

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

# Ivabradine for Adults with Stable Chronic Heart Failure: Clinical Effectiveness

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## Research Question

What is the clinical effectiveness of ivabradine for patients with stable chronic heart failure?

## Key Findings

Two randomized controlled trials regarding the clinical effectiveness of ivabradine for patients with stable chronic heart failure were identified.

## Methods

A limited literature search was conducted on key resources including Medline via OVID, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. 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 1, 2014 and March 7, 2019. Internet links were provided, where available.

## Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Adult patients with stable chronic heart failure of New York Heart Association (NYHA) class II or III and with left ventricular ejection fraction (LVEF) > 35% and ≤ 40%
<b>Intervention</b>	Ivabradine (taken with or without standard chronic health failure therapies)
<b>Comparators</b>	Placebo Standard of care
<b>Outcomes</b>	Clinical effectiveness (e.g., worsening heart failure, mortality, hospitalizations, cardiac events), safety (e.g., rate of adverse events)
<b>Study Designs</b>	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

## Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, and non-randomized studies.

Two randomized controlled trials regarding the clinical effectiveness of ivabradine for patients with stable chronic heart failure were identified. No relevant health technology assessments, meta-analyses, randomized controlled trials, or non-randomized studies were identified.

Additional references of potential interest are provided in the appendix.

## Overall Summary of Findings

Two randomized controlled trials<sup>1,2</sup> regarding the clinical effectiveness of ivabradine for patients with stable chronic heart failure were identified.

Both studies were conducted in patients with a left ventricular ejection fraction less than 40% and compared ivabradine plus beta-blockers to beta-blockers alone.<sup>1,2</sup> The authors of the first study concluded that the combination produced a favourable decrease in heart rate, while improving functional and clinical parameters of heart failure patients over the short-term.<sup>1</sup> Similarly, authors of the second study reported that a favourable decrease in heart rate and improvements in health-related quality of life could be achieved with their respective combination.<sup>2</sup>

## References Summarized

### Health Technology Assessments

No literature identified.

### Systematic Reviews and Meta-analyses

No literature identified.

### Randomized Controlled Trials

1. Hidalgo FJ, Anguita M, Castillo JC, et al. Effect of early treatment with ivabradine combined with beta-blockers versus beta-blockers alone in patients hospitalised with heart failure and reduced left ventricular ejection fraction (ETHIC-AHF): A randomised study. *Int J Cardiol.* 2016;217:7-11.  
[PubMed: PM27167103](#)
2. Sallam M, Al-Saadi T, Alshekaili L, Al-Zakwani I. Impact of ivabradine on health-related quality of life of patients with ischaemic chronic heart failure. *Curr Vasc Pharmacol.* 2016;14(5):481-486.  
[PubMed: PM27145825](#)

### Non-Randomized Studies

No literature identified.

## Appendix — Further Information

### Systematic Reviews and Meta-analyses

#### *Alternative Comparator*

3. Peck KY, Lim YZ, Hopper I, Krum H. Medical therapy versus implantable cardioverter - defibrillator in preventing sudden cardiac death in patients with left ventricular systolic dysfunction and heart failure: a meta-analysis of > 35,000 patients. *Int J Cardiol.* 2014;173(2):197-203.  
[PubMed: PM24636548](#)

#### *Alternative Population – Ejection Fraction Unspecified*

4. Hartmann C, Bosch NL, de Aragao Migueta L, Tierie E, Zytinski L, Baena CP. The effect of ivabradine therapy on heart failure patients with reduced ejection fraction: a systematic review and meta-analysis. *Int J Clin Pharm.* 2018;40(6):1443-1453.  
[PubMed: PM30173307](#)
5. Komajda M, Bohm M, Borer JS, et al. Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Eur J Heart Fail.* 2018;20(9):1315-1322.  
[PubMed: PM29806165](#)
6. Anantha Narayanan M, Reddy YN, Baskaran J, Deshmukh A, Benditt DG, Raveendran G. Ivabradine in the treatment of systolic heart failure - a systematic review and meta-analysis. *World J Cardiol.* 2017;9(2):182-190.  
[PubMed: PM28289533](#)
7. Thomsen MM, Lewinter C, Kober L. Varying effects of recommended treatments for heart failure with reduced ejection fraction: meta-analysis of randomized controlled trials in the ESC and ACCF/AHA guidelines. *ESC Heart Fail.* 2016;3(4):235-244.  
[PubMed: PM27867524](#)
8. Martin RI, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials. *Heart.* 2014;100(19):1506-1510.  
[PubMed: PM24951486](#)

### Randomized Controlled Trials

#### *Alternative Population – Other Cardiac Condition*

9. Nguyen LS, Squara P, Amour J, et al. Intravenous ivabradine versus placebo in patients with low cardiac output syndrome treated by dobutamine after elective coronary artery bypass surgery: a phase 2 exploratory randomized controlled trial. *Crit Care.* 2018;22(1):193.  
[PubMed: PM30115103](#)
10. Abdel-Salam Z, Rayan M, Saleh A, Abdel-Barr MG, Hussain M, Nammam W. I(f) current inhibitor ivabradine in patients with idiopathic dilated cardiomyopathy: impact on the exercise tolerance and quality of life. *Cardiol J.* 2015;22(2):227-232.  
[PubMed: PM25179314](#)

## *Alternative Population – Ejection Fraction Unspecified*

11. Villacorta AS, Villacorta H, Caldas JA, et al. Effects of heart rate reduction with either pyridostigmine or ivabradine in patients with heart failure: a randomized, double-blind study. *J Cardiovasc Pharmacol Ther.* 2018;1074248418799364.  
[PubMed: PM30198318](#)
12. Bohm M, Borer JS, Camm J, et al. Twenty-four-hour heart rate lowering with ivabradine in chronic heart failure: insights from the SHIFT Holter substudy. *Eur J Heart Fail.* 2015;17(5):518-526.  
[PubMed: PM25801408](#)

## Non-Randomized Studies

### *Alternative Population – Other Cardiac Condition*

13. Adorisio R, Calvieri C, Cantarutti N, et al. Heart rate reduction strategy using ivabradine in end-stage Duchenne cardiomyopathy. *Int J Cardiol.* 2019;280:99-103.  
[PubMed: PM30686494](#)
14. Sargento L, Satendra M, Longo S, Lousada N, dos Reis RP. Heart rate reduction with ivabradine in patients with acute decompensated systolic heart failure. *Am J Cardiovasc Drugs.* 2014;14(3):229-235.  
[PubMed: PM24452599](#)

### *Alternative Population – Ejection Fraction Unspecified*

15. Guzman M, Gomez R, Romero SP, et al. Prognosis of heart failure treated with digoxin or with ivabradine: a cohort study in the community. *Int J Clin Pract.* 2018;72(11):e13217.  
[PubMed: PM30248211](#)
16. Speranza M, Díaz JP, Agüero C, Alvarado A, Blanco M, Román Mora A. Ivabradine use in patients with HFrEF in the heart failure multidisciplinary program (PIC) in a private hospital: first registration and 3-years follow up, Central American (CA) region. *Rev Costarric Cardiol.* 2018;20(1).  
[http://www.scielo.sa.cr/scielo.php?script=sci\\_arttext&pid=S1409-41422018000100023&nrm=iso](http://www.scielo.sa.cr/scielo.php?script=sci_arttext&pid=S1409-41422018000100023&nrm=iso).
17. Zugck C, Stork S, Stockl G, RELIf-CHF study investigators. Long-term treatment with ivabradine over 12months in patients with chronic heart failure in clinical practice: effect on symptoms, quality of life and hospitalizations. *Int J Cardiol.* 2017;240:258-264.  
[PubMed: PM28408104](#)
18. Bagriy AE, Schukina EV, Samoilova OV, et al. Addition of ivabradine to beta-blocker improves exercise capacity in systolic heart failure patients in a prospective, open-label study. *Adv Ther.* 2015;32(2):108-119.  
[PubMed: PM25700807](#)
19. Bocchi EA, Bohm M, Borer JS, et al. Effect of combining ivabradine and beta-blockers: focus on the use of carvedilol in the SHIFT population. *Cardiology.* 2015;131(4):218-224.  
[PubMed: PM25968495](#)

20. Komajda M, Bohm M, Borer JS, et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure according to blood pressure level in SHIFT. *Eur J Heart Fail.* 2014;16(7):810-816.  
[PubMed: PM24961493](#)
21. Voors AA, van Veldhuisen DJ, Robertson M, et al. The effect of heart rate reduction with ivabradine on renal function in patients with chronic heart failure: an analysis from SHIFT. *Eur J Heart Fail.* 2014;16(4):426-434.  
[PubMed: PM24504937](#)
22. Zugck C, Martinka P, Stockl G. Ivabradine treatment in a chronic heart failure patient cohort: symptom reduction and improvement in quality of life in clinical practice. *Adv Ther.* 2014;31(9):961-974.  
[PubMed: PM25160945](#)

### Additional References – Registered Trials

23. Benstoem C, Stoppe C, Breuer T, et al. Ivabradine as adjuvant treatment for chronic heart failure. *Cochrane Database of Systematic Reviews.* 2018;4; CD013004.  
<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013004/full>. Accessed 2019 Mar 19.
24. Ain Shams University. NCT03701880: Early use of ivabradine in heart failure (ivabradine). *Clinicaltrials.gov.* Bethesda (MD): U.S. National Library of Medicine; 2018:  
<https://clinicaltrials.gov/ct2/show/NCT03701880>. Accessed 2019 Mar 19.