Appendix 5 (as supplied by the authors): Published trials on the effect of ivabradine on outcomes including mortality in patients with different cardiovascular diseases

Trials	Enrolled subjects	Findings
Fox et al. 2014, SIGNIFY[1]	Patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 bpm or more	No effect observed on primary composite end point (death from cardiovascular causes or nonfatal myocardial infarction); No effect observed on secondary end point (all-cause death, death from cardiovascular causes, death from coronary causes, coronary revascularization, admission to hospital for heart failure, myocardial infarction) Conclusions: Addition of ivabradine to standard background therapy to reduce the heart rate did not improve outcomes
Komajda et al. 2014, post hoc analysis of SHIFT[2]	SHIFT population: patients with moderate to severe heart failure and left ventricular systolic dysfunction who had heart rate ≥70 bpm and were in sinus rhythm. 2110 SHIFT patients with SBP<115 mmHg,1968 with115≤SBP<130 mmHg, and 2427 with SBP≥130 mmHg	**An effect observed on primary composite end point (cardiovascular mortality and hospitalization for worsening heart failure), hospitalization for worsening heart failure, heart failure mortality**; No effect observed on cardiovascular mortality, all-cause mortality Conclusions: Ivabradine may be useful as part of the management of heart failure patients with low blood pressure and elevated heart rate. The efficacy and safety of ivabradine are not influenced by baseline SBP
Borer et al. 2014, post hoc analysis of SHIFT[3]	12 SHIFT patients with severe and 5,973 with less severe heart failure	**Patients with heart rate ≥ 75 bpm:** **An effect observed on primary composite end point (cardiovascular mortality and hospitalization for worsening heart failure), all-cause death, cardiovascular death, hear failure death, hospitalization for worsening heart failure, hospitalization for any cause**; **Patients with heart rate > 70 beats/min:** **An effect observed on primary composite end point (cardiovascular mortality and hospitalization for worsening heart failure), hospitalization for worsening heart failure, hospitalization for any cause**; No effect observed on all-cause death, cardiovascular death, hear failure death

Appendix to: Zhang D, Shen Xl, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. *CMAJ* 2015. DOI:10.1503/cmaj.150535.

		Conclusions: heart rate reduction with ivabradine can be safely used in severe HF and may improve clinical outcomes independently of disease severity
Reil et al. 2013, SHIFT[4]	Patients from the SHIFT population (n=6505) were divided into groups with (n=912) or without (n=5593) Left bundle branch block (LBBB). Patients with moderate to severe heart failure and LV systolic dysfunction who had heart rate ≥70 bpm and were in sinus rhythm	**Patients with no LBBB:** **An effect observed on primary composite end point (cardiovascular mortality and hospitalization for heart failure), hospitalization for heart failure**; No effect observed on cardiovascular mortality, all-cause mortality; Patients with LBBB No effect observed on primary composite end point (cardiovascular mortality and hospitalization for heart failure), hospitalization for heart failure, cardiovascular mortality, all-cause mortality Conclusions: Ivabradine was safe in LBBB. Its effect was directionally similar to that in patients without LBBB, but did not reach statistical significance, possibly due to lack of power to test this effect because of the small number of LBBB patients
Fox et al. 2013, pooled analysis of BEAUTIFUL and SHIFT trials[5]	BEAUTIFUL and SHIFT populations with left-ventricular systolic dysfunction with coronary artery disease and/or heart failure, and heart rate ≥70 bpm	All patients: **An effect observed on composite end point (cardiovascular mortality or hospitalization for heart failure), hospitalization for heart failure, composite end point (cardiovascular mortality, hospitalization for heart failure, or hospitalization for myocardial infarction), hospitalization for myocardial infarction, cardiovascular death or non-fatal myocardial infarction**; No effect on cardiovascular mortality, all-cause mortality Patients with heart rate ≥75 bpm: **An effect observed on composite end point (cardiovascular mortality or hospitalization for heart failure), cardiovascular mortality, hospitalization for heart failure, all-cause mortality** Conclusions: Ivabradine may be important for the improvement of clinical outcomes in patients with left-ventricular systolic dysfunction and heart rate ≥ 70 bpm., whatever the primary clinical presentation (CAD or heart failure) or clinical status (NYHA class)

Swedberg et al. 2012, SHIFT[6]	Among SHIFT population on recommended background therapy, maximally tolerated beta-blocker doses were subgrouped as no eta-blocker,<25%, 25% to<50%, 50% to<100%, and 100% of European Society of Cardiology–suggested target doses.	**An effect observed on primary composite end point (cardiovascular death or heart failure hospitalization), hospital admission for worsening heart failure** No effect observed on cardiovascular death Conclusions: The magnitude of heart rate reduction by beta-blocker plus ivabradine, rather than background beta-blocker dose, primarily determines subsequent effect on outcomes.
Böhm et al. 2013, SHIFT[7]	The SHIFT population was divided by baseline heart rate ≥ 75 or < 75 bpm	**Patients with heart rate ≥ 75 beats/min:** **An effect observed on primary composite end point (cardiovascular mortality and hospitalization for worsening heart failure), mortality endpoints (cardiovascular mortality, all-cause mortality, death from heart failure), other points (hospitalization for worsening heart failure, all-cause hospital admission, any cardiovascular hospital admission);** Patients with heart rate < 75 beats/min: No effect observed on the above-mentioned outcomes Conclusions: The effect of ivabradine on outcomes is greater in patients with heart rate ≥ 75 bpm with heart rates achieved <60 bpm or heart rate reductions > 10 bpm predicting best risk reduction.
Komajda et al. 2013, SHIFT[8]	3922 SHIFT patients with mineralocorticoid receptor antagonist (MRA) at baseline vs. 2583 patients without.	**Patients with MRA:** **An effect observed on primary composite endpoint (cardiovascular death or hospitalization for worsening heart failure), mortality endpoints (death from heart failure), hospitalization-related endpoints (all-cause hospitalization, hospitalization for worsening heart failure, hospitalization for cardiovascular reasons);** No effect observed on mortality endpoints (all-cause death, cardiovascular death); **Patients without MRA:** **An effect observed on primary composite endpoint (cardiovascular death or hospitalization for worsening heart failure), hospitalization-related endpoints**

		(hospitalization for worsening heart failure, hospitalization for cardiovascular reasons); No effect observed on mortality endpoints (all-cause death, cardiovascular death, death from heart failure), hospitalization-related endpoints (all-cause hospitalization) Conclusions: Ivabradine improves outcomes in heart failure patients with heart rate ≥70 bpm, receiving multiple neurohormonal modulation treatments. The addition of ivabradine to multiple neurohormonal modulation should therefore be considered when the heart rate is≥70 b.p.m.
Böhm et al. 2010, SHIFT[9]	SHIFT population	**An effect observed on primary composite endpoint (cardiovascular death or hospital admission for worsening heart failure), first hospital admissions for worsening heart failure, cardiovascular death** Conclusions: High heart rate is a risk factor in heart failure. Selective lowering of heart rates with ivabradine improves cardiovascular outcomes. Heart rate is an important target for treatment of heart failure.
Swedberg et al. 2010, SHIFT[10]	6558 patients in SHIFT population	**An effect observed on primary composite end point (cardiovascular death and hospitalization for worsening heart failure), mortality endpoints (death from heart failure), other points [all-cause hospital admission, hospital admission for worsening heart failure, any cardiovascular hospital admission, composite end point (cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction)]**; No effect observed on mortality endpoints (all-cause mortality and cardiovascular mortality) Conclusions: Our results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of this disorder.
Fox et al. 2009, post hoc analysis of BEAUTIFUL[11]	Patients with stable coronary artery disease and left ventricular systolic dysfunction. Patients had to be in sinus rhythm with resting heart rate ≥ 60 bpm	**Patients with limiting angina:** **An effect observed on primary composite end point (cardiovascular death and hospitalization for heart failure or myocardial infarction), coronary endpoints (hospitalization for myocardial infarction)**;

		No effect observed on mortality endpoints (all-cause death, cardiovascular death, cardiac death), heart failure endpoints (hospitalization for heart failure, cardiovascular death and hospitalization for heart failure), coronary endpoints (hospitalization for heart failure or unstable angina, coronary revascularization); Patients without limiting angina: No effect observed on the above-mentioned outcomes Conclusions: Our analysi raises the possibility that ivabradine may be helpful to reduce major cardiovascular events in patients with stable CAD and LVSD who present with limiting angina.
Fox et al. 2008, BEAUTIFUL[12]	Patients with stable coronary artery disease and left ventricular systolic dysfunction. Patients had to be in sinus rhythm with resting heart rate ≥ 60 bpm	Total population: No effect observed on primary composite endpoint (cardiovascular death or admission to hospital for myocardial infarction or new-onset or worsening heart failure), mortality endpoints (all-cause death, cardiovascular death, cardiac death), heart failure endpoints (admission to hospital for heart failure, cardiovascular death or admission to hospital for new-onset or worsening heart failure), coronary endpoints (admission to hospital for myocardial infarction, admission to hospital for myocardial infarction or unstable angina, coronary revascularization); **Subgroup with heart rate ≥ 70 bpm:** **An effect observed on coronary endpoints (admission to hospital for myocardial infarction, admission to hospital for myocardial infarction or unstable angina, coronary revascularization)**; No effect observed on the above-mentioned other outcomes Conclusions: Reduction in heart rate with ivabradine does not improve cardiac outcomes, but could be used to reduce the incidence of coronary artery disease outcomes in a subgroup of patients who have heart rates of 70 bpm or greater.

SIGNIFY: Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease, SHIFT: The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial

References

1. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014;371:1091-1099.
2. Komajda M, Bohm M, Borer JS, Ford I, Robertson M, Manolis AJ, 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;16:810-816.
3. Borer JS, Bohm M, Ford I, Robertson M, Komajda M, Tavazzi L, et al. Efficacy and safety of ivabradine in patients with severe chronic systolic heart failure (from the SHIFT study). *Am J Cardiol* 2014;113:497-503.
4. Reil JC, Robertson M, Ford I, Borer J, Komajda M, Swedberg K, et al. Impact of left bundle branch block on heart rate and its relationship to treatment with ivabradine in chronic heart failure. *Eur J Heart Fail* 2013;15:1044-1052.
5. Fox K, Komajda M, Ford I, Robertson M, Bohm M, Borer JS, 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. *Eur Heart J* 2013;34:2263-2270.
6. Swedberg K, Komajda M, Bohm M, Borer J, Robertson M, Tavazzi L, et al. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. *J Am Coll Cardiol* 2012;59:1938-1945.
7. Bohm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol* 2013;102:11-22.
8. Komajda M, Bohm M, Borer J, Ford I, Krum H, Tase A, et al. Influence of background treatment with mineralocorticoid receptor antagonists on ivabradine's effects in patients with chronic heart failure. *Eur J Heart Fail* 2013;15:79-84.
9. Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010;376:886-894.
10. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376:875-885.
11. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. *Eur Heart J* 2009;30:2337-2345.
12. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372:807-816.

Appendix to: Zhang D, Shen Xl, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. *CMAJ* 2015. DOI:10.1503/cmaj.150535.