



Canadian  
Cardiovascular  
Society

**2025  
UPDATE**

# Heart Failure with Nonreduced Ejection Fraction

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GUIDELINE POCKET GUIDE

This pocket guide is a quick-reference tool for healthcare providers that features diagnostic and management recommendations from the Canadian Cardiovascular Society (CCS)/Canadian Heart Failure Society (CHFS) 2025 Guideline Update for Pharmacologic Management of Heart Failure With Nonreduced Ejection Fraction (LVEF > 40%).

These recommendations are intended to provide a reasonable and practical approach to care for physicians, pharmacists, nurses and other healthcare providers. As scientific knowledge, technology, and practice patterns evolve, these guidelines are subject to change and are not intended as a substitute for clinical judgement; healthcare providers should always use their individual judgement when managing clinical care in consultation with the patient, considering all individual circumstances, diagnostic and treatment options, and available resources.

Adherence to these recommendations will not necessarily produce successful outcomes in every case.

#### **CCS/CHFS 2025 Guideline Update for Pharmacologic Management of Heart Failure With Nonreduced Ejection Fraction (LVEF > 40%)**

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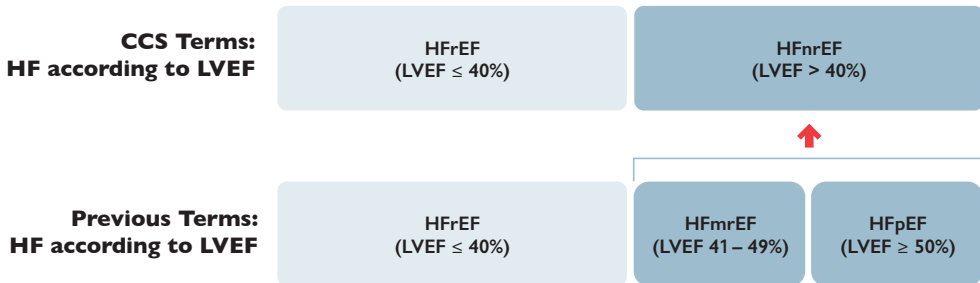
## Abbreviations

|                                                       |                                                |                                                             |
|-------------------------------------------------------|------------------------------------------------|-------------------------------------------------------------|
| ACEi, angiotensin converting enzyme inhibitors        | DM, diabetes mellitus                          | MRI, magnetic resonance imaging                             |
| AE, adverse events                                    | ECG, electrocardiogram                         | MUGA, multigated acquisition scan                           |
| AF, atrial fibrillation                               | eGFR, estimated glomerular filtration rate     | NACI, National Advisory Committee on Immunization           |
| ARB, angiotensin receptor blocker                     | GI, gastrointestinal                           | NP, natriuretic peptide                                     |
| ARNI, angiotensin receptor-neprilysin inhibitor       | GLP-1, glucagon-like peptide-1                 | NT-proBNP, N-terminal propeptide B-type natriuretic peptide |
| ARVC, arrhythmogenic right ventricular cardiomyopathy | HCM, hypertrophic cardiomyopathy               | NYHA, New York Heart Association                            |
| A1c, glycated hemoglobin                              | HF, heart failure                              | PHAC, Public Health Agency of Canada                        |
| BMI, body mass index                                  | HFH, heart failure hospitalization             | PPCM, peripartum cardiomyopathy                             |
| BNP, B-type natriuretic peptide                       | HFnrEF, HF with nonreduced ejection fraction   | QoL, quality of life                                        |
| BP, blood pressure                                    | HFrEF, HF with reduced ejection fraction       | Rx, medical prescription                                    |
| CAD, coronary artery disease                          | HTN, hypertension                              | SBP, systolic blood pressure                                |
| CBC, complete blood count                             | KCCQ, Kansas City Cardiomyopathy Questionnaire | SGLT2i, sodium-glucose cotransporter-2 inhibitor            |
| CCS, Canadian Cardiovascular Society                  | LV, left ventricle                             | TSH, thyroid stimulating hormone                            |
| CKD, chronic kidney disease                           | LVEF, left ventricular ejection fraction       | VHD, valvular heart disease                                 |
| CMP, cardiomyopathy                                   | LVH, left ventricular hypertrophy              | 6MWD, six-minute walk distance                              |
| CMR, cardiac magnetic resonance                       | MRA, mineralocorticoid receptor antagonist     |                                                             |
| CV, cardiovascular                                    |                                                |                                                             |

## Heart Failure with Nonreduced Ejection Fraction: Nomenclature

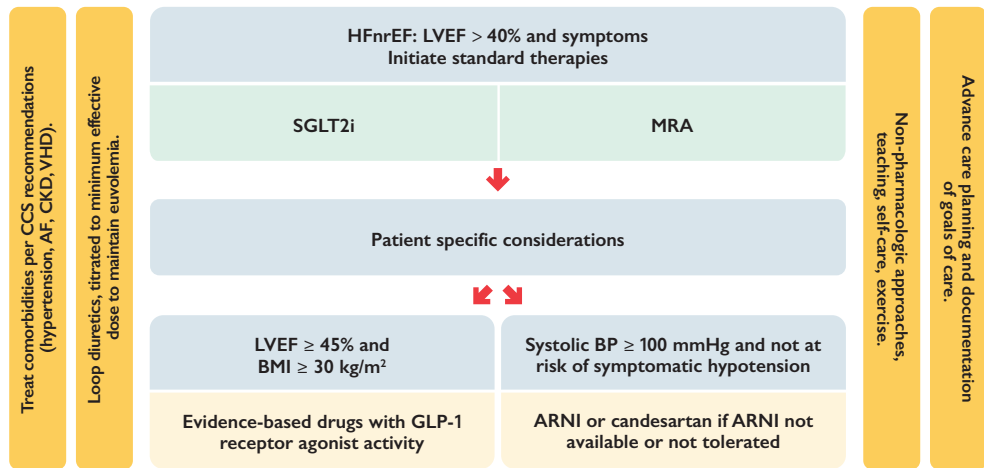
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The CCS/CHFS nomenclature for HF stratified according to LVEF due to the growing evidence that shows similar outcomes and treatment responses across the spectrum of LVEF  $> 40\%$ . The CCS has consolidated the two terms, heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF), into a single unified term – heart failure with nonreduced ejection fraction (HFnrEF).



Heart failure with improved ejection fraction, which includes patients with HF and reduced LVEF, that has improved to  $> 40\%$ , is not specifically addressed in this guideline.

# Simplified Evidence-based Treatment Approach for Reducing Heart Failure Hospitalization in People with HFnrEF



Only evidence-based medications should be used for the treatment of HF.

The literature currently does not support a specific sequence to initiating therapy within a given treatment tier.

The order of prescribing should be individualized on the basis of patient characteristics and through a shared decision-making approach.

**Strong recommendation**

**Weak recommendation**

## Summary of New HFnrEF Guideline Recommendations

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|    |                                                                                                                                                                                                                                                        |                                                   |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| 1. | We recommend the use of SGLT2i for people with HF and LVEF > 40% to reduce the risk of HFH.                                                                                                                                                            | Strong Recommendation;<br>High-Quality Evidence   |
| 2. | We recommend the use of MRAs for people with HF and LVEF > 40% to reduce the risk of HFH.                                                                                                                                                              | Strong Recommendation;<br>High-Quality Evidence   |
| 3. | We suggest the use of ARNI for people with symptomatic HF and LVEF > 40%, who are at low risk of symptomatic hypotension to reduce the risk of HFH.                                                                                                    | Weak Recommendation;<br>Moderate-Quality Evidence |
| 4. | We suggest the use of evidence-based drugs with GLP-1 receptor agonist activity and with proven efficacy for people with symptomatic HF, LVEF $\geq$ 45%, and body mass index $\geq$ 30kg/m <sup>2</sup> to reduce the risk of HFH and to improve QoL. | Weak Recommendation;<br>Moderate-Quality Evidence |



## Effect of Contemporary Therapies for Treatment of HFnrEF on Important Outcomes of Interest\*

| Agent                                  | HFH | KCCQ | 6MWD |
|----------------------------------------|-----|------|------|
| SGLT2i                                 | ✓   | ✓    |      |
| MRA                                    | ✓   |      |      |
| ARNI                                   | ✓   |      |      |
| Evidence based GLP-I receptor agonists | ✓   | ✓    | ✓    |

 Refers to efficacy for indicated outcome.

\*Note that CV mortality was assessed for all agents, serious AE was assessed for SGLT2i and GLP-I ra, and improvements in NYHA functional classification was assessed for ARNI, MRA, and SGLT2i, but there was no significant effect or improvement.

Effect is determined on the basis of statistically significant end points from meta-analyses (please refer to Supplementary Material of the guideline).

## Evidence-based Medications for the Management of HFnrEF Including Starting and Optimal Target Dose

| Drug class              | Specific agent*      | Starting dose                    | Target dose           |
|-------------------------|----------------------|----------------------------------|-----------------------|
| SGLT2i**                | Dapagliflozin        | 10 mg daily                      | 10 mg daily           |
|                         | Empagliflozin        | 10 mg daily                      | 10-25 mg daily        |
| ARNI                    | Sacubitril-valsartan | 24/26 mg or 49/51 mg twice daily | 97/103 mg twice daily |
| ARB                     | Candesartan          | 4-8 mg daily                     | 32 mg daily           |
| MRA                     | Spironolactone       | 12.5-25 mg daily                 | 25-50 mg daily        |
|                         | Eplerenone           | 25 mg daily                      | 50 mg daily           |
|                         | Finerenone           | 10-20 mg daily                   | 20-40 mg daily        |
| GLP-1 receptor agonists | Semaglutide          | 0.25 mg once weekly              | 2.4 mg once weekly    |
|                         | Tirzepatide          | 2.5 mg once weekly               | 15 mg once weekly     |

\*Only specific evidence-based medications should be used for the treatment of patients with HF.

\*\*The CCS has resources to support patients and providers about the safe prescribing and monitoring of patients receiving SGLT2i. Tools are available at [ccs.ca/guideline/cardiorenal-2022](https://ccs.ca/guideline/cardiorenal-2022).

## Mineralocorticoid Receptor Antagonist (MRA) Dosing and Up-titration Schedule for Patients with HFnrEF

| Population                                                                                          | Spiro-lactone         | Eplerenone    | Finerenone  | Up-titration and Monitoring Considerations                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------|-----------------------|---------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Starting dose for patients with normal kidney function (eGFR $\geq$ 60 mL/min/1.73m <sup>2</sup> )  | 12.5 mg – 25 mg daily | 25 mg daily   | 20 mg daily | <p>Perform bloodwork for renal function and electrolytes 1 week after initiation and after any dose change.</p> <p>Check renal function and electrolytes after any change in other medication or intercurrent illness that could influence renal function and/or electrolytes.</p> |
| Starting dose for patients with impaired kidney function (eGFR 30 to 59 mL/min/1.73m <sup>2</sup> ) | 12.5 mg daily         | 12.5 mg daily | 10 mg daily | <p>Regular surveillance of renal function and electrolytes in the stable patient on a stable dose of MRA is recommended, consider checking these parameters every 3 months.</p>                                                                                                    |



|                                                                                  |                     |               |                                                                                                                        |                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------------------------------------|---------------------|---------------|------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Starting dose if patient is at increased risk for hyperkalemia, frail or elderly | 12.5 mg daily       | 12.5 mg daily | 10 mg daily                                                                                                            | <p>Consider increasing the dose of MRA every 2 – 4 weeks until target dose achieved, if:</p> <ul style="list-style-type: none"> <li>• Serum/plasma potassium &lt; 5.0 mmol/L and,</li> <li>• eGFR &gt; 30 mL/min/1.73m<sup>2</sup> and,</li> <li>• Systolic BP &gt; 95 mmHg without symptoms of hypotension</li> </ul> |
| Target dose                                                                      | 25 mg – 50 mg daily | 50 mg daily   | <p>eGFR ≥ 60 mL/min/1.73m<sup>2</sup><br/>40 mg daily</p> <p>eGFR 30 – 59 mL/min/1.73m<sup>2</sup><br/>20 mg daily</p> | <p>Consider decreasing or stopping MRA, if:</p> <ul style="list-style-type: none"> <li>• Serum creatinine increases by &gt; 30%, or</li> <li>• Potassium &gt; 5.4 mmol/L, or</li> <li>• Symptomatic hypotension</li> </ul> <p>Discontinue MRA if potassium ≥ 6.0 mmol/L on a non-hemolyzed sample</p>                  |

## Angiotensin Receptor-Neprilysin Inhibitor (ARNI) Dosing and Up-titration Schedule for Patients with HFnrEF

| Population                                                                                                                                                                                                                                                                                                                                                                                   | Starting Dose of Sacubitril-Valsartan                                                | Up-titration and Monitoring Considerations                                                                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patient on high dose ACEi: <ul style="list-style-type: none"> <li>• Enalapril <math>\geq 10</math> mg/daily</li> <li>• Lisinopril <math>\geq 10</math> mg/daily</li> <li>• Perindopril <math>\geq 4</math> mg/daily</li> <li>• Ramipril <math>\geq 5</math> mg/daily</li> <li>• Lisinopril <math>\geq 10</math> mg/daily</li> </ul>                                                          | 36-hour washout, then start 49/51 mg twice daily                                     | Check serum creatinine, potassium, and blood pressure 1 week after ARNI initiation                                                                                                                                          |
| Patients on high dose ARB: <ul style="list-style-type: none"> <li>• Candesartan <math>\geq 16</math> mg/daily</li> <li>• Irbesartan <math>\geq 150</math> mg/daily</li> <li>• Losartan <math>\geq 50</math> mg/daily</li> <li>• Olmesartan <math>\geq 10</math> mg/daily</li> <li>• Telmisartan <math>\geq 40</math> mg/daily</li> <li>• Valsartan <math>\geq 160</math> mg/daily</li> </ul> | Start 49/51 mg twice daily (No washout period needed for patients already on an ARB) | Check serum creatinine, potassium, and blood pressure 1 week after ARNI initiation<br><br>If stable creatinine, potassium, and SBP $\geq 100$ mmHg, increase dose every 2 – 4 weeks to target dose of 97/103 mg twice daily |



|                                                                                              |                                                                                                                      |                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patients on low or medium dose ACEi, low or medium dose ARB, or those who are ACEi/ARB naïve | 36-hour washout if on ACEi then start 24/26 mg twice daily (No washout period needed for patients already on an ARB) | Consider decreasing or stopping sacubitril-valsartan, if: <ul style="list-style-type: none"> <li>• Serum creatinine increases by greater than 30%, or</li> <li>• Potassium &gt; 5.4 mmol/L</li> <li>• Symptomatic hypotension</li> </ul> |
| Severe kidney impairment (eGFR < 30 mL/min/1.73m <sup>2</sup> )                              | 24/26 mg twice daily                                                                                                 |                                                                                                                                                                                                                                          |
| Elderly patient (age > 75 years)                                                             | 24/26 mg twice daily                                                                                                 |                                                                                                                                                                                                                                          |
| Moderate hepatic impairment (Child-Pugh Class B)                                             | 24/26 mg twice daily                                                                                                 |                                                                                                                                                                                                                                          |
| Systolic blood pressure<br>≥ 120 mmHg<br>≥ 100-120 mmHg                                      | 49/51 mg twice daily<br>24/26 mg twice daily                                                                         |                                                                                                                                                                                                                                          |

## Glucagon-Like Peptide-I Receptor Antagonists (GLP-1RA): The Practical Approach of Use for HFnrEF

| Indications                                                                                                       | Contraindications                                                                                                                                                                                            | Cautions                                                                                                                                                                                                      | Initiation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Special Considerations                                                                                                                                                                                                                    | Follow-up                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>People living with NYHA II-IV HF, LVEF <math>\geq</math> 45% and BMI <math>\geq</math> 30 kg/m<sup>2</sup></p> | <ul style="list-style-type: none"> <li>Personal or family history of medullary cancer of the thyroid or multiple endocrine neoplasia type 2</li> <li>Type 1 DM</li> <li>Pregnant or breastfeeding</li> </ul> | <ul style="list-style-type: none"> <li>History of pancreatitis or pancreatic cancer</li> <li>Use of insulin or insulin secretagogue</li> <li>Already experiencing poor oral intake/nausea/vomiting</li> </ul> | <p><b>Semaglutide injectable 0.25 mg once weekly, up titrate:</b></p> <ul style="list-style-type: none"> <li>After 4 weeks 0.5 mg once weekly</li> <li>After 8 weeks 1 mg once weekly</li> <li>After 12 weeks 1.7 mg once weekly</li> <li>After 16 weeks 2.4 mg once weekly</li> </ul> <p><b>Tirzepatide, injectable, 2.5 mg, once weekly, up titrate:</b></p> <ul style="list-style-type: none"> <li>2.5 mg once weekly sc for 4 weeks</li> <li>5 mg once weekly sc for 4 weeks</li> <li>7.5 mg once weekly sc for 4 weeks</li> <li>10 mg once weekly sc for 4 weeks</li> <li>12.5 mg once weekly sc for 4 weeks</li> <li>15 mg once weekly sc</li> </ul> | <p>For people with DM:</p> <ul style="list-style-type: none"> <li>If A1c is <math>\leq</math> 8%, consider dose reduction/discontinuation of insulin secretagogue, or 10-20% reduction in insulin dose to prevent hypoglycemia</li> </ul> | <ul style="list-style-type: none"> <li>A1c (only if baseline diabetes)</li> <li>Diet</li> <li>Weight</li> <li>GI symptoms (appetite, nausea, vomiting, diarrhea, constipation)</li> <li>Adherence and ability to titrate</li> <li>Retinopathy assessment</li> <li>Quality of life</li> </ul> |



Shared decision making about symptom and weight loss benefit vs. cost and accessibility

For people with DM

- Evaluate and adjust other agents associated with hypoglycemia such as insulin secretagogues and insulin, especially if A1c is  $\leq 8\%$
- Educate about the risk of hypoglycemia

If GI side effects develop:

- Consider staying at current dose, or reducing dose
- Wait longer than 4 weeks before up titrating to next dose
- Suspend treatment temporarily
- *Consider continuing maintenance therapy at a dose lower than the maximum one, if problems persist with dose escalation*



For all people suggest:

- Eat smaller, more frequent meals, eat only when hungry, stop eating when feeling full
- Avoid eating too close to bedtime or, lying down shortly after eating
- Choose easy to digest, low fat diets
- Increase fluid intake and take in small sips but not so much that people feel full
- Choose healthy food that contains water

| Warning Signs and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Lifestyle and Risk Management                                                                                                                                                                                                                                                                                                                                                                                                                  | Drug and Device Treatment Regimen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Dyspnea                             <ul style="list-style-type: none"> <li>- With less exertion and or at rest</li> <li>- During sleep</li> <li>- When lying flat</li> </ul> </li> <li>• Fatigue with progressively less exertion</li> <li>• Increased abdominal swelling or pedal and leg edema</li> <li>• Weight gain (eg. &gt; 2 kg in 2 days)</li> <li>• Lightheaded/faint</li> <li>• Prolonged palpitations</li> <li>• Confusion</li> </ul> | <ul style="list-style-type: none"> <li>• Treat cardiovascular risk factors                             <ul style="list-style-type: none"> <li>- Control hypertension</li> <li>- Control DM</li> <li>- Smoking cessation</li> <li>- Obesity counselling</li> <li>- Routine vaccination per NACI and/or PHAC</li> </ul> </li> <li>• Sodium restriction between 2 g to 3 g/day is reasonable</li> <li>• Weigh daily if fluid retention</li> </ul> | <ul style="list-style-type: none"> <li>• Medical therapy that reduces hospitalization such as SGLT2i, MRA, ARNI or ARB, and GLP-1 receptor agonist at guideline directed doses should be emphasized as targets</li> <li>• Combination drug regimen are the standard of care</li> <li>• Diuretics may need frequent adjustment/re-adjustment</li> <li>• Target the lowest effective dose of diuretics to achieve and maintain euvolemia</li> <li>• Most will be used long term and generally life long</li> <li>• Common side effects are manageable by adjusting medication timing and may require periodic laboratory testing</li> </ul> |

## Appendix I: How is HFnrEF Diagnosed?

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HFnrEF is diagnosed when all three criteria are present:



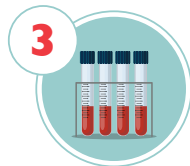
### Symptoms/signs of HF

Core symptoms of HF include: dyspnea, edema (ankles, feet, legs, abdomen), fatigue/weakness, weight gain, coughing/wheezing, reduced appetite, palpitations, cognitive changes



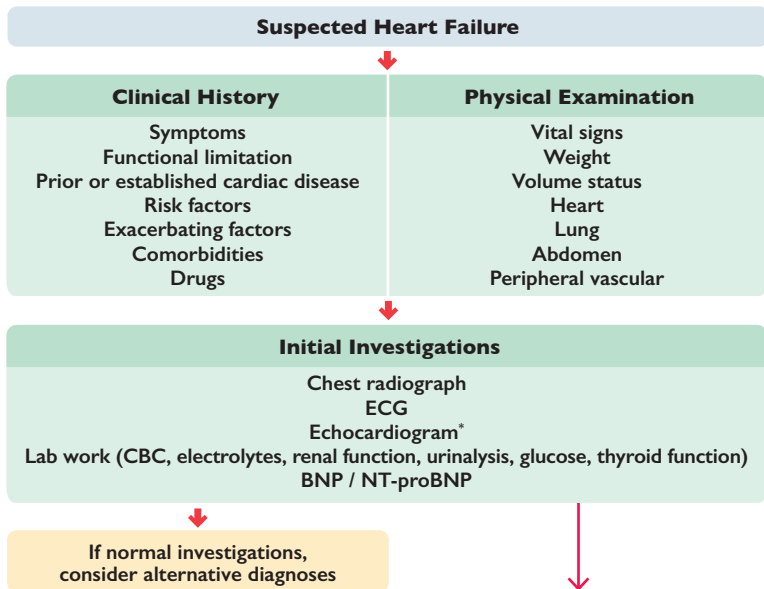
### LVEF > 40%

Based on dedicated cardiac imaging (i.e. echocardiogram, cardiac MRI, MUGA scan)

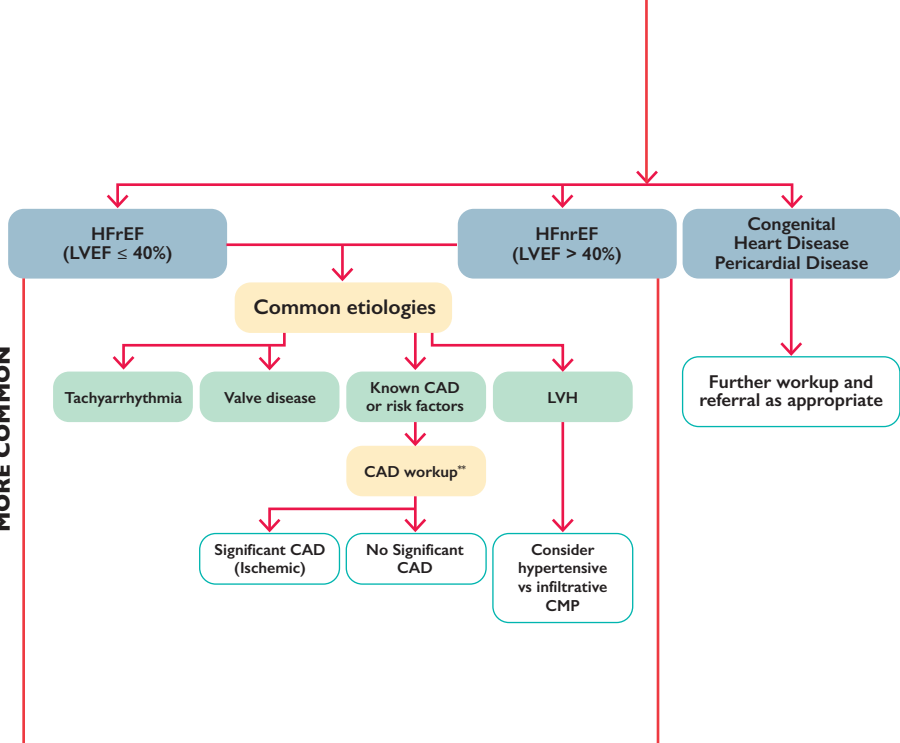


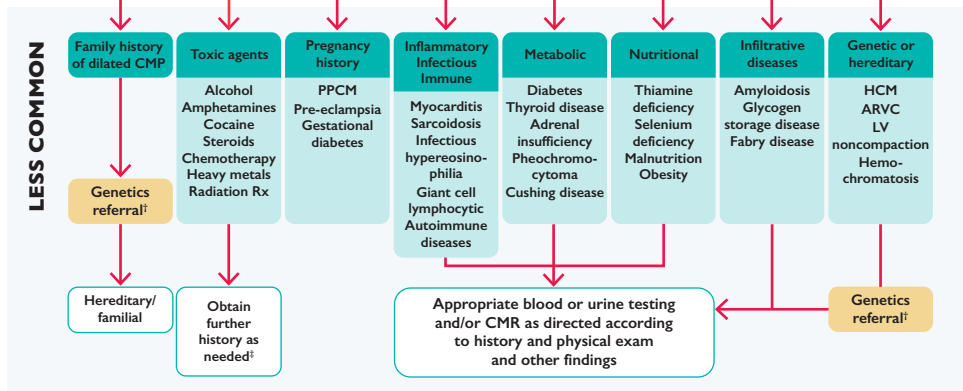
### Evidence of elevated cardiac filling pressures (at least one):

- Elevated BNP or NT-proBNP
  - Structural heart disease or diastolic dysfunction on dedicated cardiac imaging
- Hemodynamic confirmation (e.g., elevated PCWP)



**MORE COMMON**





<sup>†</sup>Includes both systolic and diastolic parameters (eg, numeric LVEF, transmitral and pulmonary venous flow patterns, or mitral annulus velocities); a preserved ejection fraction on a routine echocardiogram does not rule out the clinical syndrome of HF and therefore clinical judgment is required if other indicators point to HF as a diagnosis.

<sup>‡</sup>Patients may have mixed etiology of HF

<sup>†</sup>A detailed medical and family history may guide investigations and should be completed in all patients (see recommendation 19 in the 2017 CCS HF guideline)

<sup>‡</sup>Direct testing based on pre-test probability, availability and expertise.

Information adapted from the 2021 CCS Heart Failure pocket guide

## References

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Notes:

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