

Medical treatment of heart failure with reduced ejection fraction – aimed at reducing re-hospitalisations

The prognosis of patients with heart failure has significantly improved in the past decades with the advent of therapies such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs), ivabradine, LCZ696 and with devices such as implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy devices (CRT).¹ By contrast, patients with chronic heart failure that are hospitalised for an episode of de-compensation continue to have a high mortality and excessive hospital readmission rates.²

Hospitalisations for heart failure are frequent in treatment-naïve patients as well as in patients with chronic heart failure and in those who had been recently hospitalised because of a recent episode of de-compensation. High rates of re-hospitalisation are more frequent in patients with co-morbidities and in those with advanced heart failure.² It is estimated that nearly 50% of patients with heart failure will be re-hospitalised within 6 months of discharge, and that 70% of these re-hospitalisations are related to worsening of their heart failure.³

Precipitating factors for a new hospitalisation episode in patients with heart failure include cardiac factors such as myocardial ischaemia, new onset or rapid rate atrial fibrillation, and un-controlled hypertension.⁴ However, a sizeable proportion of hospitalisations occurring in patients with heart failure are non-cardiac or precipitated by extra-cardiac factors, such as exacerbations of COPD, infections and anaemia or by patient-related factors, such as

medication non-adherence, use of non-steroidal anti-inflammatory drugs and the effects of drug-drug interactions.⁵

Therefore, heart failure hospitalisations are relevant causes of poor prognosis and quality of life in patients with heart failure. Hospital admissions are extremely distressing for patients, especially the older ones and they are heralds of an accelerated disease progression. They are also the major driver of the economic burden of heart failure. Consequently, treatments that may positively reduce hospitalisation rates have a significant effect on quality of life, disease progression and the costs of care.

Predicting heart failure readmission

Several studies have suggested different predictors for re-hospitalisation in patients with HFrEF but, given the different models of health care (mostly private in US, mostly national health services in Europe, mixed models elsewhere), it is difficult to develop a risk model that may adequately predict the risk of readmission.

Pathophysiological indices of heart failure severity may predict higher rehospitalisation rates. Some of these indices are related to elevated filling pressures, such as jugular venous pressure, orthopnoea, echocardiographic filling patterns and plasma levels of cardiac biomarkers such as natriuretic peptides and cardiac troponins.^{1,5} Inadequate diuretic dosing or intolerance of neuro-hormonal antagonists because of hypotension or renal dysfunction are also likely indicators of de-compensation requiring re-hospitalisation. Both cardiac and non cardiac co-morbidities (atrial fibrillation, ischaemic heart disease, chronic kidney disease, diabetes mellitus, anaemia, pulmonary disease) also increase the risk for heart failure hospitalisations.¹

Heart failure hospitalisations are higher in patients with psychosocial and/or socioeconomic factors that limit adherence and treatment compliance while high adherence to guidelines implemented through disease management programs reduces re-admission rates.⁶ Therefore, evidence based therapies and international guidelines should be implemented during the in-patient and out-patient settings at all stages of the disease in patients with heart failure.

Disease management programs

These programs are a multidisciplinary, integrated approach to disease management that include different forms of patient care ranging from direct patient follow-up (outpatient clinic or at home) or remote support such as by telephone calls or telemonitoring. The DIAL trial⁷ that randomly assigned 1,518 patients

with heart failure to either routine care or an intervention with an explanatory booklet and periodic telephone calls by a nurse enforcing self-management resulted in a lower rates of heart failure hospitalisations (26.3% vs 31%) at a mean follow up of 16 months. A Dutch study including 1,023 patients with HF assigned to a control group with regular cardiologist follow up and 2 interventions with either additional basic support or intensive support by a nurse found no differences in mortality or heart failure re-hospitalisations amongst the 3 groups.⁸

A systematic review⁹ of 29 randomised controlled studies of multidisciplinary disease management programmes conducted either in a clinic or a non-clinic setting showed reduced mortality (RR 0.75, 95% CI 0.59–0.96), heart failure hospitalisations (RR 0.74, 95% CI 0.63–0.87), and all-cause hospitalizations (RR 0.81, 95% CI 0.71–0.92). Similarly programmes aimed at enhancing patient self-care activities reduced HF hospitalizations (RR 0.66, 95% CI 0.52–0.83) and all-cause hospitalizations (RR 0.73, 95% CI 0.57–0.93) but had no effect on mortality (RR 1.14, 95% CI 0.57–1.94).

Telemonitoring is used to communicate with patients and obtain health status and physiologic data (weight, ECG, fluid status etc.) remotely. A meta-analysis of 14 randomised studies suggested that remote monitoring programmes could reduce the rates of admission to hospital for chronic heart failure by 21% (95% confidence interval 11% to 31%) and all cause mortality by 20% (8% to 31%) in patients with heart failure.¹⁰ More recently, recent large randomised controlled studies using tele-monitoring or usual care yielded

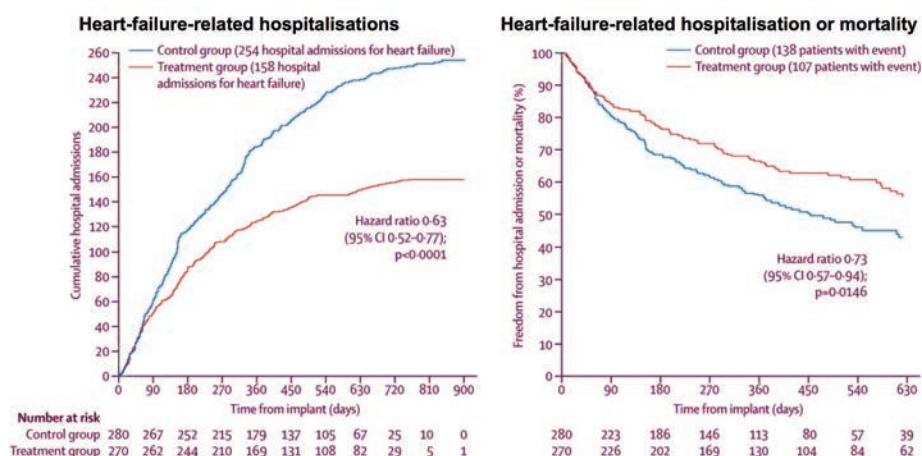


FIGURE 6.1 CHAMPION study – wireless pulmonary artery haemodynamic monitoring with CardioMEMS in heart failure

conflicting results suggesting that tele-monitoring should be tailored to the local healthcare settings.^{11,12}

On the other hand, a disease management program with therapies adjusted according to physiological signals of pulmonary artery pressures measured directly with the implantable CardioMEMS Heart Sensor has been shown to reduce by 39% heart failure hospitalizations in the CHAMPION trial.⁶ (see Figure 6.1) Furthermore, a cost-effectiveness analysis showed that integrating CardioMEMS wireless pulmonary artery pressure monitoring into the management of heart failure patients is a cost effective addition to the heart failure treatment pathway in appropriate patients.

Medical therapy aimed at reducing hospitalisations

Management of fluid overload

Prevention of clinical and subclinical congestion with adequate use of diuretics reduces re-hospitalisation rates.¹ Loop diuretic therapy is the mainstay of congestion management. Metolazone, a long-acting thiazide-like diuretic, may be used in those patients who are poorly responsive to loop diuretics but it is associated with a significant risk of hyponatraemia especially if used chronically.²

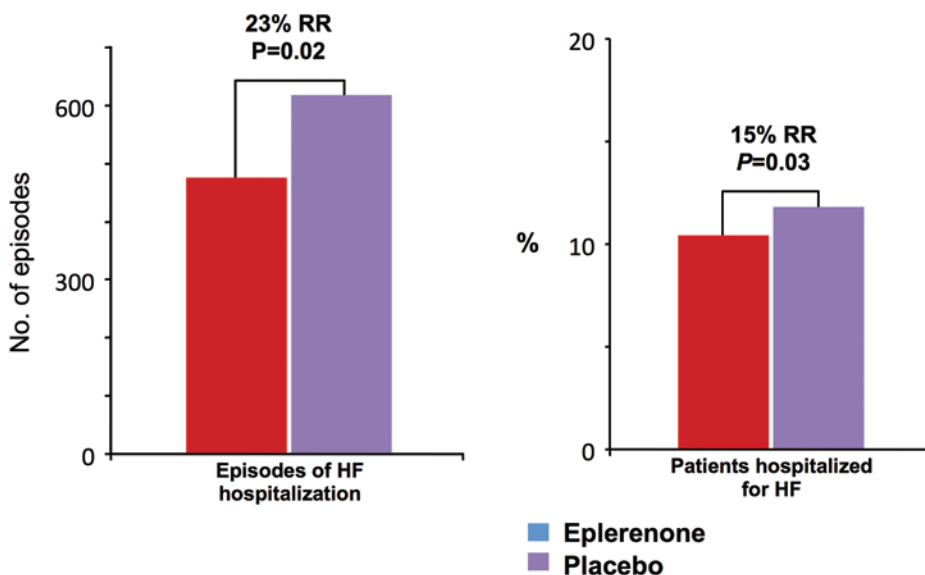


FIGURE 6.2 EPHEsus study – Effect of eplerenone on heart failure hospitalizations. From Pitt B et al, *N Engl J Med.* 2003; 348: 1309–1321

Its pulsed use has less effect on plasma sodium levels. Mineralocorticoid receptor antagonists are particularly useful in controlling fluid balance and modulating the neuro-humoral balance. Spironolactone and eplerenone both significantly reduce (35%) re-hospitalization rates and are indicated in all patients with heart failure.¹ (see Figure 6.2)

In patients with fluid retention presenting with hyponatraemia, and/or impaired renal function, the vasopressin antagonist tolvaptan should be considered although it has no effect on long term prognosis and re-hospitalisation rates.¹³

Renin-angiotensin-aldosterone system inhibitors (RAASi)

RAASi including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists (ARAs), reduce the risk for mortality and hospitalization in patients with existing HF.¹ After the CONSENSUS study (COoperative North Scandinavian ENalapril SURvival Study),¹⁴ several trials with angiotensin-converting enzyme (ACE) inhibitors, including captopril, lisinopril, ramipril, andtrandolapril, confirmed the benefit of in different clinical settings, including asymptomatic left ventricular dysfunction and post-infarction heart failure.¹⁵ ARBs have also been investigated in chronic heart failure and have been shown to reduce re-hospitalisation rates. However, given that the benefit of ARBs is sensibly less than that of ACEi they should only be used in patients who are intolerant to ACEi.¹

A meta-analysis of the large randomised controlled trials has demonstrated that RAASi reduce the risk of re-hospitalisation by 20% and that this effect is independent by the degree of left ventricular dysfunction.¹⁶ (Figure 6.3) However, the proportional effects on all end points decreased with increasing mean left ventricular ejection fraction. These findings support the indication for use of an ACEi and a MRA in all patients with HFReEF with a class IA recommendation.



FIGURE 6.3 Effect of RAASi on all cause mortality, cardiovascular mortality and hospitalisation for heart failure.¹⁶

Beta-blockers

The use of beta-blockers has been demonstrated to prevent deterioration of myocardial function, and to improve prognosis in patients with HFrEF because of their effect on the inhibition of neuro-hormonal activation. Several studies and meta-analyses have demonstrated that the prognostic benefit of beta-blockers depends on the degree of heart rate reduction rather than on the administered dose.¹⁷

Systematic reviews of the randomised trials of beta blockers in heart failure have shown a beneficial effects on mortality and hospital admissions but only in patients in sinus rhythm.¹⁸ A recent individual patient meta-analysis of 18,254 patients included in all the adequately sized randomised studies testing the effect of beta-blockers in patients with HFrEF has shown that the prognostic benefit of beta-blockers observed in patients in sinus rhythm is not seen in patients with atrial fibrillation. This meta-analysis has also shown a consistent benefit of β blockers versus placebo for hospital admission outcomes in patients with sinus rhythm while a significantly attenuated effect in those with atrial fibrillation (HR 0.78 vs 0.91 sinus rhythm vs atrial fibrillation, $p < 0.05$). Therefore, beta-blockers reduce events and hospitalisations in patients with HFrEF in sinus rhythm while in those in atrial fibrillation the extent of the benefit of beta-blockers is less clear. In patients with atrial fibrillation, however, beta-blockers are still indicated inferring their benefit from the studies conducted mostly in patients HFrEF and in sinus rhythm.

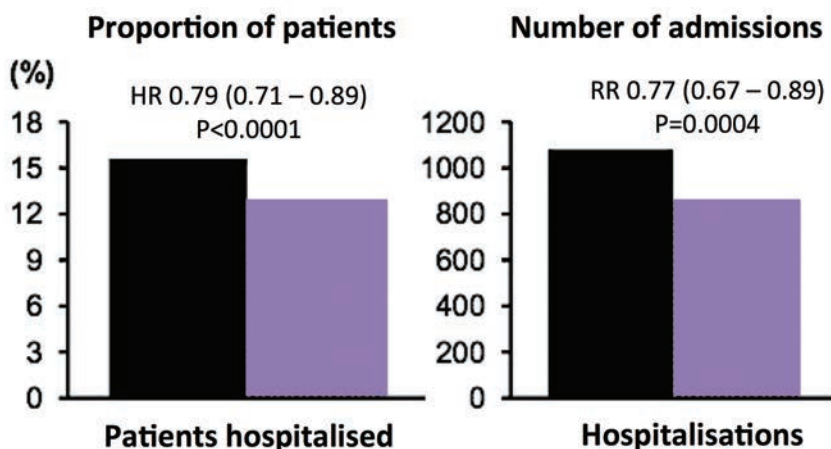


FIGURE 6.4 PARADIGM HF – Effect of LCZ696 on heart failure hospitalisations.¹⁹

Angiotensin II Receptor Nephilysin Inhibitor

The PARADIGM HF study has shown that LCZ696 is superior to Enalapril in reducing mortality and morbidity in patients with heart failure and elevated natriuretic peptide levels.¹⁹ Further to the mortality benefit, LCZ696 significantly reduced the rate of hospitalisation for heart failure compared to enalapril (hazard ratio, 0.79; 95% CI, 0.71–0.89; $P < 0.001$). LCZ696 also reduced the rates of hospitalisations for a cardiovascular reason (hazard ratio, 0.88; 95% CI, 0.81–0.95; $P < 0.001$) or for any reason (hazard ratio, 0.88; 95% CI, 0.82–0.94; $P < 0.001$). (Figure 6.4) Therefore, LCZ696 is indicated for all patients with HFrEF with symptomatic heart failure despite treatment with an ACEi (or an ARB). In this case the treatment with ACEi or ARB should be discontinued at least 36 hours before the first dose of LCZ696.

Ivabradine

In patients with stable heart failure with a heart rate above 70 beats per minute (bpm) included in the SHIFT trial (Systolic Heart failure treatment with the If inhibitor ivabradine Trial), heart rate was associated with an increased risk of cardiovascular death and heart failure hospitalizations, which translates into a 3% increase in risk for every 1-bpm increase from baseline heart rate and 15% increase in risk for every 5-bpm increase.²⁰

Heart rate reduction with ivabradine reduced the composite outcome of cardiovascular death and heart failure hospitalisation in patients with HFrEF

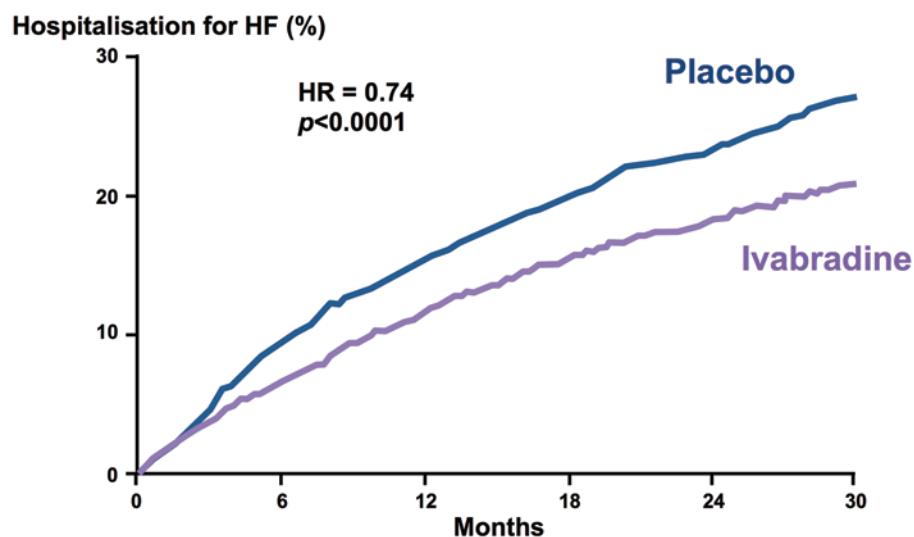


FIGURE 6.5 SHIFT study – Effect of ivabradine on heart failure hospitalisations.²¹

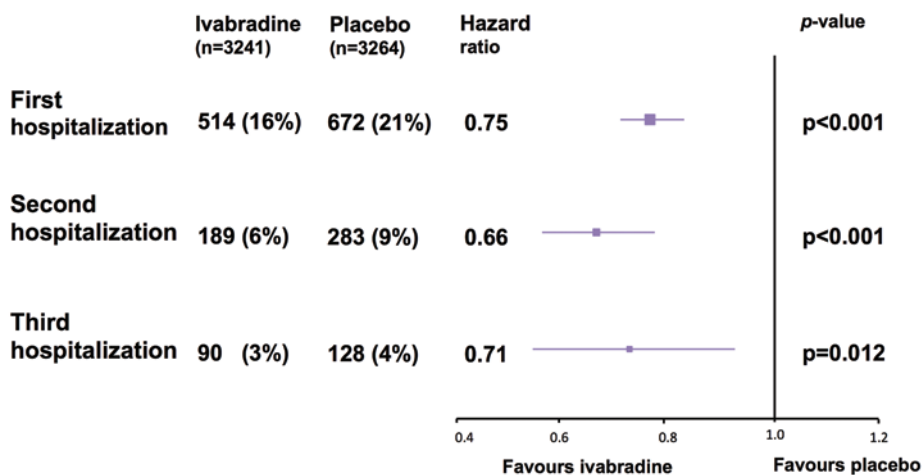


FIGURE 6.6 SHIFT study effect of ivabradine on heart failure hospitalisation.²¹

with a heart rate above 70 bpm and cardiovascular death and total mortality in the subgroup of patients with a heart rate above 75 bpm.²¹ Hospitalisations for heart failure were reduced by 26% with ivabradine, the effect appeared early and was constant throughout the study. (Figure 6.5)

Furthermore the SHIFT study showed amongst the 1,186 patients a 34% reduction in second heart failure hospitalizations among those who were admitted once and a 29% reduction among those who were admitted twice.²¹ (Figure 6.6) All-cause and cardiovascular hospitalisations were similarly reduced by ivabradine and, in patients with more than one admission, ivabradine prolonged the time to a second admission with a longer time out of hospital free of worsening heart failure. Indeed, the time from one admission to the subsequent one was prolonged by 17% by ivabradine and significantly fewer patients with HFrEF who received ivabradine during the study suffered a second hospital admission.²¹

Despite a sizeable proportion of patients included in the SHIFT trial receiving MRAs, ivabradine had a highly significant effect on outcomes, including hospitalisations for heart failure, independent of the effect of MRAs.

The SHIFT study also showed that ivabradine is effective in preventing early re-admission in patients with HFrEF who had been hospitalised for heart failure. Indeed, among those patients who suffered a first hospitalization during the study, patients receiving ivabradine had a reduced occurrence of re-hospitalisation in the following 30 days compared to those receiving placebo (IRR 0.70, $p<0.05$).²¹ These findings clearly show the benefit of ivabradine, on a background of beta-blockade, angiotensin-converting enzyme inhibitors,

mineralocorticoid receptor antagonists, and diuretics in reducing early and later re-hospitalisations for heart failure.

After discharge from heart failure hospitalization, under-treatment of patients with β -blockers and angiotensin-converting enzyme (ACE) inhibitors occurs often in patients with low blood pressure. A proportion ranging between 15% to 25% of patients discharged from hospital for an episode of decompensation have low blood pressure (ie, <120 mm Hg), which reduces the possibility to fully implement medical therapy and puts them at an increased risk for poor outcomes. The combination of higher heart rates and low blood pressure further increases event rates in patients with heart failure. In this population of patients with heart failure ivabradine showed a consistent effect on the reduction of hospitalisations and events.^{16,17} Therefore, an early initiation of ivabradine, which is not accompanied by blood pressure reduction, leads to a higher proportion of patients receiving evidence-based treatment in the year after discharge as recently shown.

Digitalis

The DIG (Digitalis Investigators Group) trial suggested that digoxin, when added to diuretics and ACE inhibitors in patients with chronic HF in sinus rhythm, decreases hospitalizations without adversely affecting survival.²² However, in DIG trial the effect of digoxin on the reduction of heart failure hospitalisations was offset by a significant increase of other cardiovascular hospitalizations (hazard ratio: 1.20; 95% confidence interval: 1.05 to 1.38).

More recently an analysis of de novo use of digoxin in adults with incident systolic heart failure included in the database of the Kaiser Permanente Northern California system showed that digoxin use was associated not only with higher rates of death (14.2 vs. 11.3 per 100 person-years) but also with higher rates of heart failure hospitalization (28.2 vs. 24.4 per 100 person-years) than non-use.²³ Therefore, digoxin has not consistently shown to reduce re-hospitalisations and its use should be limited to selected patients as outlined in other chapters.¹

The reduction in re-hospitalisation for heart failure is an important therapeutic goal in patients with heart failure, because of the effect of hospitalisations on well-being and prognosis. LCZ696 and ivabradine have been shown not only to reduce events in patients with HFrEF but also to reduce heart failure hospitalisations occurring both as first events, and as recurrent hospitalisations with a similar degree of efficacy. Given the neutral effect of ivabradine on blood pressure, this drug should be always considered in patients in sinus rhythm. LCZ696 has some blood pressure lowering effect that may limit its implementation in some patients. Therefore, in order to fully benefit from the

prognostic benefits of these two drugs patients who are still symptomatic after the administration of an ACEi a beta-blocker and a MRA should be switched to these therapies and controlling heart rate with the combination of beta-blockers and ivabradine. Treatments should be implemented with appropriate disease management programs and fluid retention should be monitored with devices like the CardioMEMS that have been proven to effectively reduce events.

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