

# Addressing Major Unmet Needs in Patients with Systolic Heart Failure: The Role of Ivabradine

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**Abstract** We reviewed clinical evidence for the use of ivabradine in systolic heart failure (HF), in which it appears to improve symptoms, improve quality of life, prevent hospitalization, and prolong survival, thereby addressing unmet needs in the management of HF. Ivabradine provides symptomatic benefits in HF on top of standard therapies, in terms of functional parameters and exercise capacity, and there is some evidence that this leads to improvements in quality of life in symptomatic HF patients, who may have dyspnea, altered exercise capacity, and fatigue. The SHIFT trial demonstrated that ivabradine has significant beneficial effects on major outcomes in HF. Ivabradine had a significant effect on pump failure death, which was reduced by 26 % ( $p = 0.014$ ), with no effect on sudden cardiac death. This is an important result since pump failure death is currently the main cause of death in HF, and also because the reductions in mortality obtained with beta-blockers and spironolactone in the last 20 years appear to be mainly due to reduction in sudden death rather than reduction in pump failure death. Ivabradine also has a beneficial effect on hospital admissions (−26 %,  $p < 0.0001$ ), which is clinically relevant since a quarter of HF patients can expect to be readmitted to hospital for HF within 1 month of discharge. Ivabradine-treated patients are also at significantly lower risk of experiencing a second or third hospitalization for worsening HF. Ivabradine clearly has a key role to play in the management of HF by

covering the main therapeutic objectives of symptoms, quality of life, and outcomes.

## Key Points

There is much clinical evidence for the use of ivabradine to address unmet needs in the management of systolic heart failure, in which it improve symptoms, improves quality of life, prevents hospitalization, and prolongs survival.

By contrast with other treatments in heart failure, ivabradine has a significant effect on pump failure death, which was significantly reduced by 26 % in a large-scale randomized controlled trial, but no effect on sudden cardiac death.

Ivabradine has also been demonstrated to have a beneficial effect on hospital admission for heart failure, which is an important marker of prognosis and remains a major objective to reduce healthcare costs.

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## 1 Introduction

Advances in the prevention, diagnosis, and management of cardiovascular disease over the last 50 years have been nothing short of spectacular. There is one notable exception to these encouraging trends: heart failure (HF) [1]. Chronic HF negatively affects quality of life with symptoms, weight gain, edema, dyspnea, and fatigue, all of which limit

activities of daily living and increase the risk of acute hospitalization [2, 3]. Depression is also very common, and occurs in 20–30 % of HF patients [4]. Acute HF, i.e., new onset of severe HF or the sudden intensification of chronic HF, including cardiac pump failure, is a life-threatening condition that requires hospitalization. It is the most common cause of hospital admission among HF patients.

HF itself is the most common cause of hospital admission in adults. Annual hospital discharges in patients with a primary diagnosis of HF have risen steadily since 1975, and now exceed 1 million per year in the USA, though there are signs that they may at last be leveling off [5, 6]. Survival after a diagnosis of HF has improved over the past 30 years; the age-adjusted death rate has declined [7–9] and the mean age at death from HF has risen [10, 11]. However, despite these modest improvements, the 5-year mortality is still approximately 50 % worse than that of many cancers [12]. The management of HF includes angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and mineralocorticoid receptor antagonists, all of which have been available for more than 20 years. More recently, devices have also been introduced. All of these interventions appear to improve survival [13], but there are clearly a number of unmet needs in HF management. The three goals of HF management remain to (1) improve quality of life by reducing symptoms, (2) avoid hospitalization, and (3) prolong survival [14]. Careful consideration of these goals suggests that there is currently a critical need for new management strategies that improve clinical outcomes.

A relative newcomer to the management strategy for systolic HF—ivabradine—may prove to fill these unmet needs. Because of the narrative character of this review, no systematic approach including assessment of reporting biases was performed [15]. Instead, this review was prepared on the basis of expert opinion, and ad hoc literature searches were used to create the bibliography on the subject. In this article, we review the clinical evidence for the use of ivabradine in systolic HF, in which it appears to improve symptoms, improve quality of life, prevent hospitalization, and prolong survival.

## 2 Effect of Ivabradine on Symptoms and Exercise Capacity

Chronic HF negatively affects quality of life with a whole range of symptoms that limit activities of daily living and increase the risk of hospitalization [1]. HF patients with systolic dysfunction generally receive diuretics, which provide symptomatic relief from pulmonary and systemic venous congestion, but do not improve long-term survival. By contrast, none of the therapies recommended by the

guidelines to improve long-term survival—ACE inhibitors, beta-blockers, or mineralocorticoid receptor antagonists—has been demonstrated to be really effective in improving symptoms [16–19].

The Australia/New Zealand Heart Failure Research Collaborative Group [19] included 415 patients with chronic stable HF and randomly assigned them to treatment with carvedilol or matching placebo. After 12 months, there was no between-group difference in treadmill exercise duration, 6-min walk test, New York Heart Association (NYHA) class, or specific activity scale score. Moreover, after 19 months, the frequency of episodes of worsening HF was similar with carvedilol and placebo. The conclusion was that carvedilol had no effect on exercise performance or symptoms in this study. In a systematic review of 15 placebo-controlled trials of beta-blockers [20], only three studies reported an improvement in 6-min walk test. Moreover, when only large multicenter trials were considered [20], only one in five comparisons showed an improvement in exercise capacity with beta-blockers.

By contrast, ivabradine has been demonstrated to provide additional and complementary symptomatic benefits to HF patients already treated with diuretic, ACE inhibitor, and beta-blocker [21]. Among patients in NYHA classes II and III, 90 % of whom presented with fatigue and dyspnea despite guideline-recommended therapy, addition of ivabradine 7.5 mg twice daily (bid) was associated with increased exercise endurance versus placebo at 3 months ( $15.4 \pm 2.6$  vs.  $28.2 \pm 3.5$  min,  $p < 0.0001$ ), corresponding to an increase in walking distance of 1.25 km. There was also a significant increase in  $VO_{2max}$  compared with baseline ( $p < 0.0001$ ) and control ( $p < 0.0001$ ). This beneficial effect on symptom alleviation also translated into a favorable improvement in NYHA functional class by one stage and an associated improvement in quality of life (Minnesota Living with Heart Failure Questionnaire) [21]. Moreover, these symptomatic improvements were correlated with a significant 16 % increase in left ventricular ejection fraction (LVEF) and a 40 % reduction in N-terminal pro-brain natriuretic peptide (NT-proBNP), underlining the strong effective correlation between clinical, echocardiographic, and laboratory parameters. Although the patients in this study had clinically stable mild to moderate HF, they remained symptomatic despite optimized medical treatment at study entry, which makes them quite representative of patients in daily clinical practice and also a challenge to treat. The results showed that treatment with ivabradine 7.5 mg bid was associated with improvement of functional parameters and exercise capacity, with fewer symptoms [21].

Although both beta-blockers and ivabradine are known to reduce resting heart rate, these differences in effect on

exercise capacity indicate they have very different modes of action [22]. Combining the two may therefore result in further benefits and cancel unwanted effects. To address this, the effect of combining the beta-blocker carvedilol with ivabradine has been evaluated in the CARVIVA-HF (CARVedilol, IVAbRADine or their combination on exercise capacity in patients with Heart Failure) trial performed in 123 beta-blocker-naïve HF patients, who were already receiving a maximal dose of ACE inhibitor [23]. The patients were randomly allocated to receive carvedilol alone (up to 25 mg bid), ivabradine alone (up to 7.5 mg bid), or ivabradine plus carvedilol combination (12.5/7.5 mg bid). The maximal dose was better tolerated for ivabradine (36/41) than for carvedilol (18/38) or the combination therapy (32/42) ( $p < 0.01$ ), and heart rate was decreased in all three groups, with the greatest reductions in patients receiving the combination. Both the distance walked on the 6-min walk test and the exercise time on myocardial oxygenation test (MVO<sub>2</sub>) significantly improved versus baseline in the ivabradine and combination groups, but not in the carvedilol group. The peak VO<sub>2</sub> and ventilatory anaerobic threshold significantly improved in patients receiving the ivabradine or the combination, but remained unchanged in the carvedilol patients ( $+3.8 \pm 2.0$  or  $+2.3 \pm 1.7$  vs.  $-0.6 \pm 1.2$  ml/kg/min,  $p < 0.01$  and  $p < 0.03$ , respectively). The peak workload increased in the ivabradine and the combination groups, versus no significant change in the carvedilol group. The fatigue index significantly improved with the ivabradine and the combination ( $-36.4 \pm 12.1$  and  $-26.5 \pm 9.5$  %, both  $p < 0.05$  vs. baseline), while there was no significant change in the carvedilol group, with a trend toward a worsening ( $-7.1 \pm 4.9$  %,  $p = 0.06$  vs. baseline) [23]. The authors concluded that the ivabradine alone or in combination with carvedilol is more effective than a higher dose of carvedilol in improving exercise capacity in stable HF patients on top of recommended doses of ACE inhibitor [23].

There are a number of possible explanations for the improved exercise capacity with ivabradine ± carvedilol, such as better coronary perfusion, preservation of left ventricular (LV) contraction and relaxation, and better peripheral blood flow. Apart from a differing effect of ivabradine and carvedilol on vasodilation on muscle perfusion, beta-blockers per se may have a detrimental effect on muscle strength.

This study also shows that HF patients allocated to the ivabradine/carvedilol combination were more likely to reach maximal therapeutic target doses of carvedilol than the patients receiving carvedilol alone (76 vs. 47 %,  $p < 0.003$ ) [23]. This suggests a supplementary advantage of combining the two agents: it facilitates up-titration of beta-blocker. There is other preliminary evidence for this

ability for patients to support higher doses of beta-blocker when treated concomitantly with ivabradine [24], in studies in which the beta-blocker up-titration schedule was also shown to be faster with ivabradine than with beta-blocker alone. These effects on beta-blocker up-titration may be related to the compensation of unwanted hemodynamic effects of beta-blocker due to the specific mode of action of ivabradine [22]. Those clinical, echocardiographic, and biological benefits provided by ivabradine, corresponding to the first available benefits, were fully confirmed in a large-scale study in 2000 HF patients in Germany [25].

### 3 Effect of Ivabradine on Quality of Life

There is now much evidence for the use of ivabradine to improve quality of life in symptomatic HF patients, who may have dyspnea at rest or on effort, altered exercise capacity, and fatigue [21, 23, 26, 27], all of which may improve in the first weeks of therapy. In a sub-analysis of SHIFT (Systolic Heart failure treatment with the I<sub>f</sub> inhibitor ivabradine Trial) [28] in 1944 patients, health-related quality of life, as recorded by the disease-specific Kansas City Cardiomyopathy Questionnaire, was found to be inversely associated with clinical events [26]. Treatment with ivabradine was found to be associated with improved health-related quality of life and better outcomes [26].

The source of this improvement in quality of life may be related to improvement in exercise capacity and symptoms. Indeed, in the study with ivabradine and carvedilol described above [23], the overall assessment of quality of life showed an improvement in patients receiving the ivabradine/carvedilol combination (from  $4.7 \pm 0.8$  to  $6.1 \pm 0.6$ ,  $p < 0.02$ ), and no change in patients receiving carvedilol (from  $4.6 \pm 0.8$  to  $4.1 \pm 0.6$ ,  $p = \text{NS}$ ). Quality of life is an important endpoint for patients with chronic disabling diseases like HF. The reported effect on quality of life with ivabradine plus carvedilol [23] is most likely related to the improved exercise capacity and reduction of the beta-blocker-related fatigue.

### 4 Effect of Ivabradine on Pump Failure Hospitalizations and Deaths

An alteration in clinical setting often precedes the worsening of HF and thus hospitalization for worsening HF, i.e., pump failure [29]. It can therefore be hypothesized that, since ivabradine 7.5 mg bid improves quality of life in standard clinical settings, it could also reduce hospitalizations for worsening HF (which is the cause of 50 % of all hospitalizations in HF patients [30]) and reduce the risk for HF death. This was evaluated in SHIFT [28], in systolic HF

patients with LVEF  $\leq 35\%$  and heart rate  $\geq 70$  bpm, who were receiving the maximally tolerated dose of beta-blocker. Indeed, this was an important trial since it evaluated the effect of a new drug on top of three guideline-recommended life-saving therapies—ACE inhibitors, beta-blockers, and mineralocorticoid receptor antagonists—in stable systolic HF patients.

Indeed, few HF patients truly benefit from a true combination of these three drug classes together, even though they are recommended. A European registry [31] reported that only 17% were receiving the optimal combination of diuretic, ACE inhibitor, and beta-blocker. Moreover, when they were prescribed, it was at lower than recommended dosage due to issues of intolerance. Results from a French registry including >50,000 HF patients [32] also confirmed the less than optimal management of HF in normal clinical practice. During the month following the first hospitalization for worsening HF, while 81% of patients were prescribed a loop diuretic, only 47% received an ACE inhibitor, 54% a beta-blocker, and 17% a potassium-sparing diuretic. Prescription of a beta-blocker, diuretic, and ACE inhibitor in combination increased from 21 to 37% during hospital stay, highlighting that globally only one HF patient in three may be treated with the guideline-recommended therapy. The BREATHE registry [33], which covered 57 hospitals in Brazil, found that 69% of HF patients were receiving an ACE inhibitor or angiotensin II receptor blocker (ARB), 60% a beta-blocker, and 49% spironolactone; unfortunately, only 17% were receiving all three drugs together. This lack of life-saving prescriptions supports the introduction of new and better-tolerated therapies.

Although there is a short-term improvement after each admission for acute HF, patients generally leave the hospital with a further decrease in cardiac function [34], which, in turn, can directly and negatively influence renal function via a decrease in cardiac output, high venous pressure, or vasodilatation. This is in line with the demonstration that every hospitalization for pump failure is a strong predictor for subsequent death [35], reinforcing the necessity of efforts via interventions that are known to reduce HF hospitalization and death.

The direct costs of HF reach 1–2% of total healthcare expenditure, and approximately two-thirds of those costs are attributable to hospitalization [36, 37]. Indeed, HF is the most frequent reason for hospitalization among older adults, and worsening HF the main reason for hospitalization for patients with HF [38]. In 2012, in 197 countries covering 99% of the world's population, the overall cost of HF was estimated at \$US108 billion per annum, and this value is predicted to rise [39]. Incident hospitalization due to worsening HF leading to acute HF requiring urgent hospitalization is associated with a significant increase in subsequent mortality in ambulatory patients with chronic

HF [38]. Moreover, repeated hospitalizations significantly contribute to hospitalization expenditure, since HF patients are rehospitalized at an alarmingly high rate, with approximately 25% of patients requiring readmission within 30 days of discharge [40] and 50% of patients within 6 months [30]. HF hospitalizations also significantly impair quality of life of patients with HF, most of whom are older adults. Together, this implies that the prevention of HF hospitalizations should be a priority for clinicians caring for patients with HF. This could be achieved with the use of interventions proven to reduce HF hospitalizations to improve patient's quality of life and reduce the burden on the healthcare system.

The primary endpoint of SHIFT was the composite of cardiovascular death or hospital admission for worsening HF [28]. The secondary endpoints included all-cause death, cardiovascular death, HF death (i.e., pump failure death), hospital admission for worsening HF, all-cause admission to hospital, or any cardiovascular admission. A hospital admission for worsening HF was defined as admission with new or increasing symptoms and new or increasing signs of the disorder, including signs of fluid retention or objective evidence of HF and a significant change in the treatment to improve HF, defined by initiation of intravenous diuretic agents or other intravenous drugs (excluding cardiac glycosides) or mechanical ventilation or mechanical support—this clearly defines the event as hospitalization for pump failure. A total of 3268 patients were randomly assigned to ivabradine 7.5 mg bid and 3290 to receive a placebo on top of demonstrated HF therapy in patients with HF predominantly of ischemic origin (68%) with low LVEF. A total of 90% were receiving a beta-blocker, 92% an ACE inhibitor or ARB, and 60% mineralocorticoid receptor antagonists. In comparison with real life, the SHIFT patients were generally much better treated than any HF patient in any country [31, 32], with at least twice as many patients on the three guideline-recommended life-saving drug classes. This gives an extraordinary strength to the results of this clinical trial.

Treatment with ivabradine 7.5 mg bid was associated with a significant reduction in the SHIFT primary endpoint and improved rate of cardiovascular deaths or hospital admissions for worsening HF by 18% versus placebo ( $p < 0.0001$ ) [28]. In clinical terms, this means that prescribing ivabradine 7.5 mg bid to just 26 HF patients for 1 year will prevent one cardiovascular death or one hospital admission for HF. Moreover, the deaths avoided are especially pump failure deaths, which were reduced by 26% ( $p = 0.014$ ), with no effect on sudden cardiac death [28]. This is a particularly important result, since pump failure death is currently the first cause of death in HF [41], independently of whether they are newly diagnosed or not [42, 43].

In this context, it has been suggested that, even though total mortality in HF patients has been substantially and significantly reduced since recommendations to include a beta-blocker and mineralocorticoid receptor antagonists in HF therapy [43], this was purely due to associated reductions in sudden death and not HF death. The effect of beta-blockers on sudden death, which is explained by inhibition of the sympathetic pathway, has been demonstrated in many clinical trials and meta-analyses [44–46]. Notably, a recent meta-analysis of 30 trials [46], which included 25,000 patients, confirmed that beta-blockers could reduce sudden death by 31 % in HF patients, with an efficacy strong enough to produce statistical reduction in cardiovascular death and even all-cause death. Interestingly, the 2 % absolute reduction in sudden death with bisoprolol in CIBIS II (Cardiac Insufficiency Bisoprolol Study II) [83 deaths with placebo (6 %) vs. 48 deaths with bisoprolol (4 %)] [44] was very similar to the 2 % absolute reduction in HF deaths with ivabradine in SHIFT [151 deaths with placebo (5 %) vs. 113 deaths with ivabradine (3 %)] [28]. These different and totally complementary benefits obtained by ivabradine and beta-blocker in improving mortality of HF patients—pump failure death on the one hand and sudden death on the other—is further support for the concomitant prescription of the two.

Another advantage of ivabradine in HF is the beneficial effect obtained on hospital admissions, which is important insofar as one-quarter of HF patients can expect to be readmitted to hospital for HF within 1 month of discharge. On top of standard therapy, treatment with ivabradine reduced hospital admissions for worsening HF by 26 % versus placebo ( $p < 0.0001$ ) [28]. In absolute terms, hospital admission for worsening HF, i.e., pump failure, was reduced by 5 %, an effect in the same range as the effect demonstrated for other guideline-recommended life-saving therapies. Notably, in the case of ivabradine, this result was obtained on top of life-saving background therapy, indicating the strength of the effect. This also explains why the endpoints of any cardiovascular hospital admission and all-cause hospital admission were significantly reduced with ivabradine [28]. Using a total time cumulative statistical approach, over about 2 years of follow-up, ivabradine-treated patients were also at significantly lower risk of a second hospitalization for worsening HF (−34 %,  $p < 0.001$ ) or a third (−29 %,  $p < 0.013$ ) than patients receiving placebo [47]. This is consistent with the conclusion that the benefit of ivabradine on HF hospitalizations is maintained over several years of therapy and, specifically, mitigates the likelihood of recurrent events in the early and late phases [48]. Another way of evaluating this effect is by the number needed to treat (NNT), i.e., the number who need to be treated to prevent one first HF admission within 1 year. This has been calculated in the

SHIFT population as 27 ( $p < 0.0001$ ) [49]. It has also been estimated that treatment with ivabradine would prevent one readmission for HF every 14 patient-years ( $p < 0.0001$ ). These findings highlight the importance of HF hospitalization as a marker of disease progression and poor outcomes in HF and emphasize the need for prevention of HF hospitalization and treatment strategies for hospitalized patients with HF to improve post-discharge outcomes. In this context, we should recall that the majority of HF hospitalized patients will not see a cardiologist during the 3 months following discharge, which means that it is important to consider initiating ivabradine before discharge.

Further analyses of the SHIFT population have shown that ivabradine improves outcomes in chronic HF independently of diabetes status, systolic blood pressure, concomitant treatment with mineralocorticoid receptor antagonists or beta-blocker, and the presence of chronic obstructive pulmonary disease [50–54]. Indeed, there was no interaction between the presence of one or more comorbidities and the effect of treatment with ivabradine on outcomes in chronic HF [55].

## 5 Safety and Acceptability of Ivabradine in Pump Failure

The acceptability of ivabradine in HF patients appears to be very good. In the SHIFT trial [28], serious adverse events occurred at a lower rate with ivabradine than with placebo ( $p = 0.025$ ), and bradycardia only led to permanent withdrawal from the study in 48 (1 %) patients receiving ivabradine on top of guideline-recommended therapy and 10 (<1 %) of those in the placebo group. Known visual symptoms of ivabradine (phosphenes) occurred in 89 (3 %) patients taking ivabradine, whereas the corresponding finding was reported in 7 (<1 %) placebo-treated patients ( $p < 0.0001$ ). The efficacy and safety of ivabradine are comparable across all age groups [56]. Moreover, they are not influenced by beta-blocker dose [57], which is a logical result since, apart from their effect on resting heart rate, beta-blockers and ivabradine have very different—and even in some points, opposing—modes of action [22] and benefits.

## 6 Discussion

Ivabradine clearly has a key role to play in the management of HF. This has been recognized by the most recent guidelines issued in Europe [58] and Brazil [59], which recommend adding ivabradine to other life-saving therapies. As we have seen above, this is expected to cover the main therapeutic objectives in HF: improvement of

symptoms and quality of life and prevention of outcomes including pump failure hospitalization and death.

ACE inhibitors are currently recommended first line in HF even though the survival benefit of enalapril in the SOLVD (Studies of Left Ventricular Dysfunction) trial [60] was observed only among the patients who were hospitalized at least once during the trial. Moreover, beta-blockers are recommended for all HF patients who can tolerate them, whatever their resting heart rate, even though the basal resting heart rate in major HF clinical trials ranges between 82 and 84 bpm [44, 61]. Ivabradine is currently authorized for patients with a resting heart rate of 75 bpm or higher. HF patients generally fulfill this condition, since patients hospitalized for worsening HF are often admitted with a resting heart rate around 90 bpm, despite maximally up-titrated beta-blocker [62].

There is also evidence for the use of ivabradine in patients with increased brain natriuretic peptide (BNP or pro-BNP) or LV dysfunction recorded via echocardiography (LVEF, volumes or pressure) [63]. This is important since the prevention of cardiac remodeling is of utmost importance to delay disease progression. The SHIFT sub-study reported a 7 ml/m<sup>2</sup> reduction in LV end systolic volume index [63, 64] amounting to benefits on reverse remodeling similar to those obtained by patients in the CARMEN (Carvedilol ACE-Inhibitor Remodelling Mild CHF Evaluation) study [65] with the combination of ACE inhibitor and beta-blocker. This is particularly striking, since ivabradine was found to have this effect in patients already treated with those therapies.

Ivabradine can be initiated very early during hospitalization, in the first days, whatever the dosage of ACE inhibitor or beta-blocker. Moreover, in case of beta-blocker initiation, there is evidence that the two can be initiated together [24] in terms of tolerability and also synergistic effects due to differing modes of action. For example, the increase in stroke volume seen with ivabradine compensates for the decrease in stroke volume seen at beta-blocker initiation and makes possible beta-blocker uptitration faster with a better tolerability, provide heart rate is monitored carefully [24]. Several small-scale off-label trials have explored the possibility of initiating ivabradine in acute HF [66–70]. One of these studies [70] compared the evolution of 203 acute HF patients receiving standard therapy with 187 acute HF patients receiving standard therapy plus ivabradine 7.5 mg bid. Interestingly, ivabradine reduced the duration of inotrope support (17.5 vs. 34.7 h with standard therapy,  $p < 0.05$ ) and the occurrence of recurrent pump failure (7.5 vs. 19.2 %,  $p < 0.001$ ) and death (10.2 vs. 16.7 %,  $p = 0.058$ ). Although these preliminary results need to be confirmed in randomized controlled trials, they indicate that early prescription of ivabradine in acute HF is possible and may even be beneficial.

In Brazil, some patients experience a special form of HF due to a parasite, *Trypanosoma cruzi*. Chagas disease affects 18 million people in South America [71], though there are also about 700,000 subjects with Chagas disease living outside South America, mainly in the USA, Europe, and Canada [72]. Chronic HF affects 20–30 % of patients with chronic Chagas disease [73], with a worse prognosis than classical systolic HF. Annual mortality in patients with Chagas cardiomyopathy with chronic HF is nearly 20 % [74], though Chagas disease is still neglected and no double-blind randomized trial has ever evaluated classical HF therapies in Chagas patients. We call for such a trial, particularly with ivabradine. Such evaluation will be important for Chagas patients throughout South America, but also in the immigration countries like the USA, where, for example in Los Angeles, one HF patient in five has Chagas disease.

In addition to the management of chronic HF, ivabradine is also indicated in some countries for the treatment of stable angina pectoris. The antianginal and anti-ischemic benefits of ivabradine have been demonstrated in a range of angina trials [75–77], and two large morbidity–mortality trials have been performed [78, 79]. The overall results of one of these, the BEAUTIFUL (MorBidity-mortality EvAlUaTion of the  $I_f$  inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) trial, were neutral [78], and additional explorations suggested that ivabradine could reduce myocardial infarction-related outcomes [78] and improve LV function [80] in coronary artery disease (CAD) patients with LV dysfunction. Six years later, SIGNIFY (Study assessInG the morbidity–mortality beNefits of the  $I_f$  inhibitor ivabradine in patients with coronarY artery disease) failed to find a treatment–placebo difference in cardiovascular outcomes in CAD patients without HF [79], but did detect an increase in a subgroup of patients considered to have angina. One unusual feature of SIGNIFY was the use of relatively high ivabradine dosages at initiation and maintenance, which included the non-registered dose of 10 mg bid. The safety of ivabradine in SIGNIFY was similar to previous experience with ivabradine, with the exception of a moderate increase in atrial fibrillation and bradycardia, which may have been due to the higher dosage of ivabradine and did not have an impact on outcomes [79, 81]. The SIGNIFY results were unexpected, and resulted in new prescribing conditions for angina patients, with an increase in heart rate threshold from 60 to 70 bpm as a criteria for initiation of treatment [82]. There was no change in the HF indication. Ivabradine dosages were maintained for both indications, with a recommendation not to exceed registered dosages. In conclusion, the results of the SIGNIFY trial did not impact the positive benefit–risk balance in HF patients as demonstrated in SHIFT.

## 7 Conclusion

Epidemiological studies systematically demonstrate that HF patients are not sufficiently treated with life-saving drugs. Ivabradine is now considered to be an integral part of HF therapy, fulfilling patients' and physicians' objectives alike, i.e., improving symptoms, reducing hospitalization, and extending survival. A recent study performed in the UK indicated that nearly one-fifth of patients meet the regulatory requirements for the prescription of ivabradine [83]. Moreover, if patients are aware of these benefits, then they may even be expected to be more compliant with treatment. Healthcare authorities, whose objectives are to reduce the cost of the disease, now also fully recognize that the use of ivabradine in HF patients is both cost effective [84] and life saving.

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