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Systematic literature review of randomized clinical trials (RCTs) on ivabradine (IVA) in heart failure (HF)

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BACKGROUND

- Heart failure (HF) is a syndrome caused by cardiac dysfunction, resulting in reduced life expectancy. It is associated with fatigue and dyspnea, induced by left (or global) ventricular dysfunction.[1] The severity of HF ranges from asymptomatic (NYHA I), followed by mild (NYHA II, slight limitation in physical activity) and moderate (NYHA III, symptoms while walking on the flat), to severe HF (NYHA IV).[2]
- HF encompasses a heterogeneous population, from those with normal left ventricular ejection fraction (LVEF) (Ejection fraction (EF)≥50%; called HF with preserved EF (HFpEF)) to those with reduced LVEF (EF<40%; called HF with reduced EF (HFrEF).[1]
- An estimated 64.3 million people are living with HF worldwide. The HF prevalence varies between 1.3% to 4% in Europe and reached 2.2% in the USA. This prevalence is predicted to increase by 46% from 2012 to 2030.[3]
- Ivabradine (IVA) is a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker that lowers the heart rate (HR) by prolonging the diastolic depolarization, which reduces the stress on the heart, thereby slowing the progression of HF and improving symptoms.[4]

OBJECTIVE

To identify published randomized clinical trials **(RCTs)** assessing **IVA** and its impact on **efficacy**, **safety**, **resource use, and patient reported outcomes (PROs)** in patients with **HFrEF**.

METHODS

- A systematic literature review was performed by searching MEDLINE®, Embase (via OVID), Cochrane CENTRAL and clinicaltrials.gov from their inception until the 07th of July 2021.
- Conference websites were additionally searched (abstracts of the events from the last 3 years [2019-2021] have been collected).
- No restrictions were applied. The review was conducted following the Cochrane guidelines for Systematic Reviews of Interventions.[15]
- Studies were selected based on the inclusion and exclusion criteria (Table 1).

Table 1: Inclusion criteria (PICOS)

PICOS	Inclusion
Population	Adult patients with HF*
Intervention	Ivabradine
Comparators	Active or non-active comparators including Procoralan® generic
Outcomes	• Efficacy (including composite outcomes)* • Safety** • Health resource use • Patient reported outcomes (PROs)
Study design	RCTs

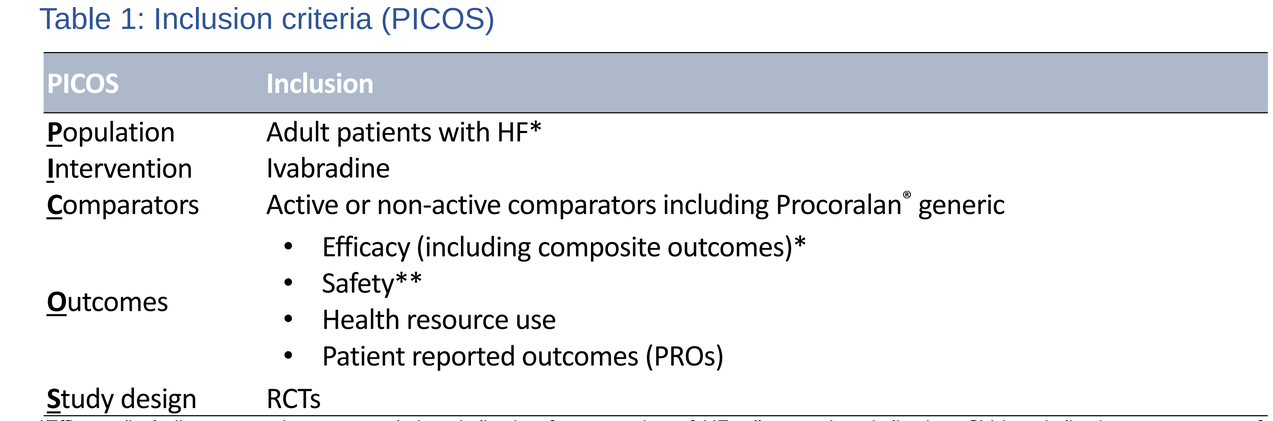
*Efficacy (including composite outcomes): hospitalization for worsening of HF, all-cause hospitalization, CV hospitalization, percentage of patients according to NYHA (New York Heart Association) Class, change in NYHA (% of patients with change/improvement, mean change), death from HF, CV (cardiovascular) death, All-cause death, reduction in HR, change in resting HR, blood pressure, change in LVEF, change in NT-proBNP, 6-minute walk test, echocardiographic parameters (LVEDVI, LVESVI, LVESV and LVEDV), oxygen consumption (peak oxygen consumption (VO2), maximal oxygen consumption (VO2 max), double product), minute ventilation/carbon dioxide production (VE/VCO2)

**Safety: total adverse events (AEs), total serious adverse events (SAEs), cardiac disorders (bradycardia, atrial fibrillation), luminous phenomena (phosphenes)

RESULTS

- Of **1,911** records identified, **24** trials (**51** publications) focusing on HFrEF patients (Figure 1) were included.
- A total of 7 studies compared IVA+ BT (background therapy) vs active comparator, while the remaining were against BT or placebo.
- **The sample size** ranged from 21 to 6,505 patients. In the pooled analysis for SHIFT and BEAUTIFUL, 11,897 patients were studied.[5]
- **The duration of follow-up** ranged from 7 days to 3 years.

Figure 1: PRISMA diagram of search results



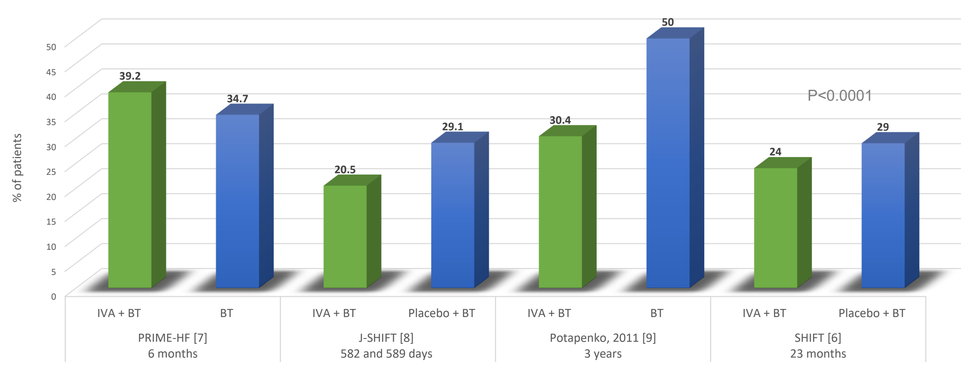
*Studies comparing different IVA doses were excluded

** Subgroup of patients of interest: NYHA class, patients with rate ≥70 or 75 or 77 bpm, Angina, renal dysfunction,, diabetes, elderly (over 65 and others cut-off above 65), blood pressure level, sex, duration of HF, NT-proBNP, etiology of HF (ischemic/non-ischemic), LVEF (<35%/≥35%, <40%/≥40%, <50%/≥50%), hypertension (yes/no), BNP (B-type natriuretic peptide), Asian patients, subgroups defined by LV diastolic dysfunction classification (grade I, II and III)

RESULTS

- In the pivotal phase 3 trial (SHIFT), treatment with IVA on top of background therapy (IVA+BT) significantly reduced the risk of **hospitalization and mortality** at 23 months (p<0.0001)[6,7,8,9].
- IVA+BT was associated with a significant reduction in HR at a median of 23 months[6,7,8,10] and a lower risk of **all-cause death and cardiovascular (CV) death**[6,7,8,11]. The majority of included studies, in this SLR, showed similar results with SHIFT (Figure 2, 3, 4).
- Subgroup analysis of the SHIFT trial shows that IVA significantly decreases **HF deaths** and **all-cause death** across age groups and HR cohorts[13].

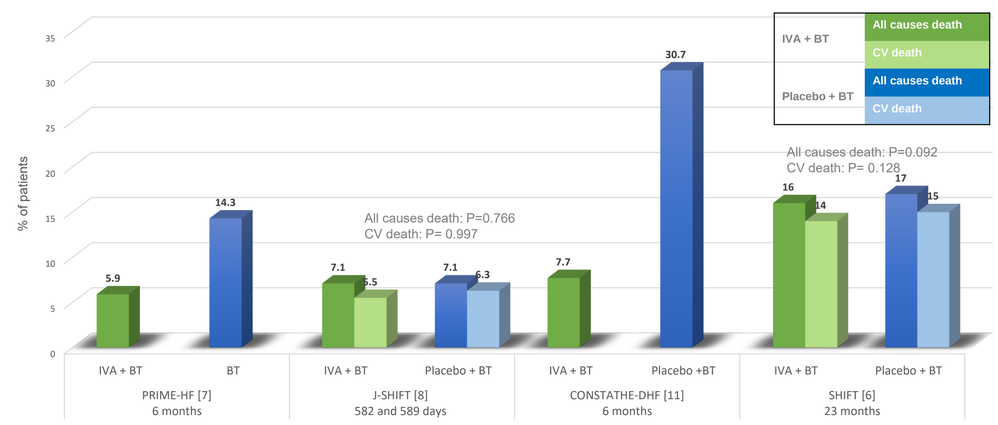
Figure 2: Composite outcomes*



* All-cause mortality or heart failure hospitalization (PRIME-HF) or
Cardiovascular death or hospital admission for worsening HF (SHIFT, J-SHIFT) or
Cardiovascular death, hospital admission for worsening HF, or hospital admission for non-fatal myocardial infarction (Potapenko, 2011)

Figure 3: Changes in heart rate (bpm)

Figure 4: All-causes death and CV death



- Statistically significant change in mean **LVEF** improvement between IVA+BT and placebo+BT arms (P<0.0001) was reported in J-SHIFT trial at the final visit (median follow-up duration 582 and 589 days).[8]
- The risk of total **adverse events (AEs)** was comparable between patients treated with IVA+BT and placebo. Encountered **serious adverse events (SAEs)** were overall lower in the IVA group compared to placebo+BT in the SHIFT trial at 23 months (45% vs 48%, respectively; p=0.025).[6,14]
- HR reduction with IVA was associated with improved HRQoL.[6,7,10] Resource use results were available mainly for hospitalization, inpatients and treatment use (data not shown).

CONCLUSIONS

- IVA was associated with a significant reduction of **HR, risks of hospitalization and deaths, improvement of LVEF level** and **HRQoL.**
- This efficacy was achieved while **reducing SAEs.**
- We emphasize the importance of **HR reduction** with IVA for the improvement of clinical outcomes in HF.

REFERENCES

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart (British Cardiac Society). 2007;93(9):1137-46;
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891-975;
3. Groenewegen A, Rutten FH, Mosterd A, et al. Epidemiology of heart failure. European Journal of Heart Failure. 2020;22(8):1342-56
4. Koruth JS, Lala A, Pinney S, et al. The Clinical Use of Ivabradine. J Am Coll Cardiol. 2017;70(14):1777-84;
5. Fox K, Komajda M, Ford I, et al. Effect of ivabradine in patients with left-ventricular systolic dysfunction: A pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. European Heart Journal. 2013;34(29):2263-70
6. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet (London, England). 2010;376(9744):875-8;
7. Mentz RJ, DeVore AD, Tasissa G, et al. PrediscHARge initiation of Ivabradine in the Management of Heart Failure: results of the PRIME-HF Trial. American heart journal. 2020:22398-105;
8. Tsutsui H, Momomura S-I, Yamashina A, et al. Efficacy and safety of ivabradine in Japanese patients with chronic heart failure - J-SHIFT study. Circulation Journal. 2019:83(10):2049-60;
9. Potapenko AV, Abdulazizov OS, Kiyakbaev GK, et al. Efficacy of ivabradine in combined treatment of patients with postinfarction systolic chronic cardiac failure. Terapevticheskii Arkhiv. 2011:83(12):19-26;
10. Mansour S, Youssef A, Rayan M, et al. Efficacy of ivabradine in idiopathic dilated cardiomyopathy patients with chronic heart failure. Egyptian Heart Journal. 2011:63(2):79-85;
11. Lofrano-Alves MS, Issa VS, Biselli B, et al. Control of sinus tachycardia as an additional therapy in patients with decompensated heart failure (CONSTATHE-DHF): a randomized, double-blind, placebo-controlled trial. Journal of heart and lung transplantation. 2016:35(10):1260-64
12. Hu DY, Huang DJ, Yuan ZY, et al. Efficacy and safety analysis of ivabradine hydrochloride treatment of Chinese patients with chronic heart failure: subgroup analysis of Chinese patients in the SHIFT study. Zhonghua xin xue guan bing za zhi. 2017:45(3):190-97
13. Bouabdallaoui N, O'Meara E, Tardif J-C, et al. Beneficial effects of ivabradine in patients with heart failure, low ejection fraction, and heart rate above 77 b.p.m. ESC Heart Failure. 2019:6(6):1199-207
14. Nct. The Influence of Heart Rate Limitation on Exercise Tolerance in Pacemaker Patients. https://clinicaltrialsgov/show/NCT02247245. 2014
15. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane. Version 6.3, 2022

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