

CADTH RAPID RESPONSE REPORT:  
SUMMARY WITH CRITICAL APPRAISAL

# Combination Use of Ivabradine with Sacubitril/Valsartan: A Review of Clinical Effectiveness and Guidelines

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## Abbreviations

ACEI	angiotensin enzyme converting inhibitor
AGREE	Appraisal of Guidelines for Research and Evaluation
ARB	angiotensin receptor blockers
ARNI	angiotensin receptor neprilysin inhibitor
CCS	Canadian Cardiovascular Society
HF	heart failure
HFmEF	Heart failure with a mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
LVEF	Left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonists
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network

## Context and Policy Issues

Heart failure (HF) is a clinical syndrome that results from a structural or functional cardiac disorder that reduces the ability of the ventricle of the heart to fill with or eject blood.<sup>1</sup> Heart failure is associated with a number of symptoms, including shortness of breath, difficulty breathing and fatigue, exercise intolerance, fluid retention, cough, and weight gain.<sup>1,2</sup> Severity of HF can be described according to the New York Heart Association (NYHA) Classification system as follows: Class I, No symptoms; Class II, Symptoms with ordinary activity; Class III, Symptoms with less than ordinary activity; and Class IV, Symptoms at rest or with any minimal activity.<sup>2</sup> Heart failure can be further categorized based on ejection fraction. Heart failure with preserved ejection fraction (HFpEF) is defined as left ventricular ejection fraction (LVEF) greater than or equal to 50%; HF with a mid-range ejection fraction (HFmEF) is defined as LVEF ranging from 41% to 49%, and HF with reduced ejection fraction (HFrEF) is defined as LVEF  $\leq$  40% according to Canadian guidelines.<sup>2</sup>

Approximately 600,000 Canadians have HF, and it is a leading cause of hospitalization in Canada.<sup>3</sup> An estimated \$2.8 billion dollars are spent each year on direct health care costs for HF in Canada.<sup>3</sup> Morbidity and mortality rates in HF remain high despite the introduction of newer treatment options. An estimated 20% of those hospitalized for HF have a readmission within 30 days and the yearly mortality rate from HF exceeds 30%.<sup>3</sup>

Management of HF may relate to the individual's NYHA classification and ejection fraction; but treatment generally involves the use of pharmacotherapies, which may include diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs).<sup>2</sup> More recently, two newer pharmacotherapies, sacubitril/valsartan and ivabradine, became available for the management of HF in Canada. Sacubitril/valsartan is an angiotensin receptor neprilysin inhibitor (ARNI) and is the only drug in this class currently available in Canada. Neprilysin is an endopeptidase that breaks down endogenous vasoactive peptides, including natriuretic peptide, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of the vasoactive substances which helps to counter the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and other maladaptive processes in HF.<sup>2</sup>

Ivabradine is a heart rate lowering drug.<sup>4</sup> In HF patients, resting heart rate is an independent predictor of cardiovascular events.<sup>2</sup> Ivabradine selectively inhibits the depolarizing  $I_f$  current in the sinus node, which regulates heart rates; thus, the pharmacological effect of ivabradine requires an individual to have sinus rhythm.

Both ivabradine and sacubitril/valsartan are indicated in Canada for the treatment of stable chronic HFrEF in patients with NYHA Class II or III.<sup>4,5</sup> However, in addition to this, the approved Canadian prescribing information specifies that ivabradine is only indicated in patients who are in sinus rhythm with a resting heart rate  $\geq 77$  beats per minute.<sup>4</sup>

Since ivabradine and sacubitril/valsartan have different mechanisms of action, this combination may be considered as a potential treatment option for those individuals who remain symptomatic despite optimized therapy with other alternatives. While both ivabradine and sacubitril/valsartan are indicated for heart failure NYHA class II or III severity, it is unclear if there is evidence from clinical trials or observational studies to support their use in combination from an effectiveness or safety perspective. As well, guidance from evidence-based practice guidelines could help to inform use of this combination in clinical practice. In 2017, CADTH reviewed ivabradine through the Common Drug Review process and noted in their recommendation that “patients who are eligible for treatment with ivabradine may also be eligible for treatment with sacubitril/valsartan” but the committee pointed out at the time of review that there was no evidence that evaluated the combination of sacubitril/valsartan and ivabradine or assessed the comparative safety and efficacy of the two treatments.<sup>6</sup> The objective of this report is to provide a summary of the evidence of clinical effectiveness and clinical practice guidelines regarding the combination of ivabradine and sacubitril/valsartan for the treatment of heart failure.

## Research Questions

1. What is the clinical effectiveness of the combination of ivabradine and sacubitril/valsartan for the treatment of heart failure?
2. What are the evidence-based guidelines regarding the combination of ivabradine and sacubitril/valsartan for the treatment of heart failure?

## Key Findings

No evidence was identified regarding the clinical effectiveness of combined ivabradine and sacubitril/valsartan for the treatment for heart failure and no evidence-based guidelines regarding the combination of ivabradine and sacubitril/valsartan for the treatment of heart failure were identified.

## Methods

### Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE All (1946– ) via Ovid, Embase (1974– ) via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were ivabradine and sacubitril/valsartan. No filters

were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2015 and January 16, 2020.

## Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Q1-2: Patients over 18 years old with heart failure, NYHA class II or III
<b>Intervention</b>	Q1-2: Ivabradine combined with sacubitril-valsartan
<b>Comparator</b>	Q1: Ivabradine, sacubitril/valsartan, any other drug treatments for heart failure NYHA Class II or III Q2: No comparators
<b>Outcomes</b>	Q1: Clinical effectiveness (e.g. cardiovascular mortality, hospitalization for worsening heart failure, sudden cardiac death, fatal or non-fatal myocardial infarction, stroke, new onset atrial fibrillation) Q2: Guidelines
<b>Study Designs</b>	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, guidelines

NYHA = New York Heart Association.

## Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 they were duplicate publications, or were published prior to 2015. Guidelines with unclear methodology were also excluded.

## Summary of Evidence

### Quantity of Research Available

A total of 55 citations were identified in the literature search. Following screening of titles and abstracts, 43 citations were excluded and 12 potentially relevant reports from the electronic search were retrieved for full-text review. Fifty-six potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, all 68 publications were excluded for various reasons, and no literature was selected for inclusion in this report. Appendix 1 presents the PRISMA<sup>7</sup> flowchart of the study selection. Additional references of potential interest are found in Appendix 2.

### Summary of Findings

#### *Clinical Effectiveness of Combination Ivabradine and Sacubitril/valsartan*

No relevant evidence regarding the clinical effectiveness of the combination of ivabradine and sacubitril/valsartan for the treatment for heart failure was identified; therefore, no summary can be provided.

### Guidelines

No relevant guidelines regarding the combination of ivabradine and sacubitril/valsartan for the treatment of heart failure were identified; therefore, no summary can be provided.

### Limitations

No evidence was identified regarding the clinical effectiveness of combined ivabradine and sacubitril/valsartan for the treatment of HF, and no evidence-based guidelines for the combination of ivabradine and sacubitril/valsartan for this indication were identified. Thus, the safety and efficacy of combined ivabradine and sacubitril/valsartan in a HF population that could have poor symptom control or difficult to manage disease remains unclear.

### Conclusions and Implications for Decision or Policy Making

No evidence was identified regarding the clinical effectiveness of combined ivabradine and sacubitril/valsartan for the treatment for heart failure.

Additionally, no evidence-based guidelines were identified regarding the combination of ivabradine and sacubitril/valsartan for the treatment of HF. However, three evidence-based guidelines, by the National Institute for Health and Care Excellence (NICE),<sup>8</sup> the Canadian Cardiovascular Society (CCS),<sup>2</sup> and the Scottish Intercollegiate Guidelines Network (SIGN),<sup>9</sup> contained recommendations for each drug individually alongside algorithms that demonstrated where combined use of ivabradine and sacubitril/valsartan might fit into the management of HFrEF. These algorithms implied a combination might be permitted, but were not formal recommendation statements (with accompanying ratings for the quality of the evidence and the strength of the recommendations) and therefore did not meet the inclusion criteria for the report. As such, these algorithms and the respective guidelines that included them were excluded from this report. Given that these guidelines represent the best currently available guidance regarding the combination of ivabradine and sacubitril/valsartan, their recommendations (and descriptions of the treatment algorithms) will be discussed briefly.

First, the NICE guidelines recommend sacubitril/valsartan as an option in HFrEF in patients with NYHA class II to IV, with an LVEF of less than or equal to 35% while taking stable dosages of ACEIs or ARBs (i.e., switching to sacubitril/valsartan in patients with a LVEF of less than or equal to 35%). Ivabradine is also recommended as an option in patients with NYHA class II to IV, who are in sinus rhythm with a heart rate of 75 beats per minute (BPM) or more, and have an LVEF of less than or equal to 35% while on combination therapy. Given the overlapping populations described by the guideline recommendations there is potential for combination use based on these recommendations and this was demonstrated in the treatment algorithm included in the guidelines.

The CCS guidelines<sup>2</sup> recommend an ARNI (i.e., sacubitril/valsartan) in place of an ACEI or ARB in patients with HFrEF who remain symptomatic despite treatment according to treatment guidelines (i.e., prior treatments optimized in accordance with guideline recommendations). Recommendations state to consider ivabradine in patients with HFrEF who remain symptomatic despite treatment according to guidelines, are in sinus rhythm, have a resting heart rate of greater than or equal to 70 BPM and have had a hospitalization within the past 12 months. In addition to these explicit recommendations, an algorithm included in the guidelines for the management of symptomatic HFrEF suggested that ivabradine may be added and ACEI or ARB may be changed to an ARNI in eligible patients

with NYHA II to IV who are in sinus rhythm, with a heart rate of greater than or equal to 70 BPM who are on triple therapy with an ACEI or ARB, MRA and BB.

The SIGN<sup>9</sup> guidelines recommend sacubitril/valsartan in patients with NYHA Class II to III HFrEF and LVEF less than or equal to 40% despite optimal treatment to replace their ACE inhibitor or ARB, with consideration given to treating those with NYHA class IV. Ivabradine is recommended in patients with NYHA Class II to IV HFrEF and LVEF less than or equal to 35%, who are in sinus rhythm, and a heart rate of greater than or equal to 75 BPM. Similar to the CCS guidelines, according to the recommendations patients also should have had a hospital admission for heart failure in the preceding 12 months prior to considering treatment with ivabradine. The treatment algorithm based on the recommendations for patients with NYHA class II to IV HFrEF includes adding ivabradine to sacubitril/valsartan, a beta blocker and MRA, for patients with ongoing symptoms if sinus rhythm heart rate is greater than or equal to 75 BPM.

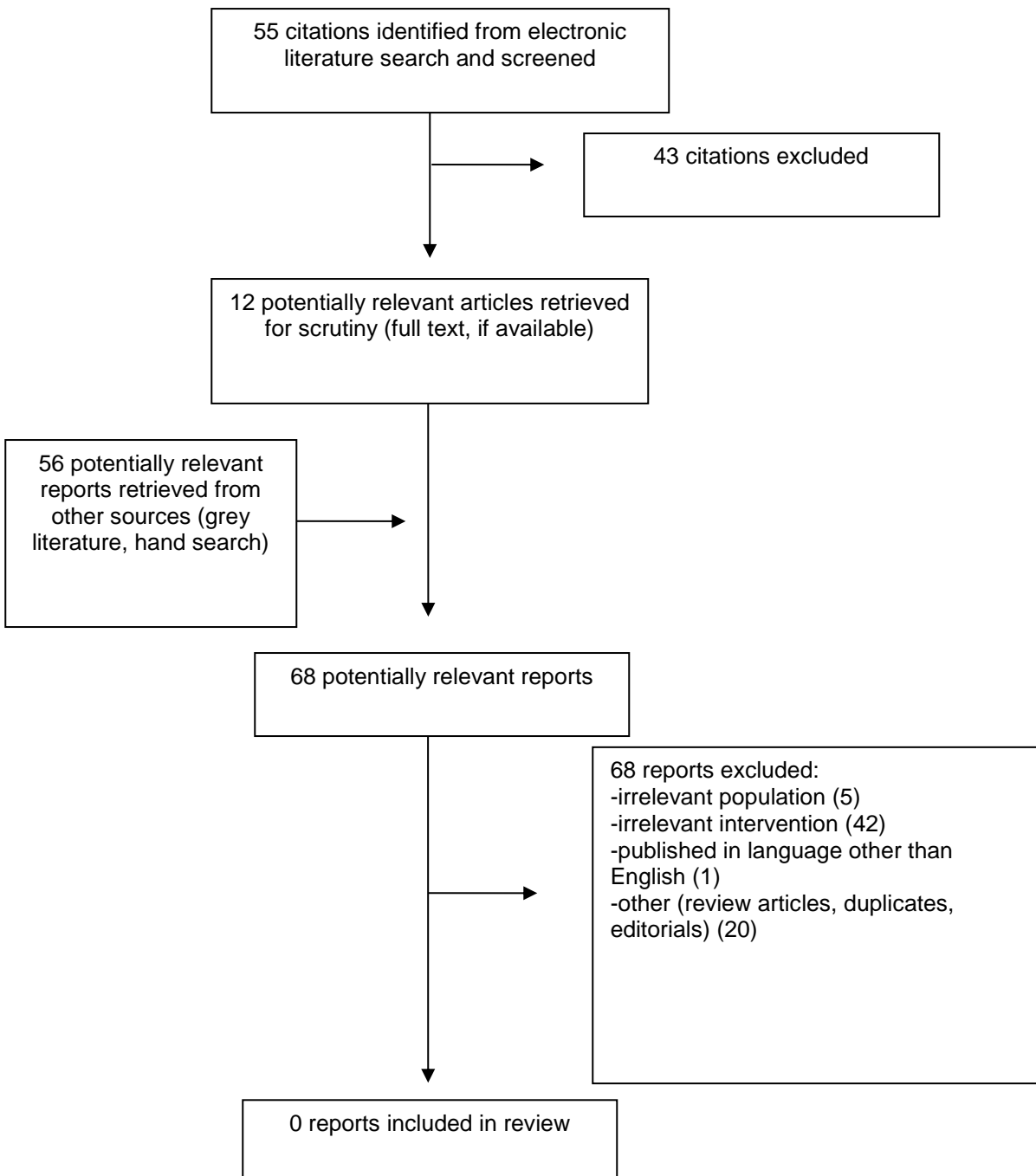
Given the lack of identified relevant literature, the combination of ivabradine and sacubitril/valsartan for the treatment of HF appears to be unsupported by published clinical trials or observational studies and clear, direct evidence-based recommendations endorsing combination use were lacking. As such, the safety and efficacy of combined ivabradine and sacubitril/valsartan in a HF population that could have poor symptom control or difficult to manage disease remains unclear. Three guidelines included treatment algorithms that showed the potential for use of combination therapy with ivabradine and sacubitril/valsartan in the treatment pathway, but there were no explicit combination recommendations supported by evidence.

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## Appendix 1: Selection of Included Studies



## Appendix 2: Additional References of Potential Interest

### Guidelines with Evidence-Based Recommendations for Ivabradine and Sacubitril/valsartan Monotherapy

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