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Ivabradine for Heart Failure

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Authors: Christine Perras, Louis de Léséleuc, Tarry Ahuja, Hannah Loshak

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Background

Heart failure (HF) is a condition characterized by reduced cardiac output occurring due to complications of cardiovascular disease.[1,2] Patients with HF will complain of fatigue and shortness of breath.[2] The condition is further categorized as HF with reduced ejection fraction and HF with preserved ejection fraction.[2] Heart failure with reduced ejection fraction is caused by left ventricular dysfunction.[2]

The New York Heart Association (NYHA) classifies HF according to the severity of symptoms, with Class I being less severe ("no limitation of physical activity; ordinary physical activity does not cause symptoms of heart failure") to Class IV being the most severe ("unable to carry on any physical activity without symptoms of heart failure, or symptoms of heart failure at rest").[1]

HF is a leading cause of hospital admissions and has a poor prognosis.[3] A population-based study of patients in Ontario showed that the age- and sex-standardized incidence of HF was 306.1 per 100,000 persons in 2007.[3] In this same study, hospitalized HF patients in Ontario had a one-year risk-adjusted mortality of 33.8%.[3] The mortality rate for HF ranged between 5% at one year and up to 50% at five years after diagnosis, depending on the severity of symptoms, heart function, age, and other factors.[3]

There is no cure for HF. The goals of therapy include improving survival, decreasing morbidity, improving functional capacity, and improving quality of life.[4] The 2017 Canadian Cardiovascular Society (CCS) guidelines recommend that symptomatic patients with HF, with reduced ejection fraction (left ventricular ejection fraction [LVEF] of 40% or less), be treated with triple therapy of angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin II receptor blocker [ARB] if intolerant to ACE inhibitors), a beta blocker, and a mineralocorticoid receptor antagonist (MRA).[4] If patients with NYHA Class II, III, or IV HF still exhibit symptoms at maximum tolerated doses of triple therapy, the guidelines recommend replacing the ACE inhibitor or ARB with an angiotensin receptor-neprilysin inhibitor (ARNI); or adding ivabradine (an I_{funny} channel inhibitor) in patients with a resting heart rate of greater than 70 beats per minute, in sinus rhythm, and with a hospitalization in the past 12 months (see Treatment Algorithm, Figure 4, page 1357 of the CCS guidelines).[4]

Sacubitril (a neprilysin inhibitor) in combination with valsartan (an ARB) and marketed under the trade name Entresto, and ivabradine (trade name Lancora), are approved for the following indications in Canada (Table 1).[5,6]

Table 1: Health Canada Indications

Sacubitril/ Valsartan (Entresto)	Ivabradine (Lancora)
Treatment of heart failure with reduced ejection fraction in patients with New York Heart Association Class II or III, to reduce the incidence of cardiovascular death and heart failure hospitalization	Treatment of stable chronic heart failure with reduced left ventricular ejection fraction (≤ 35%) in adult patients with New York Heart Association Classes II or III who are in sinus rhythm with a resting heart rate ≥ 77 beats per minute, to reduce the incidence of cardiovascular mortality and hospitalizations for worsening heart failure

Entresto and Lancora are reimbursed by most government-sponsored drug plans based on recommendations from CADTH's Canadian Drug Expert Committee (CDEC) (Table 2).[7,8]

Table 2: Canadian Drug Expert Committee Recommendations

Sacubitril/ Valsartan (Entresto)	Ivabradine (Lancora)
Treatment of heart failure with reduced ejection fraction in patients with New York Heart Association Class II or III heart failure to reduce the incidence of cardiovascular death and heart failure hospitalization, if all of the clinical criteria are met Clinical Criteria: • reduced left ventricular ejection fraction (< 40%). • patient has New York Heart Association Class II to III symptoms despite at least four weeks of treatment with a stable dose of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist in combination with a beta blocker and other recommended therapies, including an aldosterone antagonist (if tolerable) • plasma B-type natriuretic peptide (BNP) ≥ 150 pg/mL or N-terminal prohormone B-type natriuretic peptide (NT-proBNP) ≥ 600 pg/mL, or plasma BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL levels, if the patient has been hospitalized for HF within the past 12 months	Treatment of stable chronic heart failure with reduced left ventricular ejection fraction (≤ 35%) in adult patients with New York Heart Association Classes II or III who are in sinus rhythm with a resting heart rate ≥ 77 beats per minute, to reduce the incidence of cardiovascular mortality and hospitalizations for worsening heart failure, administered in combination with standard chronic heart failure therapies, if the clinical criteria are met. Clinical Criteria: • patients with New York Heart Association Class II to III symptoms despite at least four weeks of treatment with a stable dose of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker in combination with a beta blocker and, if tolerated, a mineralocorticoid receptor antagonist • patients with at least one hospitalization due to heart failure in the last year • resting heart rate must be documented to be ≥ 77 beats per minute on average using either an ECG on at least three separate visits or by continuous monitoring

Policy Issue

While the CCS guidelines recommend that both medications be considered in patients with a reduced LVEF of 40% or less, the product monograph and the CDEC recommendation for ivabradine specify a requirement for a LVEF of 35% or less. This is in contrast to sacubitril/ valsartan where the reimbursement criteria require a LVEF of less than 40%. To facilitate adjudication, the jurisdictional drug plan members would like to align the LVEF criteria of sacubitril/valsartan and ivabradine. They have asked CADTH for a review of the evidence on the ejection fraction requirement for ivabradine to include patients with an ejection fraction between 36% and 40%.

The policy question driving this request is: Should the Canadian public drug plans change their reimbursement criteria for ivabradine (Lancora) to align with the ejection fraction recommendation of the CCS guidelines?

Methods

A CADTH Rapid Response Report: Summary With Critical Appraisal[9] was commissioned to review the evidence of efficacy and safety of ivabradine to treat HF in patients with an ejection fraction of 40% or less.

The research question of the review was: What is the clinical effectiveness of ivabradine for patients with stable chronic HF and with LVEF > 35% and LVEF ≤ 40%?

The literature was searched for English-language documents published between January 1, 2014 and March 7, 2019. Table 3 provides the selection criteria used to identify the relevant literature of population, intervention, comparators, outcomes, and study designs for the Rapid Response Report.

Table 3: Selection Criteria Used in the CADTH Rapid Response Report

Population	Adult patients with stable chronic heart failure of New York Heart Association Classification II or III and with left ventricular ejection fraction > 35% and left ventricular ejection fraction ≤ 40% Studies recruiting patients with a LVEF range outside of the range of interest could be included if the mean LVEF was > 35% and ≤ 40% at baseline.
Intervention	Ivabradine (taken with or without standard chronic health failure therapies)
Comparators	Placebo, standard of care
Outcomes	Clinical effectiveness (e.g., worsening heart failure, mortality, hospitalizations, cardiac events), safety (e.g., rate of adverse events)
Study Designs	Systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Findings

No studies were identified for which the inclusion criteria specified HF patients with LVEF of greater than 35% and LVEF of less than or equal to 40%. Two studies with an inclusion criterion of HF patients with LVEF of less than 40% were evaluated in the Rapid Response Report because the mean baseline LVEF was greater than 35% and less than or equal to 40% in both the intervention and comparator groups.

One study was a randomized controlled trial and the other study was a non-randomized study; both compared ivabradine combined with carvedilol to carvedilol monotherapy (Table 4). For detailed information on the methods and findings, please refer to the Rapid Response Report published on the CADTH website at https://www.cadth.ca/ivabradine-adults-stable-chronic-heart-failure-review-clinical-effectiveness-0.

Table 4: Results of the Studies Included in the Rapid Response Report

Study Characteristics, Interventions, and Patient Characteristics at Baseline	Results	Of Note
Randomized Controlled Trial		
Sallam et al. (2016) (Oman)[10] N = 100 Study duration: 12 weeks *Intervention group (n = 50):* Ivabradine starting dose of 2.5 mg twice daily and a maximum dose of up to 7.5 mg twice daily combined with carvedilol starting dose of 3.125 mg twice daily and a maximum dose of up to 25 mg twice daily • Age (mean, SD): 62 year (9.2) • Male: 66% • RHR (mean, SD): 79 bpm (12) • NYHA classification (mean, SD): 2.6 (0.5) • LVEF (mean, SD): 37% (16) *Comparator group (n = 50):* Carvedilol starting dose of 3.125 mg twice daily and a maximum dose of up to 25 mg twice daily • Age (mean, SD): 65 years (10) • Male: 74% • RHR (mean, SD): 80 bpm (16) • NYHA classification (mean, SD): 1.6 (1.5) • LVEF (mean, SD): 38% (15)	Ivabradine combined with carvedilol was statistically significantly different from carvedilol monotherapy for the following outcomes (mean, SD): • NYHA classification: 1.5 (1.3) vs. 1.9 (0.6) P = 0.047 • CSS KCCQa score: 82 (14) vs. 71(21) P = 0.002 • CSS KCCQa score: 80 (14) vs. 68 (20) P = 0.001 • RHR, bpm: 69 (11) vs. 78 (17) P = 0.002 • HR, bpm: 71 (8) vs. 79 (10) P < 0.001 There was no statistically significant difference in LVEF: 42% (17) vs. 37% (13), P = 0.093 Sixteen adverse events were reported with combination therapy (asymptomatic and symptomatic bradycardia, hypotension, palpitations, and phosphenes) compared with 5 adverse events with carvedilol monotherapy (asymptomatic bradycardia, hypotension, and palpitations).	Interventions were added to a standard treatment regimen. The baseline characteristics of the intervention group differed from the comparator group: • statistically significantly higher prevalence of hypertension, diabetes, or hyperlipidemia • statistically significantly higher reported incidence of previous myocardial infarction • statistically significantly higher NYHA classification The number of patients in each NYHA Class was not reported. The mean baseline value of NYHA Class suggests that some patients in the comparator group were in NYHA Class I.
Prospective, Open-Label, Non-randomized Study		
Bagriy et al. (2015) (Ukraine)[11] N = 69 Study duration: 5 months *Intervention group (n = 33):* Ivabradine starting dose of 2.5 mg twice daily and a maximum dose of up to 7.5 mg twice daily combined with	Ivabradine combined with carvedilol was statistically significant different from carvedilol monotherapy for the following outcomes (mean, SD): • NYHA classification, % patients improved by at least one Class: 58 vs. 36 P < 0.05 • RHR, bpm: 61.6 (3.1) vs. 70.2 (4.4)	Allocation of treatment was decided by the investigator. Standard HF treatment (such as ACE inhibitor, ARB, statin, MRA, and diuretic) were continued during the study. The baseline characteristics of the intervention group differed from the comparator group for one parameter:

Study Characteristics, Interventions, and Patient Characteristics at Baseline	Results	Of Note
Randomized Controlled Trial		
carvedilol starting dose of 3.125 mg twice daily and a maximum dose of up to 25 mg twice daily • Age (mean, SD): 63.2 year (12.3) • Male: 64% • RHR (mean, SD): 82.7 bpm (11.3) • NYHA Classification II : 39% (n/N: 13/33) • NYHA Classification III : 61% (n/N: 20/33) • LVEF (mean, SD): 37.4% (6.3) *Comparator group (n = 36):* Carvedilol starting dose of 3.125 mg twice daily and a maximum dose of up to 25 mg twice daily • Age (mean, SD): 62.1 years (11.4) • Male: 69% • RHR (mean, SD) : 83.1 bpm (10.6) • NYHA Classification II : 42% (n/N: 15/36) • NYHA Classification III : 58% (n/N: 21/36) • LVEF (mean, SD): 36.9% (6.1)	P < 0.001 • SBP, mm Hg: 123.5 (5.7) vs. 116.4 (7.8) P < 0.001 • 6MWT, metres: 574.4 (102.3) vs. 527.2 (90.6) P < 0.001 • There was no statistically significant difference in LVEF 41.3% (6.9) vs. 38.7% (6.8), P = NS There were 5 adverse events reported with combination therapy (bradycardia or blurred vision) compared with 8 adverse events with carvedilol monotherapy (muscle or general weakness, or transient bronchial obstructions).	• statistically significantly fewer patients with hypertension. Mean doses at 5 months: *Intervention group* Ivabradine = 12.2 (SD 2.1) mg/day Carvedilol = 37.8 (SD 16.3) mg/day *Comparator group* 30.9 (SD 15.3) mg/day[b]

6MWT = six-minute walk test; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; bpm = beats per minute; CSS KCCQ= clinical summary score of the Kansas City Cardiomyopathy Questionnaire; HR = heart rate; LVEF = left ventricular fraction; MRA = mineralocorticoid receptor antagonist; NS = non-significant; NYHA = New York Heart Association; overall summary score of the Kansas City Cardiomyopathy Questionnaire; RHR = resting heart rate; SBP = systolic blood pressure; SD = standard deviation; vs. = versus.

[a] The Kansas City Cardiomyopathy Questionnaire is a self-administered instrument. The original instrument has 23 questions; the short-form KCCQ has 12 questions. The randomized controlled trial used the long version of the instrument. The overall summary score can be derived from the physical function, symptoms (frequency and severity), social function, and quality of life domains. The clinical summary score is derived from the physical function and symptoms domains. A higher score reflects better health status.[12,13 14]

[b] Dose of comparator group is statistically significantly lower compared with the dose of carvedilol used in combination with ivabradine in the intervention group, P = 0.049.

Conclusions and Implications for Decision-Making

Two studies were included in the CADTH Rapid Response Report: one randomized controlled trial and one non-randomized study. Both studies compared ivabradine combined with carvedilol to carvedilol monotherapy. Both allowed medication dose increases, up to pre-specified maximum tolerated doses. The randomized controlled trial (RCT) was a 12-week study of 100 patients, whereas the non-randomized study had 69 patients in a study duration of five months. Patients included in the studies had a mean LVEF of > 35% and ≤ 40% at baseline. The RCT was conducted in Oman and the non-randomized study was conducted in Ukraine.

The evidence of the two included studies showed greater benefits with combination therapy (ivabradine plus carvedilol) compared with carvedilol alone; however, these results pertain to surrogate outcomes such as resting heart rate and NYHA classification. In the RCT, combination therapy was also associated with improved health-related quality of life as measured by a validated instrument, the Kansas City Cardiomyopathy Questionnaire.

There are several limitations in the RCT and the non-randomized study:

- Baseline differences in patient characteristics in the RCT may imply that the ivabradine plus carvedilol group was sicker than the monotherapy group. This creates uncertainty with the interpretation of the results.
- The mean dose of carvedilol at five months was statistically significantly higher in the combination therapy group compared with the monotherapy group in the non-RCT study. The authors of the study postulated that ivabradine may have facilitated the up-titration of carvedilol.[11] The mean dose of carvedilol was not reported in the RCT.
- While patients in the non-randomized study could continue their standard HF treatments, no additional information was given regarding these medications and thus potential differences between the two groups for these medications could not be assessed. In the RCT publication, it is mentioned that the interventions were added to a standard treatment regimen, but it did not specify which one.
- The choice of treatment was determined by the investigators in the non-randomized study. The protocol advised that therapy with ivabradine be started with every other patient. No other information on treatment allocation was provided.
- For both studies, the study durations and sample sizes were insufficient to measure clinically important outcomes such as cardiac events, mortality, and long-term safety.
- In both studies, ivabradine was combined with carvedilol, a beta blocker. No evidence was identified on the effectiveness of ivabradine with other drugs (i.e., ACE inhibitors, ARB, MRA) in the population of interest. While some of these drugs may have been part of the standard HF treatments allowed in the studies, no specific information was provided on the latter, as stated earlier.

The literature search was restricted to five years and relevant studies published before 2014 would have been missed. To identify studies published before 2014, three systematic reviews[15-17] of ivabradine studies in HF patients were searched. Up to nine trials were included in these three systematic reviews, including the non-randomized study included in the Rapid Response Report, the BEAUTIFUL study, and the SHIFT study. The BEAUTIFUL and SHIFT studies are subsequently described. One additional trial published in 2011, which was conducted in patients with a mean LVEF of 39.1% (standard deviation [SD] 5.5) at

baseline, was identified.[18] This RCT of 29 patients showed no difference between ivabradine combined with a beta blocker to the beta blocker alone.

Within the literature search results of the Rapid Response review, there were many studies identified with an inclusion criterion of LVEF ≤ 40%; however, these were excluded from the review because upon further examination of the baseline characteristics of patients the mean LVEF was less than 35%. While some patients included in such trials may have corresponded to the population of interest (LVEF 36% to LVEF 40%), they would have been under-represented in the data set, severely limiting any conclusion on drug efficacy in that subpopulation.

The CCS refers to two key RCTs in its guidelines:[4] BEAUTIFUL (morBidity-mortality EvAlUaTion of the If Inhibitor Ivabradine in Patients With Coronary Disease and Left-VentricULar Dysfunction)[19] and SHIFT (the Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial).[20] SHIFT was the pivotal study submitted to Health Canada for the regulatory approval of ivabradine (Lancora). In both trials, the mean LVEF at baseline was less than 35%.

- In BEAUTIFUL, 10,917 patients with stable coronary artery disease that met the inclusion criteria of LVEF < 40% were enrolled. The mean LVEF at baseline was 32.4% (SD 5.5) and 32.3% (SD 5.5). Ivabradine showed no significant improvement in cardiac outcomes compared with placebo. In a pre-specified subgroup of patients with a baseline heart rate of ≥70 beats per minute (bpm), ivabradine reduced the incidence of the secondary end point of fatal and non-fatal myocardial infraction.[4,19]
- In SHIFT, 6,558 patients with symptomatic HF that met the inclusion criteria (LVEF of ≤ 35%, in sinus rhythm with a heart rate of ≥70 bpm, admitted to hospital for worsening HF within the previous 12 months, and on stable background treatment of a beta blocker) were enrolled. The mean LVEF at baseline was 29.0% (SD 5.1) for the ivabradine group and 29.0% (SD 5.2) for the placebo group. The primary end point was the composite of cardiovascular death or hospital admission for worsening HF. There was an 18% decrease in the primary outcome, but ivabradine did not reduce all-cause or cardiovascular mortality.[4,20]

Finally, it is worth noting that both the *2017 ACC/AHA/HFSA [American College of Cardiology/American Heart Association Guideline/Heart Failure Society of America] Focused Update of the 2013 ACCF/AHA [American College of Cardiology Foundation/American Heart Association] Guideline for the Management of Heart Failure and the 2016 ESC [European Society of Cardiology] Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure* set a LVEF threshold of ≤ 35% for ivabradine (Table 7.3.2.11, page 786 in the ACC/AHA guideline and pages 2151 and 2152 in the ESC guidelines).[21,22]

Policy Implications and Options

There is insufficient quantity and quality of evidence for recommending for or against an expansion of the ivabradine LVEF criteria. The bulk of the evidence seems to have been conducted in patients with a baseline LVEF of < 35% even in trials that specified a LVEF of less than 40% as one of their inclusion criteria.

Thus, the effectiveness of ivabradine in patients with a LVEF of > 35% and ≤ 40% has not been firmly established and, hence, no conclusions can be made. Possible policy options regarding the reimbursement criteria of ivabradine include:

- maintaining the status quo; the reimbursement criteria for ivabradine would not be expanded to include patients with a LVEF between 36% and 40%
- changing the reimbursement criteria for ivabradine to align with the CCS recommendation to include patients with a LVEF between 36% and 40%; this option would not be aligned with the Health Canada indication
- consider reimbursing ivabradine in patients with a LVEF between 36% and 40% as a last resort and on a case-by-case basis; for example, in patients who do not respond to or are intolerant of the comparator drugs.

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