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Current Challenges in the Management of Heart Failure
Michel Komajda, MD

The management of chronic heart failure (HF) with low ejection fraction (EF) has changed considerably over the past 30 years: the introduction of angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, angiotensin-receptor blockers, mineralocorticoid-receptor antagonists and recently, the I_f blocker, ivabradine, has led to a significant reduction in overall mortality and HF mortality. Recently, a trial testing a dual inhibitor blocking the angiotensin-II receptor and nephrilisin, the enzyme responsible for B-type natriuretic peptide degradation, showed that this complex molecule improved clinical outcomes compared with the ACEI enalapril. However, challenges remain in the management of HF, with suboptimal implementation of guideline-recommended therapies, a changing profile of patients who are older and have multiple comorbidities and a high rate of early rehospitalization for HF. Use of devices such as implantable cardiac defibrillators and cardiac resynchronization therapy are also associated with an improvement in outcomes in this condition. HF with preserved EF (HFpEF), a growing fraction of the HF population, remains a clinical dilemma: no pharmacological intervention has so far demonstrated any convincing benefit on outcome. Heterogeneity of the populations tested, role of comorbidities, difficulties in identifying patients with HFpEF, as well as a mismatch between the clinical phenotypes and the treatments tested, can explain the failure to find beneficial interventions. Overall, the management of HF after discharge remains fragmented and concerted action by all professionals concerned is needed. (Circ J 2015; 79: 948–953)

Key Words: Cardiac resynchronization therapy; Dual inhibitors; Heart failure; Implantable cardiac defibrillators

The management of heart failure (HF) has considerably changed during the past 30 years with the introduction of both major classes of drugs and devices. Angiotensin-converting enzyme inhibitors (ACEIs), β-adrenergic blockers, angiotensin-receptor blockers (ARBs), mineralocorticoid-receptor antagonists (MRAs), “funny” channel (I_f) blockers and more recently, dual inhibitors blocking nephrilisin and angiotensin receptors have been shown to improve mortality and morbidity in large randomized clinical trials including patients with mild to moderate chronic HF and reduced ejection fraction (EF).1–17 Similarly, implantable cardiac defibrillators (ICDs) and cardiac resynchronization therapy (CRT) have shown benefit on the prevention of sudden cardiac death (SCD)18 in patients with mild to moderate HF with low systolic function, and on cardiovascular mortality and morbidity19–22 in both severe and in moderate HF with reduced EF. There are, however, areas where there is a lack of evidence or a gap in knowledge despite numerous pharmacological or non-pharmacological attempts at treatment. This includes in particular acute HF and HF with preserved EF (HFpEF) where little or no progress has been made. In addition, lengthy and recurrent hospitalizations for HF remain a burden on health-care systems because of the costs incurred and the associated poor quality of life.

The objective of this review is to discuss the successes and the failures in the management of this condition and to identify remaining challenges.

Chronic HF With Low EF: A Success Story
Evidence-based medicine in HF has been essentially developed in patients with low EF.

Pharmacotherapy (Table 1)
Two key randomized controlled trials using enalapril in approximately 2,800 patients, CONSENSUS and SOLVD in mild, moderate or severe symptomatic patients have demonstrated that the addition of an ACEI to diuretics and in most cases digoxin and/or spironolactone significantly reduced overall mortality by approximately 20%.1–3 In symptomatic patients enrolled in SOLVD there was also a significant reduction of HF hospitalizations. Finally, the benefit of ACEIs on death or HF hospitalization was also demonstrated in 3 large trials enrolling patients with HF and/or left ventricular dysfunction after acute myocardial infarction (SAVE, TRACE, AIRE).4 These impressive results led to the recommendation in international guidelines of using ACEIs as first-line therapy in chronic HF with low EF.5

The evidence supporting the use of β-blockers in the same indication comes from the results of the large clinical trials published in the late 90s or early 2000s: the U.S. carvedilol studies showed a reduction in mortality with carvedilol.6 This
program was followed by 3 randomized clinical trials, CIBIS II (bisoprolol), MERIT HF (metoprolol succinate CR/XL) and COPERNICUS (carvedilol), which enrolled almost 9,000 patients and showed consistent results with a mortality reduction of approximately one-third and a reduction in HF hospitalizations on top of background medication including ACEIs.7-9 These positive results were later confirmed in the elderly population (≥ 70 years) enrolled in SENIORS, where nebivolol reduced significantly the composite of death or HF hospitalizations and other clinical endpoints.8-12 However, at that time only 11% of the patients were treated with a β-blocker. More recently, the EMPHASIS HF trial demonstrated that addition of eplerenone to mildly symptomatic patients treated with ACEIs or ARBs and β-blockers reduced significantly by 37% cardiovascular mortality or HF hospitalizations and other clinical endpoints.12 European Society of Cardiology (ESC) guidelines therefore recommend considering this class of drug in all patients with HF and low EF and with persistent symptoms despite ACEIs or ARBs if ACEIs are not tolerated and β-blockers. ARBs are recommended as an alternative to ACEIs in patients who are intolerant to this class following the publication of CHARM alternative, which demonstrated that in patients with low EF and intolerance for ACEIs, candesartan reduced cardiovascular mortality or HF hospitalization by 23%.13

Two additional trials, Val Heft (valsartan) and CHARM added, explored the potential benefit provided by a combination of an ARB with an ACEI.14,15 There was a reduction in HF hospitalizations, and in CHARM added there was a reduction in cardiovascular death. However, because the magnitude of the benefit brought by this combination was smaller than that of the combination of an ACEI with a MRA, this class of drug is now primarily indicated as an alternative to ACEIs in the case of intolerance.

Ivabradine is a drug that inhibits the “funny” (If) channel in the sino-atrial node and slows down heart rate in patients in sinus rhythm. The magnitude of heart rate reduction is directly dependent on the baseline heart rate and is more pronounced in patients with a markedly elevated heart rate.16

This new drug was tested on top of ACEIs/ARBs, β-blockers and in the majority of cases, a MRA in a large, controlled randomized trial including patients with mild to moderate HF, low EF and in sinus rhythm with heart rate ≥70 beats/min.16 There was a significant (18%) reduction in the primary composite endpoint of cardiovascular death or HF hospitalization. The reduction of cardiovascular death or all-cause death alone was not significant whereas HF hospitalizations were reduced by 26%. A significant improvement in quality of life was also observed, as well as a reverse remodeling effect.23,24 Ivabradine is now recommended for symptomatic patients with low EF, in sinus rhythm ≥70 beats/min despite treatment with maximally tolerated β-blocker (or when β-blockers are contraindicated), ACEI/ARB and a MRA.

There are therefore 5 available classes of drug that favorably influence outcomes of patients with chronic HF with reduced EF and the current guidelines of the European Society of Cardiology recommend an additive strategy starting with ACEI (or ARB if not tolerated), β-blocker, MRA and finally ivabradine for patients in sinus rhythm and with elevated heart rate.

Recently, a large randomized controlled trial evaluated a dual inhibitor (LCZ 696) blocking the ARB receptor and nephrilisin, the enzyme that cleaves B-type natriuretic peptide (BNP) and makes it inactive, in a large population of mild to moderate chronic HF patients.17 In PARADIGM-HF, the comparator was enalapril 20 mg/day. The trial was prematurely interrupted because of benefit: there was a significant 20% reduction of the composite endpoint of cardiovascular mortality or HF hospitalization, of cardiovascular mortality alone (20%) (which was the predefined trigger for recommending early termination), as well as all-cause death (16%) and of HF hospitalizations (21%). Overall, the safety was good; there were more episodes of hypotension but renal tolerability was

### Table 1. Pharmacological Classes Used in Heart Failure: Studies and Effects

<table>
<thead>
<tr>
<th>Class</th>
<th>HFpEF Effect on morbidity/mortality</th>
<th>HFrEF Effect on morbidity/mortality</th>
</tr>
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<tbody>
<tr>
<td>ACEIs</td>
<td>(CONSENSUS–SOLVD)</td>
<td>(PEP CHF)</td>
</tr>
<tr>
<td>ARBs</td>
<td>(CHARM Alternative)</td>
<td>(I-PRESERVE)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>(Carvedilol US Programme CIBIS II MERIT HF COPERNICUS)</td>
<td>(HF hospitalization) CHARM-PRESERVED</td>
</tr>
<tr>
<td>MRAs</td>
<td>(RALES–EMPHASIS HF)</td>
<td>(HF hospitalizations TOP CAT)</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>(SHIFT)</td>
<td>?</td>
</tr>
<tr>
<td>LCZ 696</td>
<td>(PARADIGM-HF)</td>
<td>?</td>
</tr>
<tr>
<td>Digoxin</td>
<td>(HF hospitalizations) (DIG)</td>
<td>–</td>
</tr>
<tr>
<td>Diuretics</td>
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ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRAs, mineralocorticoid-receptor antagonists.
better and cough was significantly less frequent than with enalapril, and the frequency of angioedema, a well-known side effect of blockers of neprilysin, related to the increase in bradykinin plasma concentration, was only slightly higher than in the control group.

These impressive results should lead to a substantial revision of the currently recommended strategy and to a replacement of ACEIs as first-line therapy by this new complex molecule in order to further reduce adverse outcomes in chronic HF with low EF.

There are, however, pending questions, including the market price and the definition of the population that should receive LCZ 696 (simple clinical criteria or restriction to patients with evidence of increased BNP/N-terminal pro-BNP, a criterion used for inclusion in the trial).

These important matters are currently subject to discussion with regulatory agencies.

**Implantable Devices (Table 2)**

Because a substantial number of deaths occur suddenly in HF and are presumed to be related to a fatal ventricular arrhythmia in most cases, prevention of SCD is a major goal, particularly in patients with mild to moderate symptoms in whom SCD is more prevalent than in those with more advanced HF. Neurohumoral modulators, particularly β-blockers and MRAs, reduce significantly the risk of SCD, but they do not prevent it. Class I antiarrhythmic agents are contraindicated in HF with low EF and amiodarone failed to demonstrate any benefit on mortality in a large clinical trial comparing standard therapy, amiodarone and ICD. The trial (SCD-Heft) enrolled 2,521 patients with EF <35% in NYHA class II or III, without prior ventricular arrhythmia. The ICD strategy led to a 23% relative risk reduction in all-cause mortality. Primary prevention by ICD is therefore recommended for patients in class II or III with a good life expectancy >1 year after a sufficient period of optimization of medical therapy (≥3 months) in order to reduce the risk of SCD in patients with chronic HF of ischemic or nonischemic origin.

CRT was developed in the early 2000s in patients with severely symptomatic HF despite optimal therapy, low EF <35% and wide QRS. COMPANION compared 3 strategies: conventional therapy, CRT and CRT plus ICD. CARE HF compared CRT with conventional therapy alone. The 2 trials demonstrated that CRT alone or combined with an ICD reduced all-cause mortality and HF hospitalizations significantly compared with conventional therapy (24% and 36%, respectively, for CRT and CRT-D in COMPANION, 36% for CRT in CARE HF). There was also a benefit on symptom improvement, quality of life and ventricular remodeling.

The benefit of CRT was later evaluated in mild to moderate HF patients in 2 controlled trials: MADIT CRT and RAFT. In these trials the thresholds for EF and QRS duration at inclusion were different from those used in trials with more severe patients: ≤30% for EF in both trials, QRS duration ≥130 ms in MADIT CRT and ≥120 ms in RAFT. Moreover, the 2 strategies compared in each of these trials were optimal therapy plus ICD vs. optimal therapy vs. CRT plus ICD (CRT-D).

The conclusions of the 2 trials were similar and showed that CRT-D reduced the composite of all-cause death or HF hospitalization, although mortality alone was not reduced in MADIT CRT. There was also an improvement in symptoms and quality of life. These 2 trials also showed that QRS duration and morphology (left bundle branch block (LBBB) vs. non-LBBB) influenced the outcome: the maximal benefit was observed patients with very wide QRS >150 ms and in those with a LBBB morphology and a QRS duration ≥130 ms. These thresholds have been used in the ESC guidelines for the use of CRT in patients with mild symptoms of HF.

The possibility of using CRT in patients with QRS <120 ms and evidence of mechanical dyssynchrony has been tested recently in Echo-CRT. The trial was prematurely interrupted upon recommendation by the Data Safety Monitoring Board because of an excess in mortality and futility. There is therefore no indication for CRT in patients with narrow QRS duration.

One area of uncertainty is atrial fibrillation because the CRT trials listed above excluded this condition, with the exception of RAFT in which 13% of the patients had atrial fibrillation at inclusion. Although a subgroup analysis did not show a significant interaction between basal rhythm and CRT effect, it is based on a limited number of patients and therefore the evidence is weak. Another area of uncertainty is patients with a conventional indication of cardiac pacing who were excluded from clinical trials. Considering that conventional right ventricular pacing can lead to cardiac function deterioration and modifies the normal sequence of mechanical activation, ESC guidelines therefore recommend CRT in severely symptomatic HF and low EF, irrespective of QRS duration, as well as in less symptomatic patients requiring conventional pacing but with a low class level of recommendation.

These multiple progresses made in both pharmacology and devices have undoubtedly improved the outcomes of patients with chronic HF with low EF. Only 20 years ago the annual mortality rate was approximately 16% in the placebo arm of SOLVD. In the SHIFT trial published in 2010, the rate had dropped to 9%. In addition, mortality rate related to HF as the cause of death has been halved in the time between those 2 trials. The difference is not observed only in populations enrolled in clinical trials, which are by definition highly selected. An analysis of mortality directly related to HF in 8 European...
countries shows that it has been constantly falling over the past 15 years.\textsuperscript{26}

All-cause mortality remains, however, very high after a hospitalization for acute HF; in the Euro Observational Study on HF the annual mortality rate was 17% and the cause was cardiovascular in 60% of cases.\textsuperscript{37}

**Challenge of Hospitalization and Rehospitalization**

The fact that life-saving medications do not always translate into a reduction in hospitalizations and, notably, early rehospitalizations, in the general population is a matter of concern. Although recent data from all US discharge summaries of HF hospitalizations show a decline over time,\textsuperscript{28} it remains the major cause of referral to hospital, as shown by an analysis of hospitalizations in Sweden.\textsuperscript{29}

The 4–6 weeks following discharge is known as a “vulnerable phase”, associated with high rates of mortality and rehospitalization for HF.\textsuperscript{28} The risk of dying in the first 30 days after an index hospitalization is increased 6-fold compared with patients not hospitalized. Similarly, in the EVEREST trial, 25% of patients were rehospitalized during the same period of time after an index hospitalization for decompensated HF.\textsuperscript{31} In an analysis of hospital discharge summaries in the USA, HF was first as the condition for recurrent hospitalizations.\textsuperscript{32} An analysis in elderly patients hospitalized for HF in the USA suggests a bidirectional trend, with a reduction in post-discharge mortality but an increase in early rehospitalization rates.\textsuperscript{33} Because hospitalization represents approximately 70% of the cost related to the management of HF, it is not surprising that the cost of HF management should more than double between 2010 and 2030 in the USA.\textsuperscript{34}

In addition, the specific management of acute HF has not changed over the past 20 years. A number of trials using very different drugs, such as new inotropes, arginine vasopressin antagonists, nesiritide, adenosine receptor A1 antagonists or endothelin-receptor antagonists, failed to demonstrate any improvement in short- or mid-term outcomes and the ESC guidelines still recommend that intravenous diuretics, oxygen, opiates if needed, nitrates, or “old” inotropes play a central role in the management of this condition.

Several explanations can be put forward to explain the explosion of rehospitalizations related to HF: (1) patients who previously died now survive at the expense of an increase in the rehospitalization rate; (2) a changing profile of HF patients who are older and have often multiple comorbidities that can make the management of their condition more complex because of contraindications or intolerances and puts them at higher risk of rehospitalization due to increased frailty; (3) suboptimal titration of life-saving drugs, which is observed in all registries (a recent survey conducted by the ESC suggests that, at best, 25–30% of patients reach the target dose of β-blockers\textsuperscript{37}); and (4) a fragmented chain of command is frequently observed when patients leave the hospital, resulting in a gap in follow-up care after discharge and many patients do not see any healthcare professionals for a long period of time. In a national survey conducted in France, only 29% of the patients had consulted a cardiologist in the first 3 months after discharge from hospital.\textsuperscript{35}

Solutions to this worrying situation include better patient education schemes so that every HF patient is aware of the objectives of their treatment, of the symptoms of decompensation, of the most common side effects of drugs used to manage their condition and of dietary requirements. This approach has been shown to be effective, but is limited in very elderly patients with cognitive disorders, for whom the role of the family becomes crucial.

The use of serial biomarker measurements is another way to address this issue and a recent meta-analysis has shown that a natriuretic peptide-guided strategy reduced HF rehospitalizations by approximately 25%.\textsuperscript{36} Of note, however, the magnitude of the benefit on mortality was observed only in younger patients (<75 years) and there was no benefit on all-cause death in older patients, who represent the majority of HF populations.

Telemedicine using structured telephone calls or remote monitoring of biomarkers is another tool to improve outcomes and reduce HF hospitalizations, although not all studies show benefit.\textsuperscript{37} One limitation to the development of telemedicine is the fact that it is generally not reimbursed and therefore the medical time spent for this approach does not generate any fee.

**HFrEF: A Clinical Dilemma**

Unlike what is observed for HFrEF, all attempts to reduce the mortality and morbidity rates of HFrEF have failed (Table 1).

One trial (PEP CHF) tested the ACE I, perindopril, in an elderly population of 850 patients and failed to demonstrate any benefit on the primary outcome of all-cause mortality or HF hospitalization.\textsuperscript{38} Two trials tested an ARB: CHARM-PRESERVED evaluated candesartan in a group of 3,023 patients,\textsuperscript{39} and 1-PRESERVE tested irbesartan in an elderly population of 4,128 patients.\textsuperscript{40} In CHARM-PRESERVED, there was a nonsignificant trend in risk reduction of the primary endpoint of cardiovascular death or HF hospitalization, which was driven by a reduction in HF hospitalizations. In 1-PRESERVE, there was no significant reduction in the composite of all-cause death or cardiovascular hospitalizations and no secondary endpoint showed any trend in favor of irbesartan. Recently, the TOPCAT trial testing spironolactone showed only a nonsignificant 11% relative risk reduction of the primary composite of cardiovascular death, HF hospitalization or aborted cardiac arrest.\textsuperscript{41} HF hospitalization was the only component of the primary endpoint that showed a significant reduction and the trial was criticized because of huge geographic variations in event rates.

Recently, the SUPPORT study evaluated the addition of an ARB, olmesartan, on top of existing therapy in a large population of patients with hypertension, stable HF and preserved EF.\textsuperscript{42} It concluded that the addition of the ARB was not associated with improved outcomes, induced more episodes of renal impairment and that the combination of an ACEI, olmesartan and a β-blocker was associated with more cardiovascular events.

These results are all the more worrying because this subset of patients represents a growing part of the overall HF population.\textsuperscript{43} Several factors can explain the disappointing results observed in the large, randomized clinical trials, as well as in the proof of concept studies. One explanation is that patients with HFrEF are usually older and have multiple comorbidities, which makes them more complicated to manage.\textsuperscript{44,45}

Another reason, possibly related to the greater noncardiac comorbidity burden, is that the relative proportion of noncardiovascular death is greater in HFrEF than in HFrEF.\textsuperscript{46} Another explanation is that the diagnosis of HFrEF is challenging because it requires the combination of signs and symptoms of HF, a “preserved” EF >50% and objective evidence of abnormal diastolic filling, left ventricular filling or relaxation.\textsuperscript{47} This third component may be difficult to evi-
progress has been made in improving patients’ outcomes. Another cause of failure is the heterogeneity of patients enrolled in large clinical trials with regard to age or natriuretic plasma levels, suggesting that these patients are at different stages of their disease. Factors related to the trials also play a role: difficulties in recruiting patients have resulted in prolonged recruitment periods of time with associated drop out/drive in issues.

Finally, drug factors may play a role. The understanding of the pathophysiology of HFpEF remains suboptimal and a uniform approach to its management may not work, because several phenotypes of this condition have been described. The recent failure of the RELAX trial to demonstrate any benefit of sildenafil, a phosphodiesterase 5 inhibitor, may be attributable to the fact that the patients did not have pulmonary hypertension unlike what was required in small previous trials or to the fact that the pathophysiological defect is not an increased degradation of cGMP but rather an insufficient production of cGMP. Future trials testing direct soluble guanylate cyclase stimulators should provide an answer to this question.

Recently, the PARAMOUNT trial tested the dual inhibitor LCZ696 in a group of 286 patients and showed that compared with valsartan there was a favorable change in NT-proBNP at 12 weeks. Based on these preliminary results and on the positive results of PARADIGM-HF, a large outcome trial in patients with HF and low EF, PARAGON, has been initiated to evaluate this new molecule in a large population of HFpEF patients.

Several other proof of concept studies are currently evaluating other strategies including ivabradine, exercise training or a direct soluble guanylate cyclase stimulator.

In summary, HFpEF remains a challenging condition with imperfectly understood pathophysiology, difficult diagnosis and heterogeneous phenotype, all factors that make the management of this condition difficult and which explain why no progress has been made in improving patients’ outcomes.

Conclusions

The management of HF has considerably changed during the past 30 years, with the wide dissemination of neurohormonal therapies and, to a lesser extent of implantable devices including ICDs and CRT.

Progress made has exclusively concerned chronic HF with low EF and it translates into an overall reduction in mortality and hospitalizations because of HF.

However, the burden of hospitalizations and particularly of rehospitalization remains.

No progress has been made in HFpEF or in acute HF. Because of the cost of the management of HF, and the high prevalence of this condition in the elderly, we need to develop new concepts and novel therapies, to improve the implementation of life-saving medications and to better coordinate the action of the professionals involved in the management of this condition, including cardiologists, general practitioners, nurses and dieticians.

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References


