# SHIFT: Ivabradine [LANCORA] versus Placebo in Chronic Systolic Heart Failure [1]

**Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine Trial**

## BOTTOM LINE

- In **SHIFT**, patients with stable moderate to severe HF-rEF NYHA Class II 49%, Class III 50%,; mean LVEF 29% in sinus rhythm & a resting HR ≥70bpm treated with ivabradine, compared to placebo, had:
  - ↓ risk of CV death or hospital admission for worsening of HF (ARR 5%, NNT=20/1.9years)
    - the primary endpoint (composite of both CV death or hospital admission for worsening of HF) was driven by hospitalization, as CV & all-cause mortality alone were non-statistically significant
    - subgroup analyses: this benefit was most prominent in those with a baseline HR of ≥77bpm, & primary endpoint was NS for those on ≥50% of target β-blocker
  - ↑risk of symptomatic bradycardia (NNH=25), asymptomatic bradycardia (NNH=20), phosphenes (NNH=50), & AF (NNH=100)
- The **SHIFT** trial was published in 2010. Ivabradine was approved by Health Canada in February 2017, & is indicated for treatment of stable chronic HF (NYHA Classes II-III) with reduced LVEF (≤35%) & a resting HR of ≥77bpm. Clinical experience in Canada is lacking; however, ivabradine is approved / used in other countries (since 2015 in US, 2005 in Europe).
- At time of print, ivabradine is not on the Saskatchewan Drug Plan; cost $38 (2.5mg BID), $66 (5mg BID) & $113 (7.5mg BID)/month.
- Either ivabradine or digoxin may be considered as an add-on to HF triple therapy to further ↓ HR see below comparison. The β-blocker should be titrated to the target or maximally tolerated dose prior to adding either of these agents.

## BACKGROUND

- A raised resting HR has been linked to an ↑ risk of morbidity & mortality in HF patients. A resting HR of 50 to 60bpm is considered an acceptable target, providing the patient is not experiencing symptomatic bradycardia. Some HF patients will have a raised resting HR (HR >70bpm) despite being on the target or maximally tolerated β-blocker dose.[2]
- Ivabradine is a selective inhibitor of the $I_f$ current in the sinoatrial (SA) node, which is a relatively new class of medication with a unique mechanism of action. The $I_f$ current controls spontaneous electrical pacemaker activity in the SA node, which subsequently determines HR. Ivabradine inhibits the $I_f$ current, thereby ↓ HR (without ↓BP or acting on cardiac ion channels or receptors).
  - Ivabradine can also inhibit the $I_h$ current in the retina, resulting in visual disturbances (e.g. phosphenes).
- The 2015 CCS HF Companion suggested ivabradine may be considered in patients on standard HF triple therapy (i.e. ACEi/ARB/ARNI + β-blocker + MRA) with ↑ HR (>70-75bpm) after β-blocker titration is complete.[2] The 2016 ACC/AHA/HFSA and 2016 ESC HF Guidelines have incorporated ivabradine into their updated recommendations for patients with symptomatic HF (NYHA class II-III) with LVEF ≤35%, in sinus rhythm & a resting HR of ≥70bpm despite triple therapy, [ACC/AHA/HFSA & ESC IIa(B)] or contraindications to β-blockers.[ESC IIa(C),3,4]
- **Ivabradine versus Digoxin:**
  - at time of print, there are no published head-to-head trials comparing ivabradine to digoxin in patients with HF-rEF
  - In 2012, a UK research group conducted a retrospective analysis of the **DIG** trial data (digoxin versus placebo in HF-rEF patients in sinus rhythm) using the **SHIFT** primary composite endpoint.[5] The investigators concluded ivabradine & digoxin's benefit of reducing CV death or HF hospitalization was the same (ARR 5%, NNT=20), which was driven by a reduction in HF hospitalization (**SHIFT** ARR 5%, NNT=20; **DIG** ARR 8%, NNT=13) as CV death was non-statistically significant in both data sets.[5]
  - the baseline patient characteristics between the **DIG** and **SHIFT** trials were similar (e.g. age, HR, LVEF, NYHA class, comorbidities); ACEi/ARB and diuretic usage was also similar, however, β-blocker & MRA use was not reported in the **DIG** trial [5,6]
  - compared to digoxin, ivabradine has less real-world experience / post-marketing surveillance, cannot be used in AF patients, is more expensive & not listed on the SK Drug Formulary; however, ivabradine has less drug interactions, does not need to be dose adjusted in renal dysfunction, & does not require therapeutic drug monitoring
- Ivabradine has also been studied in **stable coronary artery disease**, however this is not an approved indication in Canada:
  - **BEAUTIFUL**:[7] ivabradine vs placebo in 10,917 patients with CAD & LVEF <40% x 19 months
    - CV death, hospitalization for MI, hospitalization for new/worsening HF (primary endpoint): NS
    - subgroup analysis: patients with a baseline resting HR ≥70bpm had ↓ hospitalizations for acute MI (p=0.001) & ↓ hospitalizations for acute MI or unstable angina (p=0.023) compared to those with a baseline resting HR of <70bpm
  - **SIGNIFY**:[8] ivabradine vs placebo in 19,102 patients with CAD without HF & a HR of ≥70bpm x 27.8 months
    - CV death or non-fatal MI: NS (subgroup analysis: ivabradine↑ risk in patients with activity-limiting angina, p=0.02 for interaction)
    - ↑ risk of AF with ivabradine (ARI 1.5%, NNH=67)

## TRIAL BACKGROUND [1,9]

**DESIGN**: event-driven, multinational 37 countries, 677 centers, randomized, double-blind, placebo-controlled, parallel-group ITT trial with concealed allocation. Funding: Servier. Enrollment: October 2006 to June 2009.

**INTERVENTION:** ivabradine 7.5mg BID versus placebo, in addition to standard HF therapy

**Study Phases:**

①run-in phase without study treatment x 14 days, then
②ivabradine 5mg BID or placebo x 14 days, then
③if resting HR >60 bpm: ↑ ivabradine to 7.5mg BID; if resting HR 50 to 60 bpm: continue ivabradine 5mg BID; if resting HR <50 bpm or symptomatic bradycardia: ↓ ivabradine 2.5mg po BID x 14 days
④dose reassessed at Day 28 & q4 months and adjusted as above; if resting HR <50bpm or persistent symptomatic bradycardia: discontinuation of therapy

**INCLUSION:** patients ≥18 years with moderate to severe HF, LVEF ≤35%, sinus rhythm, resting HR of ≥70bpm, stable symptomatic chronic HF for ≥4 weeks, admitted to the hospital within the last 12 months due to worsening HF, on optimal drug therapy for ≥4 weeks prior.

**EXCLUSION:** HF due to congenital heart disease or primary severe valvular disease; any of the following events in the past 2 months were also excluded: MI, ventricular or AV pacemakers pacing ≥40% of the day, permanent atrial fibrillation/flutter, or symptomatic hypotension; CRT started within previous 6 months.

Patients were not allowed to take non-DHP CCBs, class I antiarrhythmics, and strong CYP3A4 inhibitors.

**POPULATION**: at baseline: n=6505 6558 randomized but 7 patients were not dispensed the drug, one site was removed due to misconduct

- mean age 60.4 years (SD 11.4yrs), 11% ≥75 years, 76% ♂, 89% Caucasian
- mean HR 79.9 bpm (SD 9.6 bpm), LVEF 29% (SD 5.1%), NYHA: class II ~49%, class III ~50%, class IV ~ 2%
- mean duration of HF 3.5 years (SD 4.2 years); primary cause of HF: ischemic 68%, non-ischemic 32%
- HTN 66.5%, MI 56%, DM 30.5%, stroke 8%, history of atrial fibrillation or flutter 8%
- **HF therapy at randomization:** ACEi/ARB ~93%, β-blocker 89.5%, diuretic 83.5%, antialdosterone agent (i.e. MRA) ~60%, digoxin ~22%, devices (CRT or ICD) 3.5%
- **Type of β-blocker & mean daily dosage**: 45% carvedilol (mean dose 25mg/day), 25.5% bisoprolol (mean dose 6.2mg/day), 14% metoprolol succinate (mean dose 90mg/day), 10% metoprolol tartate (68mg/day), 3% nebivolol (5.9mg/day), 2% other
  - 26% at β-blocker target dose, 56% at ≥50% β-blocker target dose
  - reasons for not reaching target dose: 44.5% hypotension, 32% fatigue, 14% dyspnea, 12.5% dizziness, 6% bradycardia, 9.5% other
  - 11% were not on a β-blocker (reasons ~35% COPD, ~19% hypotension, 10.5% asthma, 8% cardiac decompensation, 6% dizziness or bradycardia, ~5% Raynaud or PAD, 12% other)

## RESULTS

median follow-up: 22.9 months/1.9 years (IQR 18-28 months)

**TABLE 1: EFFICACY**

| CLINICAL ENDPOINTS | IVABRADINE 7.5MG BID n=3268 | PLACEBO n=3290 | ARR/ARI HR (95% CI) | NNT/NNH /1.9 YEARS | COMMENTS |
|---|---|---|---|---|---|
| **PRIMARY ENDPOINT** | | | | | |
| CV death or hospital admission for worsening of HF | 24% (n=793) | 29% (n=937) | ↓5% 0.82 (0.75-0.90) | 20 | - Primary composite endpoint<br>▪ driven by hospitalization<br>▪ non-statistically significant for those on ≥50% of their β-blocker target dose<br>- Kaplan-Meier curves separated within the 1st 3 months, & benefit was maintained<br>- HR net reduction:<br>▪ Day 28: 10.9 bpm (95% CI 10.4-11.4)<br>▪ 1 year: 9.1 bpm (95% CI 8.5-9.7)<br>▪ End of the study: 8.1 bpm (95% CI 7.5-8.7)<br>- mean dose 6.4mg (SD 1.6mg) at Day 28, 6.5mg (SD 1.6mg) at 1 year<br>▪ 1 year to end of study: 70% on target dose<br>▪ 49% were on at least 50% of their β-blocker target dose (was 56% at baseline) |
| **SECONARY ENDPOINTS** | | | | | |
| All-cause mortality | 16% (n=503) | 17% (n=552) | NS | - | |
| CV mortality | 14% (n=449) | 15% (n=491) | NS | - | |
| HF mortality | 3% (n=113) | 5% (n=151) | ↓2% 0.74 (0.58-0.94) | 50 | |
| All-cause hospital admission | 38% (n=1231) | 42% (n=1356) | ↓4% 0.89 (0.82-0.96) | 25 | |
| Hospital admission for worsening HF | 16% (n=514) | 21% (n=672) | ↓5% 0.74 (0.66-0.83) | 20 | |
| Any CV hospital admission | 30% (n=977) | 34% (n=1122) | ↓4% 0.85 (0.78-0.92) | 25 | |
| CV death, hospital admission for worsening HF, or non-fatal MI | 25% (n=825) | 30% (n=979) | ↓5% 0.82 (0.74-0.89) | 20 | |
| Improvement in NYHA class | 28% (n=887) | 24% (n=776) | ↑4% | 25 | |
| Patient-reported Global Assessment Improvement | 72% (n=2118) | 68% (n=2017) | ↑4% | 25 | |
| Physician-reported Global Assessment Improvement | 61% (n=1888) | 57% (n=1772) | ↑4% | 25 | |
| **SUBGROUP ANALYSES – Primary Composite Endpoint** (p-value for interaction = 0.029) | | | | | |
| Baseline HR <77bpm (n=3144) | 21.4% (n=339) | 22.8% (n=356) | NS | - | |
| Baseline HR ≥77bpm (n=3357) | 27.4% (n=454) | 34.2% (n=581) | ↓6.8% 0.75 (0.67-0.85) | 15 | |

**TABLE 2: SAFETY**

| CLINICAL ENDPOINTS | IVABRADINE 7.5MG BID n=3232 | PLACEBO n=3260 | ARR/ARI, HR (95% CI) | NNT/NNH /1.9 YEARS |
|---|---|---|---|---|
| Discontinuation rates | 21% (n=682) | 19% (n=605) | ↑2%, 1.14 (1.02-1.27) | 50 |
| Serious adverse events | 45% (n=1450) | 48% (n=1553) | ↓3% | 34 |
| HF adverse event | 25% (n=804) | 29% (n=937) | ↓4% | 25 |
| Symptomatic bradycardia | 5% (n=150) | 1% (n=32) | ↑4% | 25 |
| Discontinuation due to symptomatic bradycardia | 1% (n=20) | <1% (n=5) | ↑0.5% | 200 |
| Asymptomatic bradycardia | 6% (n=184) | 1% (n=48) | ↑5% | 20 |
| Discontinuation due to asymptomatic bradycardia | 1% (n=28) | <1% (n=5) | ↑0.7% | 143 |
| Atrial fibrillation | 9% (n=306) | 8% (n=251) | ↑1% | 100 |
| Phosphenes* | 3% (n=89) | 1% (n=17) | ↑2% | 50 |

*defined as transient enhanced brightness in a restricted area of the visual field

## STRENGTHS, LIMITATIONS, & UNCERTAINTIES

**STRENGTHS:**
- clinically meaningful endpoints & clinically relevant subgroup analyses
- provided baseline information on type of β-blocker and mean daily β-blocker dose
- blinded adjucation of outcomes
- only 0.05% (n=3) of patients were lost to follow-up

**LIMITATIONS:**
- subgroup analysis suggests ivabradine's benefits only apply to those with a baseline HR of ≥77 bpm
- while reflective of real world experience, only half of the patients were able to reach ≥50% of their target β-blocker dose
- the percentage of patients from Canada or North America was not reported

**UNCERTAINITIES:**
- the percentage of patients enrolled with devices (CRT, ICD) is lower than North American practice
- some patients required a reduction in their β-blocker dose during the study
- 49% were at least 50% of their target β-blocker dose (was 56% at baseline)
- efficacy & safety of ivabradine in patients with paroxysmal or persistent AF (permanent AF was an exclusion criteria, 8% of patients had a history of AF or Aflutter at baseline)
- efficacy & safety of ivabradine in older adults (mean age 60.4 years (SD 11.4yrs), 11% ≥75 years)
- no published trials have directly compared digoxin to ivabradine for HF-rEF
- unknown how many patients received the lowest ivabradine dose, & whether there was benefit

**RxFILES RELATED LINKS**

- Heart Failure Treatment Overview: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Heart-Failure.pdf

♂=male **ACC/AHA/HFSA**=American College of Cardiology/American Heart Association/Heart Failure Society of America **ACEi**= angiotensin converting enzyme inhibitor **AE**=adverse event **AF**=atrial fibrillation **Aflutter**= atrial flutter **ARB**=angiotensin receptor blocker **ARI**= absolute risk increase **ARNI**=angiotensin receptor-neprilysin inhibitor **ARR**=absolute risk reduction **AV**= atrioventricular **β**=beta **BID**=twice daily **BP**=blood pressure **bpm**=beats per minute **CAD**=coronary artery disease **CCS**=Canadian Cardiovascular Society **CI**=confidence interval **COPD**=chronic obstructive pulmonary disease **CRT**=cardiac resynchronisation therapy **CV**=cardiovascular **DHP CCB**= dihydropyridine calcium channel blocker **DM**=diabetes mellitus **ESC**=European Society of Cardiology **HF**=heart failure **HF-rEF**=heart failure with reduced ejection fraction **HR**=heart rate/hazard ratio **HTN**=hypertension **ICD**=implantable cardioverter defibrillator **$I_f$**=funny current **IQR**=interquartile range **ITT**=intention to treat **LVEF**=left ventricular ejection fraction **MI**=myocardial infarction **MRA**=mineralocorticoid receptor antagonist **n**=number **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-statistically significant **NYHA**=New York Heart Association **PAD**=peripheral artery disease **prn**=as needed **SA**=sinoatrial **SD**=standard deviation **sx**=symptom **yrs**=years

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**REFERENCES**

1. Swedberg K, Komajda M, Böhm M, et al; **SHIFT** Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010 Sep 11;376(9744):875-85.
2. Howlett JG, Chan M, Ezekowitz JA, et al. The **Canadian Cardiovascular Society Heart Failure Companion**: Bridging Guidelines to Your Practice. Can J Cardiol. 2016 Mar;32(3):296-310.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2016 **ACC/AHA/HFSA** Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016 Sep 27;68(13):1476-1488. PMID: 27216111.
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 **ESC Guidelines** for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Rev Esp Cardiol (Engl Ed). 2016 Dec;69(12):1167. PubMed PMID:27894487.
5. Castagno D, Petrie MC, Claggett B, McMurray J. Should we SHIFT our thinking about digoxin? Observations on ivabradine and heart rate reduction in heart failure. Eur Heart J. 2012 May;33(9):1137-41. PMID: 22408030.
6. Digitalis Investigation Group (**DIG**). The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997 Feb 20;336(8):525-33. PubMed PMID: 9036306.
7. Fox K, Ford I, Steg PG, et al; **BEAUTIFUL** Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Sep 6;372(9641):807-16.
8. Fox K, Ford I, Steg PG, et al; **SIGNIFY** Investigators. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med. 2014 Sep 18;371(12):1091-9.
9. Swedberg K, Komajda M, Böhm M, et al. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (**SHIFT**). Eur J Heart Fail. 2010 Jan;12(1):75-81