated, with no residual cardiac fibrosis or risk of recurrence. Even then, withdrawal should be conducted after a full discussion with the patient regarding the risk of WHF, and should be gradual, with close monitoring of symptoms and LV function. An RCT showed HF relapse after withdrawal of HF therapy in dilated cardiomyopathy patients.[32]

Newer therapies for HFpEF are emerging and include the glucagon-like peptide-1 (GLP1) receptor agonist semaglutide, particularly for the obesity phenotype HFpEF, as well as the non-steroidal MRA finerenone.[33,34,36] In addition, the non-steroidal MRA finerenone and the interleukin-6 inhibitor ziltivekimab is currently under investigation in an ongoing phase 3 trial.[36]

The FINEARTS-HF and STEP-HFpEF trials offer new insights into heart failure with preserved ejection fraction (HFpEF). The FINEARTS-HF trial studied the effects of finerenone, a non-steroidal MRA in patients with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF). The trial demonstrated that finerenone significantly reduced total WHF events and cardiovascular death when compared to placebo. Over a median of 32 months, the drug reduced total WHF events by 18% and showed a consistent benefit across different subgroups of patients, including those already taking SGLT2i.The STEP-HFpEF and STEP-HFpEFDM trials investigated the use of semaglutide, a GLP-1 receptor agonist, in non-diabetic and diabetic patients with HFpEF and obesity. The studies demonstrate that weekly injections of semaglutide 2.4 mg led to significant improvements in quality of life, exercise capacity, and body weight in this population.

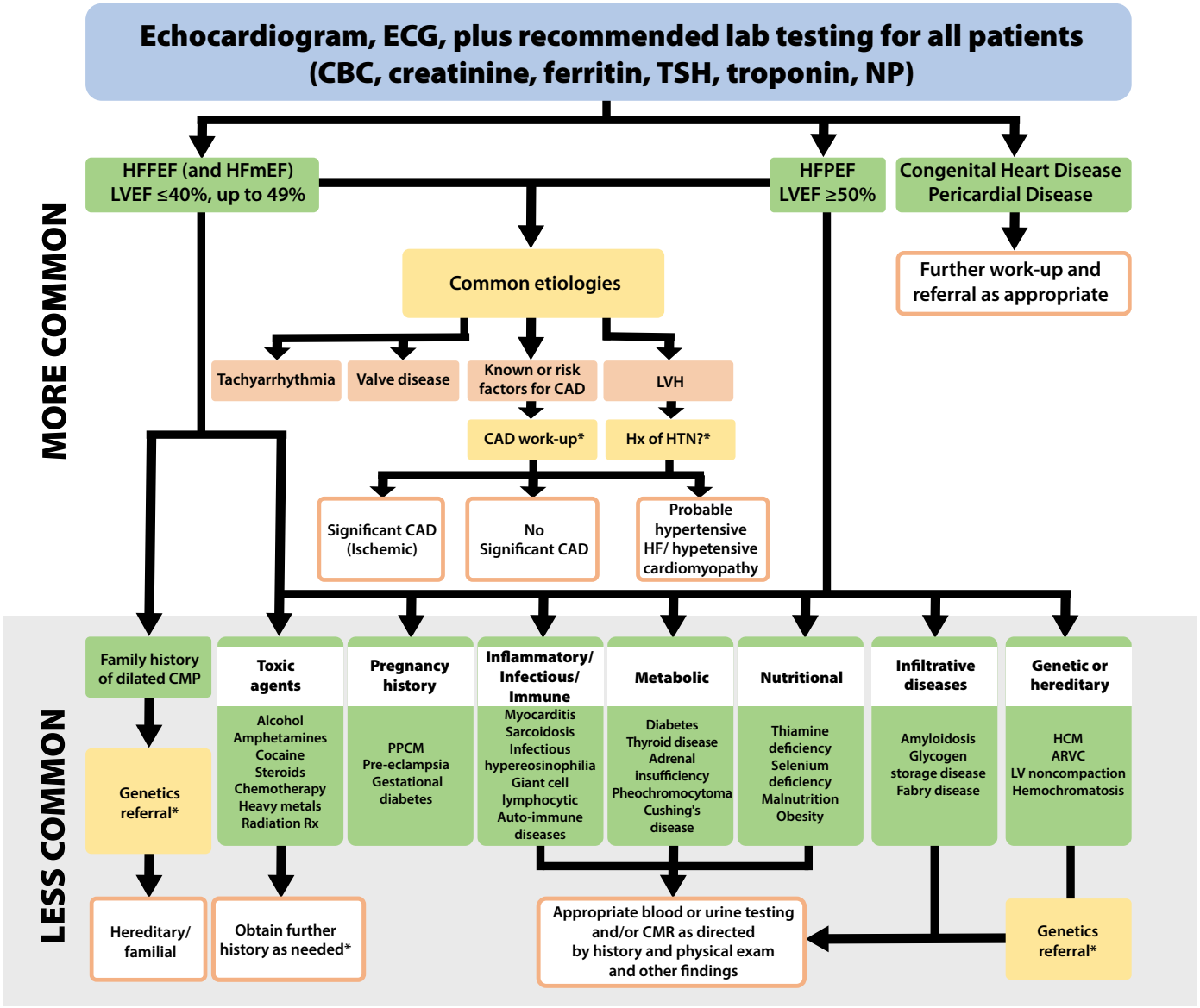

Figure 3. Classification and work-up of HF etiology; a*dapted from Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Mrioslaw R, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, Leblanc M-H, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can Journal of Cardiology 33 (2017):1342-1433.*

General guidance as to the workup to identify the most probable etiology for a patient's heart failure (HF). At all stages, a thorough clinical history and physical exam should aid in the selection of additional investigations. A detailed family history is invaluable, especially in patients who are younger or do not have an obvious etiology. Testing should be placed in context of the pretest probability, availability, and expertise of the test. More common etiologies (eg, coronary artery disease, hypertension) should be considered first, and further testing should be encouraged if another etiology is suspected in addition to a more common etiology (eg, hemachromatosis in a patient with known coronary artery disease).

*Patients might have mixed etiology of HF. A detailed medical and family history might guide investigations and should be completed in all patients. Direct testing on the basis of pretest probability, availability, and expertise.

Abbreviations: ARVC: arrhyth- mogenic right ventricular cardiomyopathy, **CAD:** coronary artery disease; **CBC:** complete blood count, **CMP:** cardiomyopathy, **CMR:** cardiac magnetic resonance, **ECG:** electrocardiogram, **HCM:** hypertrophic cardiomyopathy, **HFmEF:** heart failure with a midrange ejection fraction, **HFPEF:** heart failure with preserved ejection fraction, **HFrEF:** heart failure with reduced ejection fraction, **HTN:** hypertension, **Hx:** history; **LV:** left ventricle, **LVEF:** left ventricular ejection fraction, **LVH:** left ventricular hypertrophy, **NP:** natriuretic peptide, PPCM: peripartum cardiomyopathy, **Rx:** prescription; **TSH:** thyroid-stimulating hormone.

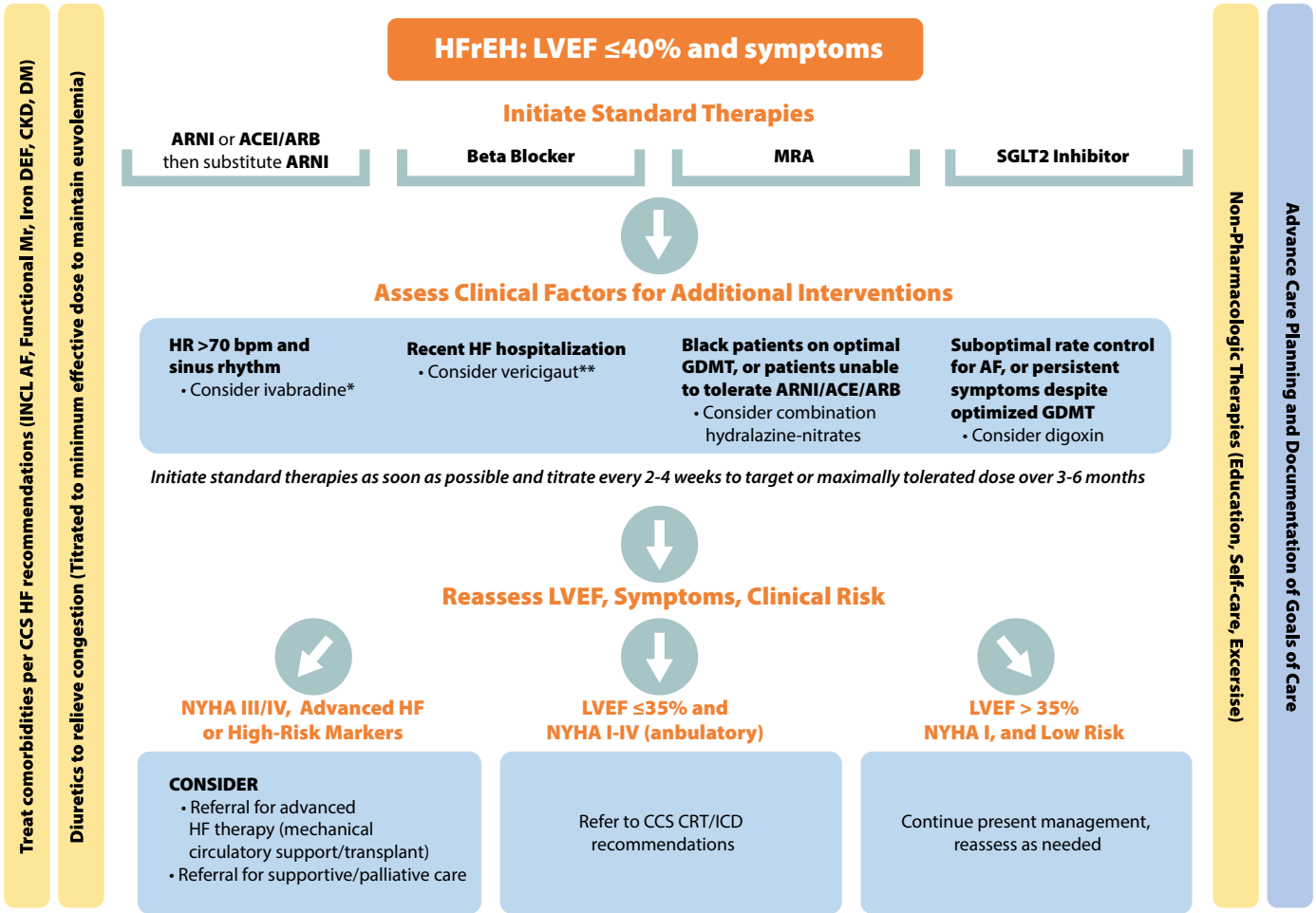

Figure 4. Canadian Cardiovascular Society/Canadian Heart Failure Society algorithm for management of HFrEF; a*dapted from McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz J, Giannetti N, Heckman GA, Howlett JG, Koshman SL, Lepage S, Mielniczuk L, Moe GW, O'Meara E, Swiggum E, Toma M, Zieroth S, Anderson K, Bray SA, Clarke B, Cohen-Solal A, D'Astous M, Davis, M, De S, Grant ADM, Grzeslo A, Heshka J, Keen S, Kouz S, Lee D, Masoudi, FA, McKelvie R, Parent M-C, Poon S, Rajda M, Sharma A, Siatecki K, Storm K, Sussex B, Van Spall H, Yip AMC, CCS/CHFS Heart Failure Guidelines Update: Defining a New, Pharmacologic Standard of Care of Heart Failure with Reduced Ejection Fraction, Canadian Journal of Cardiology 37(2021) 531-546.*

Simplified treatment algorithm for management of heart failure (HF) with reduced ejection fraction (HFrEF). Standard therapies are applicable to most patients with HFrEF for reducing cardiovascular mortality and hospitalization for HF. Additional, pharmacologic therapies should be individualized on the basis of clinical factors as outlined in the text. Every attempt should be made to initiate and titrate therapies with the goal of medication optimization by 3-6 months after a diagnosis of HFrEF. Throughout the patient journey, nonpharmacologic therapies should be prescribed, along with judicious use of diuretics to maintain euvolemia. Evidence also supports interventions to treat important comorbidities including iron deficiency, atrial fibrillation (AF), and functional mitral regurgitation (MR) in selected patients.

*Health Canada has approved ivabradine for patients with HFrEF and heart rate (HR) ≥77 bpm in sinus rhythm.

**Vericiguat is not yet approved for use in Canada.

Abbreviations: ACEI: angiotensin converting enzyme inhibitor, **ARB:** angiotensin receptor blocker; **ARNI:** angiotensin receptor-neprilysin inhibitor, **CCS:** Canadian Cardiovascular Society, **CKD:** chronic kidney disease; **CRT:** cardiac resynchronization therapy, **DM:** diabetes mellitus, **GDMT:** guideline-directed medical therapy, **ICD:** implantable cardioverter difibrillator, **LVEF:** left ventricular ejection fraction, **MRA:** mineralocorticoid receptor antagonist; **NYHA:** New York Heart Association; **SGLT:** sodium glucose transport

Key findings from the trials include:

- A substantial improvement in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), reflecting better symptoms and physical limitations.
- Greater weight loss compared to placebo, with a net 8.4% reduction in body weight at 52 weeks seen in the combined studies.
- Enhanced functional capacity, shown by an increase in 6-minute walk distance.
- Improvement in a hierarchical endpoint that includes death, HF events and KCCQ-CSS
- Reduction in inflammation markers such as C-reactive protein (CRP)

Together, these studies give promise for the use of non-steroidal MRAs (finerenone) and GLP1RA (semaglutide) in HFpEF, adding to the evidence already seen with SGLT2i. These agents share benefit in the treatment of the cardiovascular-kidney-metabolic syndrome, with inflammatory dysfunctional adipose tissue being the root cause.

Role of Family Physicians

Family physicians stand in a unique position in the spectrum of HF care. This starts with the prevention and management of HF risk factors, extends to maintaining a high index of suspicion, early diagnosis, starting treatment with GDMT, and referring patients to cardiologists. As HF progresses, coordination of care becomes crucial, with patients often requiring multiple services including cardiac rehabilitation, pharmacy reconciliation, diet intervention, home care, and palliative care. Collaborative care with the HF team is equally important, focusing on patient education, monitoring of clinical status, medication adjustments to avoid WHF events, particularly after HF hospitalization. Family physicians hold a critical position in defending against the HF tsunami wave.

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Vascepa®: **Power to reduce the risk of cardiovascular events**[1]

Vascepa® (n=4,089) demonstrated reductions in the risk of CV events vs. placebo (n=4,090) (both in combination with statins)*[1]

2° endpoints

CV death[†‡]

↓**20%**

(HR 0.80; 95% CI [0.66, 0.98])

(event n=174 vs. 213)

Non-fatal MI[†]

↓**30%**

(HR 0.70; 95% CI [0.59, 0.82])

(event n=237 vs. 332)

Non-fatal stroke[†]

↓**29%**

(HR 0.71; 95% CI [0.54, 0.94])

(event n=85 vs. 118)

Vascepa® demonstrated a significant 25% reduction on instantaneous risk of time to **1st occurrence of cardiovascular death, MI, stroke, coronary revascularization or hospitalization for unstable angina (5-point MACE)** vs. placebo **(NNT=21,** 1° endpoint).*[1] (HR 0.75 [95% CI: 0.68, 0.83]; p<0.0001)

There was no statistically significant difference in risk between the Vascepa® and placebo groups for all-cause mortality.

REDUCE-IT® was a placebo-controlled trial with a 4.9-year median follow-up of **statin-treated adult patients** with **elevated triglycerides** and **a high risk of cardiovascular events** due to established cardiovascular disease or diabetes with at least 1 other CV risk factor.*[1]

Vascepa® (icosapent ethyl [IPE]) is indicated to reduce the risk of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization or hospitalization for unstable angina) in statin-treated patients with elevated triglycerides, who are at high risk of cardiovascular events due to:

- established cardiovascular disease, or
- diabetes, and at least one other cardiovascular risk factor[1]

***Vascepa®** is listed by all major private insurance plans.*[4]

To learn more about Vascepa® public and private coverage, visit ***www.vascepa.ca***

See the recommendations in the 2021 CCS Guidelines for Dyslipidemia[2], and the 2020 Canadian Stroke Best Practice Recommendations.[3]

Clinical use:

Not indicated for pediatric use.
May be used in patients ≥65 years of age. Use in geriatrics is not associated with differences in safety or effectiveness, but greater sensitivity of some older individuals cannot be ruled out.

Relevant warnings and precautions:

- Not recommended in combination with or substituted for other products that contain omega-3 fatty acids
- Increased incidence of bleeding
- Increased risk of atrial fibrillation or flutter requiring hospitalization
- Potential for anaphylactic reaction to fish and/or shellfish
- Periodic monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in patients with hepatic impairment is recommended during therapy with Vascepa®
- Fertility
- Not recommended in pregnancy and nursing

For more information:

Please consult the Vascepa® Product Monograph at https://pdf.hres.ca/dpd_pm/00065525.PDF for important information relating to adverse reactions, drug interactions, and dosing/administration information which have not been discussed in this piece. The Product Monograph is also available by calling HLS Therapeutics Inc. at 1-833-266-3423.

*8,179 statin-treated adult patients with elevated serum triglyceride levels (≥1.5 mmol/L to <5.6 mmol/L) who were also at high risk for atherothrombotic events. Patients either had established CVD or were at high risk for CVD and were randomized to either Vascepa® or placebo. Patients with established cardiovascular disease were at least 45 years of age and had a documented history of coronary artery disease, cerebrovascular or carotid disease, or peripheral artery disease. Patients with other risk factors for cardiovascular disease were at least 50 years of age and had diabetes and at least one additional major cardiovascular risk factor. 5-point MACE was defined as time to first occurrence of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. Most patients at baseline were taking at least one other cardiovascular medication including anti-hypertensives (95%), anti-platelet agents (79.4%), beta blockers (70.7%), angiotensin-converting enzyme (ACE) inhibitors (51.9%), and angiotensin receptor blockers (ARB) (27.0%), with 77.5% taking either an ACE inhibitor or ARB. At baseline, while on stable background lipid-lowering therapy, the median LDL-C was 1.9 mmol/L.
†Incidence rates of CV events per 100 patient years (Vascepa® vs. placebo): cardiovascular death, 1.0 vs. 1.2; non-fatal myocardial infarction, 1.4 vs. 2.0; non-fatal stroke, 0.5 vs. 0.7.
‡CV death includes adjudicated cardiovascular deaths and deaths of undetermined causality.
‖Comparative clinical significance has not been established.
CCS, Canadian Cardiovascular Society; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

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