

Heart Failure: Novel and Emerging Therapies

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Submitted: January 29, 2020. Accepted: February 5. Published: April 8, 2020. DOI: 10.22374/cjgim.v15iSP1.419.

Abstract

Heart failure (HF) is increasing in prevalence and continues to have poor prognosis despite using up-to-date guideline-directed medical treatment and device intervention. There is a dire need for new therapies that can improve patient outcomes. New recently tested medical and interventional therapies have proven effective in reducing the morbidity, mortality and improving the quality of life for patients with HF and these therapies are discussed in details in this review. Ongoing large-scale clinical trials are underway to determine the efficacy and safety of novel therapies of HF. Development of these medical and interventional therapies are improving our understanding of HF and paving the way to better clinical outcomes.

Résumé

La prévalence de l'insuffisance cardiaque (IC) augmente et le pronostic reste mauvais malgré l'utilisation de traitements médicaux et de dispositifs d'intervention conformes aux directives les plus récentes. Il y a un besoin urgent de nouvelles thérapies qui peuvent améliorer les résultats des patients. De nouvelles thérapies médicales et interventionnelles récemment testées se sont avérées efficaces pour réduire la morbidité et la mortalité et améliorer la qualité de vie des patients atteints d'HF. Ces thérapies sont examinées en détail dans cette revue. Des essais cliniques à grande échelle sont actuellement en cours pour déterminer l'efficacité et la sécurité des nouvelles thérapies de l'HF. Le développement de ces thérapies médicales et interventionnelles améliore notre compréhension de l'HF et ouvre la voie à de meilleurs résultats cliniques.

Heart failure (HF) is a complex syndrome that is increasing in prevalence, and ranges from 1–2% across different countries and regions.¹ Despite advances in therapy in the last two decades, HF-related morbidity and mortality remains high. The one-year mortality of patients with a new diagnosis of HF remains as high as 19%.²

Current standard medical therapies for HF include ACE inhibitors, beta-blockers, and mineralocorticoid receptor antagonists.³ Recent additions to standard therapy include neprilysin inhibitors for patients with HF with reduced ejection

fraction (HFrEF) and ivabradine for HFrEF patients with a heart rate >70 beats per minute in normal sinus rhythm. Device-based therapies such as internal cardiac defibrillator (ICD) implantation and cardiac resynchronization therapy (CRT) have proven to be effective in appropriately selected patient populations.⁴

Within the last few years, new HF therapies have emerged (Table 1). The purpose of this review is to outline some of the emerging therapies that have proved efficacious and to shed light on promising therapies that are still being evaluated in randomized-controlled trials.

Table 1. Summary of Novel and Emerging Heart Failure Therapies and the Evidence Supporting Their Use.

Drug/ Intervention	Clinical Trial	Findings	Comments
Emerging Efficacious Therapies			
Sodium-glucose Cotransporter-2 Inhibitors	DAPA-HF	This study demonstrates reductions in composite of cardiac death and HF hospitalization in diabetic and non-diabetic patients with HFrEF.	The DELIVER (NCT03619213) and EMPEROR-Preserved (NCT03057951) studies are ongoing to assess the efficacy of SGLT-2 inhibitors in patients with HFpEF
Transcatheter mitral valve repair	COAPT	Transcatheter MV repair for secondary mitral regurgitation in patients with severe LV systolic dysfunction reduced HF hospitalization and all cause mortality.	Results are discrepant from MITRA-FR, highlighting the importance of appropriate patients selection.
Atrial Fibrillation Ablation	CASTLE-AF	Pulmonary vein isolation reduced composite outcome of HF hospitalization and all cause mortality in patients with moderate to severe LV dysfunction who had failed or declined medical rhythm or rate control.	Caution regarding external validity. Physicians need to be careful in selecting appropriate patients. No ongoing trials at present.
Potential Emerging Therapies			
Omecamtiv Mecabril	GALACTIC-HF	This phase III trial is investigating the effect of oral cardiac myosin activators on mortality and time to first HF event in patients with chronic HFrEF.	
Vericiguat	VICTORIA	This trial is investigating the effect of oral soluble guanylate cyclase stimulator on the composite of cardiac death and HF hospitalization in patients with LVEF < 45%.	

Emerging Efficacious Therapies

SGLT-2 Inhibitors

Sodium-glucose co-transporter (SGLT)-2 inhibitors are among the newest oral diabetes medications that have been proven to be effective and safe in the treatment of type 2 diabetes mellitus (T2DM).⁵ Large scale RCTs of different SGLT-2 inhibitors have found improvements in diabetic control, weight loss, systolic blood pressure, albuminuria, and renal dysfunction.^{6,7} A meta-analysis of trials that assessed the effect of SGLT-2 inhibitors on cardiovascular outcomes in patients with T2DM with coronary artery disease found a moderate reduction in the risk of adverse cardiovascular events.⁸ Many of these studies also described a reduction in rates of HF admission associated with the use of these agents.⁷⁻¹⁰

Subsequently, the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial aimed to determine

the efficacy of dapagliflozin in patients with HF irrespective of presence or absence of diabetes. In this trial, 4744 patients with LVEF <40%, NYHA class II-IV and an elevated NT-proBNP were randomized to dapagliflozin 10 mg daily or placebo. All patients received guideline-directed medical and device HF therapy. The primary end point was a composite of worsening HF (defined as unplanned hospitalization or urgent visit requiring intravenous HF therapy) or cardiovascular death. The median duration of follow up was 18.2 months. The results showed that dapagliflozin therapy was superior to placebo in reduction of the primary composite end point (16.3% vs. 21.2%; hazard ratio [HR]=0.74, 95% confidence interval [CI]: 0.65–0.85; number-needed-to treat [NNT] = 21, 95% CI: 15–38), mostly driven by reduction in HF hospitalization (HR=0.70, 95% CI: 0.59–0.83). The HR of all-cause mortality was 0.83 (0.71 to 0.97) indicating that, if anything, dapagliflozin may be

associated with less risk of all cause death. In a pre-specified analysis of secondary endpoints, patients randomized to the dapagliflozin group experienced a clinical improvement in HF symptoms as assessed by the Kansas City Cardiomyopathy Questionnaire (58.3% vs. 50.9%; odds ratio [OR]= 1.15, 95% CI: 1.08 to 1.23). The safety of dapagliflozin was demonstrated in this trial as there was no significant difference between the treatment groups in regards to medication discontinuation, volume depletion, renal side effects and risk of significant hypoglycemia.¹¹

DAPA-HF demonstrated that dapagliflozin therapy in patients with HF_{rEF} is efficacious and safe in both diabetic and, importantly, non-diabetic patients, suggesting that the improvements seen in HF end points are independent of the glucose lowering effects of this agent. Multiple physiological mechanisms have been proposed to explain the cardiovascular benefits of SGLT-2 inhibitors, including an osmotic diuretic effect mediated by relative glucosuria, changes in myocardial metabolism, changes in cellular ion transport, modulation of renal function, and changes in sympathetic nervous system activation.¹² Regardless of the exact mechanisms for each patient or patient group, the effectiveness as seen by clinical trials is the ultimate test of their utility.

Further studies are ongoing to characterize the efficacy of SGLT-2 inhibitors in the treatment of other subsets of patients with HF such as those with HF_{pEF}. DELIVER (NCT03619213) and EMPEROR-Preserved (NCT03057951) are phase III trials that are in the process of evaluating the efficacy of dapagliflozin and empagliflozin in addition to standard medical therapy in patients with HF_{pEF}.

Transcatheter Mitral Valve Repair

Secondary mitral regurgitation is a complication of left ventricular dysfunction. Left ventricular dysfunction can result in annular dilation and the tethering of chordae tendinae and papillary muscles, leading to incomplete coaptation of the mitral valve leaflets.¹³ Secondary mitral regurgitation is a clinically significant phenomenon associated with increased morbidity and mortality.^{14,15} To date, the management of these patients has focused on symptom control, and surgery, when tested in small randomized trials has shown no benefit or harm. Currently, indications for mitral valve surgery in patients with secondary mitral regurgitation include persistent NYHA III-IV symptoms (class IIb) and mitral valve surgery in the setting of concomitant other cardiac surgery (class IIa).¹⁶

The COAPT trial randomized 614 patients with secondary mitral regurgitation to the intervention group (transcatheter mitral valve repair in addition to standard therapy) or standard therapy alone. Symptomatic patients with HF_{rEF} with moderate

to severe mitral regurgitation and left ventricular ejection fraction 20–50% were included. To be eligible, patients had to have persistent symptoms despite maximal medical and device therapy, they had to be non-surgical candidates, and they required review by a HF team that focused on medical therapy assessment. Patient with concomitant severe valvular disease or with pulmonary hypertension were excluded. After a median follow-up of 22.7 months, the primary end-point of HF-hospitalization was lower in the intervention than standard therapy group (HR=0.53; 95% CI: 0.40–0.70; NNT=1.3, 95% CI: 1.9–7.9) as was the secondary end point of all cause mortality (HR=0.62; 95% CI: 0.46 - 0.82; NNT=5.9, 95% CI 3.9 - 11.7). At 12 months follow-up, 96.6% of patients in the intervention group were free of device-related complications.¹⁷

It is noteworthy that the results of COAPT are not consistent with results from MITRA-FR trial, where patients with secondary mitral regurgitation were randomized to mitral valve clip in addition to standard medical therapy or medical therapy alone. In this trial, mitral valve clip was not shown to be of significant benefit for the outcome of cause mortality or HF-hospitalization (odds ratio [OR]=1.16, 95% CI: 0.73–1.84).¹⁸ The discrepancy in results between these seemingly comparable trials may be explained by the severity of mitral regurgitation (less severe in MITRA-FR based on echocardiographic measures), study size and design, length of follow up, and reasons related to the technique and safety of the procedure.¹⁹ Nevertheless, they highlight the caution that must be exercised in patient selection for this complex procedure.

The COAPT trial has established the benefit and safety of transcatheter mitral valve repair in selected patients with secondary severe mitral regurgitation. However, the incorporation of this procedure into standard care of eligible patients is currently limited by uncertain cost-effectiveness and availability of skilled practitioners.

Catheter Ablation for Atrial Fibrillation in HF Patients

Atrial fibrillation (AF) and HF often coexist and, collectively, worsen the progression of both diseases.²⁰ Up to 37% of patients with a new diagnosis of AF had HF and 57% of patients with a new diagnosis of HF had AF.²¹ A meta-analysis showed that comorbid AF in patients with HF was associated with increased mortality.²² This questions whether an emphasis on rhythm control could provide clinical benefit to patients with HF and comorbid AF. Other than amiodarone, and sotalol for patients with left ventricular ejection fraction >35%, antiarrhythmic medications are not suitable for patient with HF.²³ In addition, sotalol is associated with significant arrhythmias and amiodarone is associated with well-known long-term side effects.

The CASTLE-AF trial enrolled 363 patients with left ventricular ejection fraction < 35%, NYHA II-IV symptoms, and paroxysmal or persistent AF in whom rhythm control could not be achieved. These patients were randomized to catheter ablation or medical rate or rhythm control. In the ablation arm, the aim of catheter guided ablation was to isolate the pulmonary vein and restore normal sinus rhythm. All patients received guideline directed medical therapy and had an ICD implanted or CRT if indicated. Patients in the medical therapy arm received standard medical therapy for AF (30% rhythm control, 70% rate control). Both groups received guideline-directed medical therapy for HF. The primary outcome was a composite of all cause mortality and hospitalizations for HF. Secondary outcomes included mortality, hospitalization due to HF, cardiac death and CVA. After a median follow-up of 37.8 months, the ablation therapy arm showed a reduction in the composite primary endpoint compared to the medical therapy arm (28.5% vs. 44.6%; HR=0.62; 95% CI: 0.43 - 0.87) as well as a reduction in all cause mortality (HR=0.53), HF hospitalization (HR=0.56), and cardiovascular death (HR=0.49). The safety of this procedure was not clearly assessed in this trial.²⁴

Although the CASTLE-AF trial demonstrated the efficacy of catheter ablation in the establishment of rhythm control in carefully selected HF patients, it has important limitations. The results of this trial are specific to patients who failed or refused rhythm control and thus should not be generalized to all patients with HF and AF. Moreover, the results are inconsistent with the CABANA trial, which was not specific to a HF population, and showed that catheter ablation in addition to standard medical therapy did not improve the composite outcome of death, disabling stroke, severe bleeding, or cardiac arrest at 12 months (HR=0.86; 95% CI; 0.65 - 1.15).²⁵

Emerging Therapies Omecamtiv Mecbril

The use of inotropic agents in HF has not been shown to improve mortality or reduce hospitalization.²⁶ Different mechanisms to explain these observations have been proposed, including triggering arrhythmias and increasing myocardial oxygen demand.²⁷ Omecamtiv mecabril (OM) is a cardiac myosin activator that is being studied for its potential to increase the stroke volume of HF patients without some of the deleterious effects associated with existing inotropic medications, and as such, not considered an inotrope based on its mechanism of action.²⁸

In the myosin-actin contraction cycle, the hydrolysis of myosin bound ATP to myosin bound ADP and phosphate prepares myosin head-ATP-phosphate complex for binding with actin filaments. By binding to the catalytic domain of the myosin head and increasing the rate of ATP hydrolysis, OM increases

cardiac contractility by increasing the proportion of myosin heads available for actin binding. In doing so, contractility is increased without an increase in cardiomyocyte oxygen consumption or intracellular calcium levels.²⁷⁻³¹

The ATOMIC-HF trial randomized 606 patients with acutely decompensated HFrEF to a 48 hours intravenous infusion of OM or placebo. Inclusion criteria specified that patients must have a left ventricular ejection fraction < 40%, elevated BNP (>400 pg/mL or > 600 pg/mL if they had AF), and persistent dyspnea two hours after 40 mg furosemide infusion. No difference in the primary end point of dyspnea relief between the OM and placebo groups was observed, however, the OM group demonstrated prolonged systolic ejection time (SET), decreased end systolic left ventricular diameter, and higher plasma troponin levels.³⁰

The COSMIC-HF trial, a phase II trial, was able to demonstrate the pharmacokinetics and optimal oral dose of OM. In this RCT, patients with symptomatic HFrEF were randomized to 20 weeks of placebo, 25 mg OM twice-daily, or 50 mg OM twice-daily. Overall, oral OM therapy was shown to be safe and well tolerated in patients with HFrEF.²⁸ The ongoing phase III GALACTIC-HF study (NCT02929329) is investigating the effects of OM in reducing cardiovascular death or HF events in patients with chronic HFrEF. This phase III trial has enrolled over 8,000 patients, randomized to dose titrated oral OM or placebo therapy arms. The primary outcome of interest will be the time to cardiac death or first HF event. The estimated conclusion date is January 2021.³²

Vericiguat

In normal physiology, nitric oxide (NO) released by endothelial cells regulates the development and tone of vascular smooth muscle cells in the heart, kidney, and circulatory system.^{29,33} The release of NO from endothelial cells increases the production of cGMP. Through a complex signaling cascade, cGMP leads to reduced intracellular calcium levels and vasomotor tone.³⁴ In HF, endothelial cell dysfunction and increased levels of reactive oxygen species result in decreased NO availability and deleterious vascular smooth muscle dysregulation.^{35,36}

Soluble guanylate cyclase activators stimulate sGC independent of NO signaling.³⁷ Riociguat is a sGC stimulator that has been shown to be effective in the treatment of chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension.³⁸ The VICTORIA trial (NCT02861534), a study of vericiguat, another sGC stimulator, in patients with chronic HFrEF is still ongoing.³⁹ More than 5000 patients with chronic HF with NYHA II-IV symptoms, LVEF < 45%, HF hospitalization within 6 months, and elevated BNP were randomized to placebo or vericiguat 2.5,

5.0, or 10.0 mg PO daily. The primary outcome of interest is a composite end-point of cardiac death or HF hospitalization.

Conclusions

Although our understanding of the genetics and etiology of HF has improved in the last two decades, the prognosis of patients diagnosed with HF has not changed appreciably. Amongst the newly established therapies, SGLT-2 inhibitors offer the promise of additional medical therapy that can be applied to a general HF population with moderate to severe left ventricular systolic dysfunction. Interventional therapies such as the mitral valve clip and AF ablation may improve important patient related outcomes; however, their applicability is limited to highly selected patient populations. None of these therapies have been strongly recommended by current practice guidelines, but it is expected that this may change in their next iteration. The ongoing large-scale studies of OM and vericiguat outlined above offer the promise of improving outcomes in patients with HF.

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