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Special Article

Mind the Gap: Current Challenges and Future State of Heart Failure Care

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ABSTRACT

The past decade has seen many advances in the management of heart failure (HF) that have improved survival and quality of life for patients living with this condition. A number of gaps remain in our understanding of the pathophysiology of HF, and the application of emerging treatment strategies is an exciting but daunting challenge. It is possible that advances in genetic evaluation of cardiomyopathy will provide a more refined approach to characterizing HF syndromes, whereas large-scale clinical trials on the horizon should further clarify the role of novel pharmacologic agents and invasive therapies. Cardiac repair and regeneration hold great promise, but a number of pragmatic issues will limit clinical application in the near term. Replacing cardiac function with ventricular assist devices represents significant progress

RÉSUMÉ

Au cours de la dernière décennie, la prise en charge de l'insuffisance cardiaque (IC) a connu de nombreuses avancées qui ont permis d'améliorer la survie et la qualité de vie des patients qui sont atteints de cette affection. Plusieurs lacunes subsistent dans notre compréhension de la physiopathologie de l'IC, et l'application de stratégies thérapeutiques émergentes représente un défi à la fois stimulant et impressionnant. Il est possible que les progrès réalisés en matière d'évaluation génétique de la cardiomyopathie permettent d'approcher de manière plus fine la caractérisation des syndromes d'IC, tandis que les essais cliniques à grande échelle annoncés devraient clarifier le rôle des nouveaux agents pharmacologiques et traitements invasifs. La réparation et la régénération cardiaques sont

Heart failure (HF) has historically portended a poor prognosis, with a substantial burden imposed on patients, caregivers, and the Canadian health care system.[1] Recognizing that the disease trajectory for an individual patient can be quite variable and difficult to predict, the onset of HF symptoms often triggers an inexorable decline associated with progressive disability and eventually death. However, the past several years have yielded a number of milestone achievements in our understanding of the disease and provided much cause for optimism. For example, Canadian data suggest that the incidence of new-onset HF may be declining overall; a 32% reduction in HF incidence was observed in Ontario over a 10-year period from 1997-2007,[2] and age- and sex-standardized HF mortality and hospitalization rates declined in Canada by 23% and 27%, respectively, over a similar period.[3] Publication of the comprehensive Canadian Cardiovascular

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in the management of advanced disease; however, unacceptable rates of complications and costs need to be addressed before broader use in the general HF population is feasible. The ability to personalize care is limited, and the optimal model of disease management in the Canadian context remains uncertain. The emergence of biomarker-guided management and remote monitoring technologies might facilitate a more personalized approach to care in an effort to maintain health and stability and to prevent worsening HF. Ultimately, a greater understanding of how and when to intervene in the setting of acute HF should translate into improved outcomes for the highest-risk subgroup of patients. This review highlights key challenges in the management of HF and highlights the progress toward an ideal future state.

porteuses d'immenses promesses, mais, à court terme, plusieurs questions pratiques limiteront leur application clinique. Le remplacement de la fonction cardiaque par des dispositifs d'assistance ventriculaire constitue un progrès appréciable dans la prise en charge de la maladie au stade avancé; toutefois, il faut trouver une solution aux taux de complications inacceptables et aux coûts associés à cette technologie avant d'envisager leur utilisation à plus grande échelle dans la population générale des personnes atteintes d'IC. La capacité d'offrir des soins personnalisés est limitée, et le modèle optimal de prise en charge de la maladie dans le contexte canadien demeure incertain. L'émergence de la prise en charge en fonction des biomarqueurs et des technologies de surveillance à distance pourrait faciliter l'avènement d'une approche thérapeutique plus adaptée à chaque patient dans le but de maintenir la santé de ce dernier et la stabilité de son état ainsi que de prévenir l'aggravation de l'IC. En fin de compte, une meilleure compréhension du moment et des modalités appropriées de l'intervention en cas d'IC aiguë devrait se traduire par une amélioration des résultats chez les patients appartenant au sous-groupe le plus à risque. La présente analyse met en lumière les principaux défis de la prise en charge de l'IC et les progrès réalisés sur la voie d'un état optimal.

Society's Heart Failure Guidelines in this issue of the *Canadian Journal of Cardiology* represents the culmination of a 10-year knowledge translation effort and provides an opportunity to reflect on the current state of HF care and its continued evolution.

A decade ago, HF guidelines focused on the importance of neurohormonal blockade with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers plus β-blockers for patients with a reduced ejection fraction (EF).[4] Mineralocorticoid receptor antagonism was reserved only for patients with severe HF symptoms and disability. Indications for prophylactic implantable cardioverter defibrillators (ICDs) were relatively well established when the Canadian Cardiovascular Society HF guidelines were published in 2006; however, candidate selection for cardiac resynchronization therapy (CRT) has been refined to reflect its indication in minimally symptomatic patients.[5] There was also equipoise with respect to coronary bypass surgery for ischemic cardiomyopathy, and long-term mechanical circulatory support (MCS) with continuous-flow left ventricular assist devices (CF LVADs) was in the early stages of investigation. Repair, regeneration, and restoration of heart function with cell- and bioengineering-based therapy was in its infancy, and genetic evaluation of cardiomyopathies was very limited. Disease management clinics had been well established to provide comprehensive HF care, but technology for monitoring patients outside the clinic setting was relatively basic.

Looking ahead, the future state of HF care should be highly personalized, with great precision around diagnosis, and should take advantage of evidence-based therapies that prevent disease progression, reliably improve heart function, and can be delivered according to the needs of the individual patient. Indeed, much progress has been made in the past 10 years. However, with the growing armamentarium of tools for diagnosing and managing HF, gaps are exposed and new questions arise. The purpose of this review is to highlight some of the ongoing challenges in the diagnosis and treatment of HF and to highlight progress toward an ideal future state (Fig. 1, Table 1).

Mind the Gap: Current Challenges and Uncertainties

Defining HF subtypes

Currently, classification of HF is primarily based on the presenting phenotype; HF with reduced EF (HFrEF; implies EF $<$ 40%) vs HF with preserved EF (HFpEF; implies EF $>$ 45%-50%). Historically, this distinction has been important because it often relates to the underlying cause, pathophysiology, and more importantly, approach to treatment. In the chronic ambulatory HF setting, eg, these distinct groups of patients differ with respect to prognosis and response to pharmacologic treatment, particularly neurohormonal blockade.[6] The differential neurohormonal activation profiles and response to disease-modifying drug therapy suggests an incomplete understanding of pathophysiology and raises the possibility that HFpEF is a fundamentally different disease process. Alternatively, HFpEF may reflect a more heterogeneous group of patients for whom response to treatment may be more unpredictable. Indeed, the mode of death in HFpEF remains poorly characterized in clinical trials and observational studies, and it is unclear whether this syndrome reflects a high-risk cardiovascular phenotype per se or whether associated comorbidities have the greatest impact on prognosis.[7] In an attempt to further categorize patients by EF, some authors have proposed a third category known as HF with midrange EF (HFmrEF; EF, 40%-50%).[8] Recent data confirm an intermediate prognosis for this group of patients and implies a gradient of HF severity according to EF.[9]

Better characterization of the causes of HF and a better understanding of the key pathophysiologic derangements across the spectrum of EFs might improve our ability to deliver more disease-specific and personalized HF care. It is anticipated that advances in imaging and genotyping, eg, will help refine prognosis, predict response to therapy, and inform timing of interventions along the disease continuum.

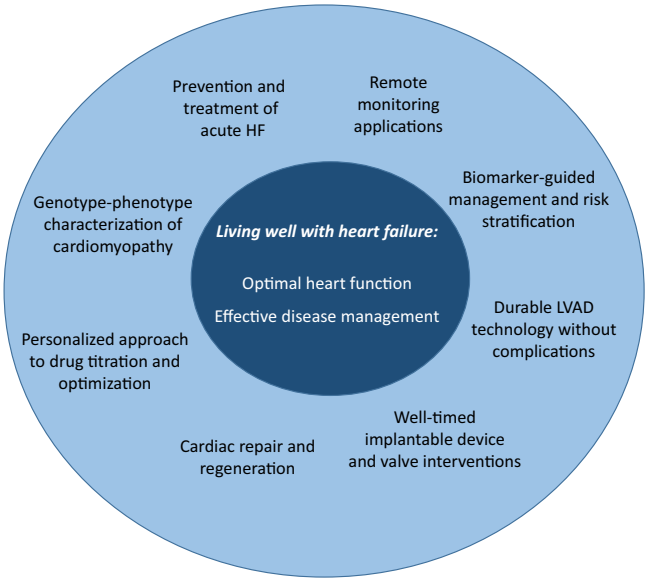

Figure 1. Overview of the ideal future state of personalized and patient-centred heart failure (HF) care and the progress required to achieve this goal. LVAD, left ventricular assist device.

Pharmacologic therapy—gaps in evidence-based treatment

Beyond diagnosis, a personalized approach to HF management will take into account patient-specific factors in designing a treatment strategy. In this regard, there are many outstanding questions surrounding the efficacy of combination therapy with newer drugs, the sequence in which they should be introduced, and whether their benefits can be extrapolated to real-world patients outside of clinical trials.

For example, although both ivabradine and sacubitril/valsartan have been shown to improve clinically important outcomes in selected HFrEF cohorts,[10,11] there is a paucity of data from clinical trials on the efficacy and safety of these therapies used in combination. Given that these drugs exert their beneficial effects through different mechanisms (heart rate reduction in the case of ivabradine and neurohormonal modulation in the case of sacubitril/valsartan), there is every reason to believe that their effects may be additive, although no current evidence exists to support this hypothesis. Further, among patients who are candidates for both therapies, there is a lack of clarity as to the sequence in which these drugs should be initiated; patient-specific factors, including heart rate, functional status, ventricular geometry, and EF, may help guide the clinician. Finally, whether these agents will benefit patients who are candidates for implantable devices or valve interventions or those with other HF phenotypes (eg, HFpEF or HFmrEF) remains to be seen. As our understanding of the biological characteristics of HF expands, it may be possible to customize treatment strategies based on specific disease states, and better characterization of pharmacogenetics will further enable a precision approach to HF care.

Interventional approaches to improve cardiac function: identifying the right intervention at the right time

Advances in interventional and surgical treatments for HF have occurred in parallel with advances in medical therapy. Well-established invasive therapies such as ICDs and CRT have undergone continuous refinement with respect to patient selection, and the magnitude of benefit of these interventions may change over time as pharmacologic therapy improves. For example, a recent study of primary prevention ICDs in the setting of nonischemic cardiomyopathy showed no overall survival benefit compared with contemporary medical therapy, which has generated more uncertainty about the role of ICDs in this population.[12] Indeed, invasive therapies are generally indicated only if patients have residual risk or disability despite optimal medical therapy. The definition of "optimal medical therapy" is very much a moving target, and it is possible that important patient subgroups may not benefit from devices in the current era of improved pharmacologic management.[12]

Novel interventions such as percutaneous mitral valve repair are gaining a foothold in patients with HF and functional mitral regurgitation. Early experience is promising; however, long-term data are limited, and it remains unclear at which stage of disease patients should be considered for this and other invasive therapies.[13] Ongoing randomized trials such as the **C**ardiovascular **O**utcomes **A**ssessment of the MitraClip **P**ercutaneous **T**herapy for Heart Failure Patients with Functional Mitral Regurgitation Trial (COAPT) should help further define the role of percutaneous mitral valve repair in HF (ClinicalTrials.gov: NCT01626079). Similarly, major improvements in LVAD technology have created a shift in application; once reserved for bridging critically ill patients to cardiac transplantation, LVAD support is increasingly used for destination therapy (DT).[14] This is particularly germane in the field of advanced HF in which transplantation as definitive cardiac replacement therapy will remain limited by the lack of donor supply for the foreseeable future. Whether LVADs will evolve to the point that they can be reliably used in patients with earlier stages of HF is also uncertain, and a number of current limitations must be overcome.[15]

Beyond device and mechanical therapies, cellular and bioengineering interventions for repairing and restoring heart function hold great potential. Currently, myriad challenges must be addressed for safe and effective translation into the clinical domain. For example, what is the optimal source of cells and tissues? What is the best timing and method of delivery to the heart? What is the mechanism of benefit? How do cell and tissue therapies integrate with the myocardium and contribute to functional improvement? Whether clinical application is realistic within a reasonable time horizon is uncertain.

Disease management approach to HF—system-wide challenges

Multidisciplinary disease management programs are associated with improved HF outcomes from both a patient and systems perspective.[16] The growing prevalence of HF, coupled with variable and inadequate access to care (particularly in rural communities) and a relative lack of qualified HF care providers, limits the broad applicability of this care model. As such, there is continued interest in identifying disease management strategies that leverage novel technologies to deliver optimal HF care.

To date, there has not been broad use of remote monitoring (RM) technologies; this may result from limitations in

Table 1. Key elements of an idealized HF care model and progress needed for implementation

Key element of optimal HF care	Progress required
Prevention and treatment of acute HF	Enhance understanding of pathophysiology of decompensation Ongoing evaluation of vasodilator, decongesting, and inotrope therapies
Remote monitoring applications	Identify optimal parameters to maintain clinical stability Actionable and cost-effective monitoring strategies
Biomarker-guided management and risk stratification	Identify ideal biomarker target Identify right treatment in response to changes in biomarker value
Durable LVAD technology without complications	Clinical trials and registries to inform optimal pump settings, antithrombotic strategies Miniaturization of VAD technologies with enhanced hemocompatiblity
Well-timed implantable device and valve interventions	Clinical trials and registries to refine patient selection for ICD, CRT, and percutaneous valve interventions
Cardiac repair and regeneration	Enhanced cell engraftment, survival, and function at site of injury Optimal use of biomaterials for scaffolding and function Proof of concept studies and well-designed outcome trials of regenerative medicine strategies
Personalized approach to drug titration and optimization	Outcome studies of novel therapies for HFrEF, HFpEF Assessment of combination contemporary therapy Assessment of drug efficacy in patients with varying causes, phenotypes, genotypes, and comorbidities
Genotype-phenotype characterization of cardiomyopathy	Leveraging novel gene sequencing techniques Determination of gene variant significance Identification of genetic risk and phenotypic expression

CRT, cardiac resynchronization therapy; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; ICD, implantable cardioverter device; LVAD, left VAD; VAD, ventricular assist device.

predicting HF decompensation, heterogeneity of populations studied, improvements in HF therapy over time, and care providers' reticence to act on acquired data.[17]

Prognostic biomarkers and clinical risk scores may help to identify those patients at highest risk of adverse events and may further provide important target pathophysiological targets that inform management and enable triage to a more comprehensive level of HF care.[18] Whether this approach would result in better outcomes remains unclear. Regardless, the scale of the HF epidemic necessitates a comprehensive health care system that supports patients and their caregivers, manages capacity, and ensures equitable access to optimal HF care.

Although falling outside the scope of this review, other practical challenges for effective disease management include the difficulty translating clinical advances and knowledge into practice and the care of patients with multiple chronic conditions. Guideline dissemination and related knowledge translation activities are important elements; however, more rigorous, reproducible, and scalable approaches using implementation science protocols are required to optimize the uptake of best practice recommendations for disease management.[19] The issues surrounding real-world management of HF in older patients and those with frailty or multiple comorbidities has been the subject of much discussion, and the reader is referred to a couple of excellent recent reviews that have explored the topic in detail.[20,21]

Acute HF—in search of a solution

Acute HF (AHF) is a harbinger of a poor prognosis,[1] and management remains challenging. It is unclear whether short-term interventions aimed at improving symptoms will meaningfully impact longer-term outcomes,[22,23] and efforts have primarily focused on treating the hemodynamic perturbations that characterize the AHF state. Congestion, as a hallmark of AHF, is associated with worse outcomes and is often inadequately addressed.[24] Nevertheless, setting defined hemodynamic goals and using invasive measures to direct therapy have not improved outcomes.[25] Recently published trials of inotropic, ultrafiltration, and novel vasoactive therapies to target congestion and improve loading conditions have also been disappointing, despite inclusion of a broad spectrum of patients with HF.[22,23,26,27] It is possible that early intervention and effective decongestion will not translate into improved downstream outcomes and that AHF reflects a state of persistent vulnerability despite aggressive symptom control.

Potential Solutions and Emerging Strategies

Innovations in personalized medicine: clinical application of genetics in the diagnosis of cardiomyopathy

Genetic causes of HF span multiple syndromes, including hypertrophic, arrhythmogenic, and dilated cardiomyopathies. The diagnostic yield of currently available genetic testing varies across these diseases, ranging from 40%-50% for hypertrophic cardiomyopathy to 15%-25% for dilated cardiomyopathy in initial reports.[28] Characterizing the underlying genetic cause of these cases can guide therapy. For example, clarifying that left ventricular (LV) hypertrophy is caused by variants in transthyretin or Fabry disease can allow targeted therapies, including RNA silencing, isoform stabilizers, and enzyme replacement.[29,30] Further, genetic diagnosis allows for directed family screening.

Over the past decade, genetic testing has moved toward the forefront of clinical practice, with applications in cardiovascular (CV) medicine that include long-QT syndrome, familial hypercholesterolemia, and Marfan syndrome as common examples.[31] Greater application of genetic testing has largely resulted from cost reduction and the increased efficiency made possible by next-generation sequencing (NGS). NGS is capable of sequencing at scale. Mapping and assembly of "short reads" generated by NGS to a reference genome allows the discovery of genetic variants.[31]

Currently, the majority of genetic testing for cardiomyopathies is performed using gene panel testing, although broad sequencing approaches may be helpful in specific cases. Several commercially available disease-specific genetic testing panels exist, and the reported diagnostic yield is variable.[28] Recently, many of these gene variants were reviewed in comparison with large population scale genomic data sets,

revealing over-representation in the unaffected population of variation in some genes previously thought to be pathogenic.[32] Thus the inclusion criteria for genes in panel-based tests may change as our diagnostic precision evolves.

Although techniques such as NGS have emerged as powerful tools, sequencing does have some technical limitations; moreover, assessment of variant pathogenicity remains an imperfect process. Humans differ at millions of genetic positions, yet only a very small amount of this variation is truly causative of disease. The increasing availability of large genomic databases from unaffected individuals helps narrow the list of rare variants to those that are not prevalent in the general population.[33] However, despite these advances, our burgeoning knowledge of the genome remains inadequate to assign pathogenicity to many rare variants (known as variants of uncertain significance [VUS]). VUS in genes known to cause disease creates significant clinical equipoise regarding predictive testing and diagnosis.

In the field of genetic cardiomyopathies, a number of exciting advances are being made in our ability to evaluate variant pathogenicity. For example, in the genome overall, machine learning techniques have been used to predict variant pathogenicity based on large population-based data sets.[34] In dilated cardiomyopathy, analysis of data from diseased and healthy populations demonstrated that variant position predicted pathogenicity in titin and myosin.[35] Further, genetic variants predicted to shorten gene coding sequences (truncating variants) found in the general population correlate with magnetic resonance imaging evidence of eccentric remodelling and have been associated with peripartum cardiomyopathy.[36]

Finally, it is worth acknowledging that the results of genetic testing in HF, including the identification of VUS for affected individuals and presymptomatic family members, can create additional concerns with respect to future life planning, employment, or insurability. Recent legislation in Canada, known as the Genetic Non-Discrimination Act (available at www.laws-lois.justice.gc.ca), protects individuals from the disclosure or use of genetic test results outside of medical care. However, it must be emphasized that expert review is crucial to interpretation of genetic testing results, and genetic counsellors are fundamental to the clinical care of families with inherited disease.

Looking ahead, it is anticipated that the advances in genetic evaluation described in this article will improve the precision of genetic cardiomyopathy diagnostics and expand the current definition of cardiomyopathy to include models of genetic risk beyond more rudimentary classification of HF based on phenotype or EF alone. Greater diagnostic precision for patients with HF will enhance the potential to provide highly personalized pharmacologic and invasive treatment.

Emerging pharmacologic treatment: clinical trials on the horizon

Although there are many drugs in development for HF, only those currently in phase III mortality/morbidity trials have the potential to influence guidelines and clinical practice in the immediate future. However, even with this restricted perspective, there are more compounds at an advanced stage of testing in HF than ever before. Table 2 lists key drug trials that may impact HF management in the short term.

Table 2. Anticipated clinical trials of pharmacologic therapy for chronic heart failure

COMMANDER-HF	Cardiovascular Outcome Modification, Measurement and Evaluation of Rivaroxaban in Patients With Heart Failure
VICTORIA	Vericiguat Global Study in Subjects with Heart Failure With Reduced Ejection Fraction
GALACTIC-HF	Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure
DAPA-HF	Dapagliflozin Heart Failure trial
EMPEROR	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure
PARAGON-HF	Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction

HF with reduced EF

The largest of the ongoing phase III trials is **C**ardiovascular **O**utcome **M**odification, **M**easurement **and** **E**valuation of **R**ivaroxaban in Patients With **H**eart **F**ailure (COMMANDER-HF) (ClinicalTrials.gov: NCT01877915), which is testing the hypothesis that an anticoagulant (rivaroxaban) might improve the composite outcome of death from any cause, myocardial infarction, or stroke in patients with HF with reduced ejection fraction (HFrEF) of ischemic cause who are in sinus rhythm and have recently been treated for an episode of decompensation.[37] Implicit in this hypothesis is the suggestion that some deaths in patients with HFrEF result from coronary thrombosis, cerebral thrombosis (or thromboembolism), and pulmonary venous thromboembolism.

More recently, **Veric**igua**t** Gl**o**bal Study in Subjects With Heart Failure With Reduced Eject**i**on Fr**a**ction (VICTORIA) has been initiated to test the hypothesis that compared with placebo, the guanylate cyclase stimulator vericiguat will reduce the risk of CV death or HF hospitalization in patients with HFrEF, a recent exacerbation, and elevated natriuretic peptide (NP) levels (ClinicalTrials.gov: NCT02861534). By increasing intracellular cyclic guanosine monophosphate, vericiguat acts through the same second-messenger system as do NPs and has vasodilator as well as other actions.[38]

Global **A**pproach to **L**owering **A**dverse **C**ardiac Outcomes **T**hrough **I**mproving **C**ontractility in **H**eart **F**ailure (GALACTIC-HF) is testing the hypothesis that the cardiac-specific myosin activator omecamtiv mecarbil will be superior to placebo in reducing the risk of CV death or worsening HF events in patients with HFrEF, recent decompensation, and elevated NP levels (ClinicalTrials.gov: NCT02929329). Omecamtiv mecarbil prolongs LV ejection time, thereby improving systolic function (although it must be dosed carefully so as not to shorten diastole to the point of compromising coronary perfusion).[39]

Intravenous (but not oral) iron has been shown to improve symptoms, quality of life, and functional capacity in patients with HFrEF in relatively small and short-term trials.[40] Now four larger and longer trials are testing whether this treatment might also reduce the risk of CV death and HF hospitalization

(ClinicalTrials.gov: NCT02937454, NCT03037931, NCT03036462, and NCT02642562).

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a new class of treatment used to lower blood glucose levels in patients with type 2 diabetes mellitus. By blocking proximal tubular reabsorption of filtered glucose, SGLT2 inhibitors cause glycosuria, osmotic diuresis, and natriuresis. In addition to reducing hemoglobin A1c, blood pressure, and body weight, the SGLT2 inhibitor empagliflozin was shown to reduce the risk of CV (and all-cause) death, as well as HF hospitalization in patients with type 2 diabetes and CV disease (but not HF in 90% of cases).[41] Whether this type of treatment might be beneficial in patients with established HF is not known but is being tested in 2 new trials in patients with chronic HFrEF, symptoms, and elevated NP levels. Trials testing dapagliflozin (**Dapa**gliflozin **H**eart **F**ailure trial [DAPA-HF]) and empagliflozin (**Emp**agliflozin Outcom**e** T**r**ial in Patients With Chr**o**nic Hea**r**t Failure With **Reduced** Ejection Fraction [EMPEROR-Reduced]) are enrolling patients with HFrEF with and without diabetes in part because of the high prevalence not only of diagnosed diabetes in HF but also of prediabetic dysglycemia (ClinicalTrials.gov: NCT03036124 and NCT03057977).[42]

HF with preserved ejection fraction

Two large trials are under way in patients with HFpEF. The **P**rospective Comparison of **Ar**ni with **A**rb **G**lobal **O**utcomes i**n** **H**eart **F**ailure with Preserved Ejection Fraction (PARAGON-HF) trial is comparing sacubitril/valsartan with valsartan (ClinicalTrials.gov: NCT01920711).[43] The other is a sister trial to EMPEROR-Reduced and is comparing empagliflozin with placebo (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction [EMPEROR-Preserved]) (ClinicalTrials.gov: NCT03057951).

Innovations in replacing and repairing heart function: evolution of ventricular assist devices to replace native heart function

In 2001, the **R**andomized **E**valuation of **M**echanical **A**ssistance for the **T**reatment of **C**ongestive **H**eart Failure (REMATCH) trial was published and provided the first randomized trial evidence that MCS in the form of an implantable LVAD could improve both longevity and quality of life.[44] The REMATCH trial enrolled 68 patients in the treatment arm and evaluated a pulsatile device that was not designed to function for more than 2 years. Shortly thereafter, the era of CF LVADs began, first with the Heartmate II (Thoratec, Pleasanton, CA) and then the HeartWare (Medtronic, Minneapolis, MN) VADs. In stark contrast to REMATCH, the HeartMate II **B**ridge to **T**ransplant **T**rial (BTT) recruited 133 patients and reported a 1-year survival of $> 70\%$.[45] Similarly, the Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) trial recruited 140 patients and reported a remarkable 86% survival at 1 year.[46]

Results from this "second-generation" VAD technology were a disruptive force in the surgical management of HF. VAD implantation in North America and Europe began to explode. The **Inte**ragency **R**egistry for **M**echanically **A**ssisted **C**irculatory **S**upport (INTERMACS) registry was developed to track clinical outcomes after implantable VAD therapy; VAD volumes grew from 4000 reported implants in 2012 to $>$ 20,000 implants by 2017.[14] With increasing clinical experience, a variety of adverse events associated with VAD therapy became apparent, and new problems arose.

Although aortic insufficiency was seen and recognized with pulsatile pumps, de novo aortic insufficiency became evident in almost 20% of patients during the first year of support with a CF-LVAD.[47,48] Another unexpected complication associated with CF-LVAD support was the development of gastrointestinal (GI) bleeding, occurring in almost 30% of recipients.[49,50]

Although many theories exist about the mechanism, there has been very little progress in the prevention of GI bleeding complications, which are associated with major morbidity.[51]

A more recent observation has been an unexpected and abrupt increase in the rate of pump thrombosis with the HeartMate II LVAD.[52] Although the initial pump thrombus rate reported in the BTT trial was 3%, Starling et al.[52] reported an 8.4% rate of confirmed thrombus in the real-world setting.

The HeartMate 3 LVAD was designed to address these concerns by adding intermittent speed reduction to a continuous centrifugal flow design, which provides artificial pulsatility. In addition to the artificial pulse, the HeartMate 3 has novel design features to enhance biocompatibility.[53] The recently reported Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) trial evaluated the clinical impact of these design changes.[54] In this report, 6-month outcomes are presented for patients in the short-term cohort who were assigned to the new centrifugal-flow pump group ($n = 152$) or to the commercially available axial-flow pump group ($n = 142$). The trial met its primary end point (composite of survival free of disabling stroke or reoperation to replace or remove the device at 6 months after implantation), and the HeartMate 3 device was found to be superior to the HeartMate II, primarily because of the lack of reoperation for pump thrombus. There were no reported pump thrombus events in any patient who received a HeartMate 3, and there were no significant differences between the 2 pumps in the rates of other major complications, including right HF, stroke, major infection, or bleeding.

Despite improvements in LVAD technology and biocompatibility, a number of unanswered questions remain with respect to minimizing residual complications. Are there additional design strategies that can mitigate stroke, infection, and bleeding? Will improvements in medical management, including a more focused effort on postoperative blood pressure control, improve device function and prevent complications?

Clearly, to advance the field of MCS to treat patients with less advanced HF and to see greater uptake of DT LVAD implantation for patients who are not transplant candidates, unacceptable rates of adverse events must be addressed. Indeed, one of the first trials to examine MCS in a less ill population was terminated early. The premature completion of the **R**andomized **E**valuation of **V**AD **Inter**ve**n**tion before **I**notropic **T**herapy (REVIVE-IT) trial was a setback for the entire field.[15] In contrast, the recent **R**isk Assessment and

Comparative Effectiveness **o**f Left Ventricular **A**ssist **D**evice and **M**edical Management in **A**mbulatory Heart Failure **P**atients (ROADMAP) study provided a signal of benefit for LVAD use for more stable ambulatory patients with advanced HF.[55] Canadian experience suggests that slightly > 10% of LVADs are implanted as a DT strategy,[56] and this approach has yet to meet usual cost-effectiveness benchmarks for broader applicability.[57] Improved outcomes and a reduction in complications would likely make DT a more feasible long-term cardiac replacement strategy.[58]

Innovations in replacing and repairing heart function: strategies for regeneration and repair of heart function

Tissue engineering offers the theoretical promise of a healthy new organ to replace a failing heart, and the field has advanced rapidly.[59] Such approaches face significant technical and translational hurdles. More practical and targeted tissue engineering strategies aim to repair, recover, and regenerate host cardiac tissues by leveraging endogenous repair pathways, and this can be accomplished using genes, cells, or biomaterial scaffolds as therapy. When discussing the current advances toward clinical translation for these therapeutic strategies, it is necessary to consider both the promise and the harsh realities of regenerative medicine for CV disease.

Cardiac gene therapies directly alter heart cell genes in an effort to enhance endogenous cardiac repair and restore function.[60] Gene therapy for HF has targeted a number of key CV pathways that include calcium-regulating proteins, apoptotic cellular pathways, β-adrenergic systems, G-protein signalling, proangiogenic proteins, and stem cell activators.[61] A number of randomized clinical trials for gene therapy in patients with HF have been published. The Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) and **A**AV1-CMV-Serca2a **Gen**e **T**herapy Trial in **H**eart **F**ailure (AGENT-HF) trials (phase II) aimed to rectify cardiomyocyte dysfunction by restoring SERCA2a (calcium-regulating protein) expression and activity through intracoronary adeno-associated viral gene transfer. Although both trials demonstrated favourable safety profiles, they failed to meet key study end points.[62,63] Similarly, **S**tromal Cell-Derived Factor-1 Plasmid **T**reatment f**or** **P**atients With **H**eart **F**ailure (STOP-HF) (phase II) sought to bolster endogenous stem cell—mediated repair by transferring a gene encoding a stem cell—activating protein, SDF-1; the primary end point was not met.[64] Finally, the adenovirus 5 encoding adenylyl cyclase 6 (Ad5.hAC6) in heart failure trial (phase II) aimed to improve calcium handling by transferring a gene encoding AC6, an adenylate cyclase. The authors concluded that 1-time intracoronary administration of AC6 at the highest tested dose improved LV function more than standard medical therapy in patients with HF; however, the trial had a number of serious limitations.[65]

Clinical gene therapy for HF is probably safe, but a number of translational hurdles and issues must be addressed before further adoption into practice. Important considerations include optimal selection and delivery of DNA vectors to ensure high transfection efficiency with low immunogenicity and the uncertain effects of targeting a single gene in a disease that involves many complex molecular mechanisms and pathways. Combining genetic manipulation with other strategies, such as cell therapy, may circumvent some of the current translational challenges.

Endogenous stem/progenitor cells can be isolated, expanded, and delivered into tissues with the promise of regeneration. Given that CV tissues are well known to be poorly regenerative compared with other organ systems, there is enthusiasm for cell therapy in HF.[66] Many wonder why regenerative cell therapy is not currently a conventional treatment for HF; cell therapy is continually challenged with poor cell engraftment and survival in failing myocardium. Mechanisms of benefit remain unclear, and functional benefits of cell therapy may be less regenerative and more restorative through release of prorepair paracrine factors.[66] To that end, investigators have focused on designing clinical trials that potentiate the paracrine effects of transplanted cells.[67]

Despite numerous translational hurdles, cell therapy has been evaluated in clinical trials (Table 3).[68-72] Confirmatory evidence of benefit and safety will be important and may be forthcoming from international multicentre phase III trials such as the **B**one **A**cute **M**yocardial **I**nfarction (BAMI) trial, A **D**ouble-blind, **R**andomized, Sham-procedure-controlled, Parallel-group **E**fficacy and Safety Study of **A**llogeneic **M**esenchymal Precursor Cells [CEP-41750] in Patients With Chronic **H**eart **F**ailure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology (DREAM-HF), and **C**ongestive **H**eart Failure C**a**rdiopoietic **R**egenerative **T**herapy (CHART-2) (ClinicalTrials.gov: NCT01569178, NCT02032004, and NCT02317458). Such pivotal clinical trial evidence is needed before clinical use in HF; however, cell therapy trials face design challenges to confirm clinical efficacy. For example, assessment of cardiac performance and recovery of function is more complex in patients than in preclinical controlled animal models of human disease. Many trials use EF as a surrogate end point for treatment efficacy, and it may be insensitive and confounded by other clinical and hemodynamic factors. Specific prorepair pathways such as angiogenesis, cell death, and extracellular matrix (ECM) remodelling may mediate functional benefits but are not directly measurable in human patients.[73] Second, selecting appropriate patients for such therapies is difficult. Early after myocardial infarction, some patients may not have significant baseline LV dysfunction despite ischemic injury, and the therapeutic efficacy may therefore be masked.[68] For studies that apply cell therapy as an adjunct to conventional surgical therapies, such as **Imp**lantation of **A**utologous **C**D133^{+} **S**tem Cells in Patients Undergoing **CABG** (IMPACT-CABG), it is difficult to discern whether the positive effects are caused by cell therapy or are the result of conventional treatments such as surgical revascularization.[70]

Finally, tissue engineering using acellular biological scaffolds is gaining momentum, particularly decellularized biological tissue—derived matrices that retain bioactive properties. ECM is a biological structural scaffold with bioactive properties that can be leveraged to stimulate myocardial repair without the underlying safety concerns of an immunogenic response. To date, there is substantial evidence from preclinical studies that outlines the cardioprotective benefits of ECM biomaterials in the failing heart.[74,75] Given that cell therapy may confer functional benefits through paracrine effects,[76] it is conceivable that bioactive acellular matrix scaffolds could have similar paracrine effects without

Table 3. Summary of the strengths, limitations, and key clinical trials pertaining to application of gene, cell, and acellular scaffold therapies

Type	Strengths	Challenges	Key HF trials (< 5 y)	Lessons learned	
Gene therapy	Offers means of restoring expression and activity of proteins otherwise lost in HF (calcium regulatory proteins) May bolster expression and activity of key proteins to enhance effects to greater than baseline (proangiogenic factors, stem cell factors)	Little consensus on most suitable vector for gene delivery (viral vs nonviral) Vector delivery method Targets single genes Off-target effects	CUPID 2[62] STOP-HF[64] Ad5.hAC6[65] AGENT-HF[63]	Ad5.hAC6 trial showed significant improvement in LV function at highest doses; phase III trial under way AGENT-HF showed no beneficial effect but was prematurely terminated and therefore underpowered	All 4 trials showed favourable safety profiles compared with placebo controls CUPID trials failed to meet their study end points STOP-HF showed improvement in EF in patient group with lowest pretreatment EF
Cell therapy	Stem/progenitor cells can be isolated from patient's own body Isolated stem/progenitor cells can be re-engineered to enhance their therapeutic effects Offers potential of cardiogenesis and de novo tissue regeneration	Little consensus on which cell population offers most therapeutic benefit (eg, pluripotent vs mesenchymal vs bone marrow derived vs cardiac derived) Unclear therapeutic window Poor cell survivability and engraftment in host tissue Clinical trial design issues may be masking potential benefit of cell therapy in humans	REGENERATE-AMI[68] Allogeneic MPC[69] IMPACT-CABG[70] CHART-1[71]	All 4 trials demonstrated favourable safety and feasibility profiles REGENERATE-AMI showed small nonsignificant improvement in LVEF; precursor to phase III BAMI trial Allogeneic MPC trial suggested therapeutic benefit from high-dose allogeneic MPCs; precursor to phase III DREAM-HF trial	IMPACT-CABG showed no significant improvement in functional outcome; precursor to IMPACT-CABG II trial CHART-1 identified that patients with most severe LV dilatation (baseline LVEDV 200-370 mL) benefit may be greater from cell therapy; precursor to CHART-2 trial
Acellular bioscaffold therapy	Reservoir of regenerative growth factors and matricellular proteins Can be further enhanced with stem cells or cardioprotective growth factors for enhanced therapeutic effect Few translational hurdles relative to gene or cell therapy	Uncertainty as to which tissue source yields the most therapeutic bioscaffold for the heart Uncertain of which delivery method of bioscaffold yields most therapeutic benefit (patch or injectable?) Shortage of clinical trials in patients with HF	AUGMENT-HF[72] VentriGel injectable trial (ongoing) CorMatrix-ECM epicardial patch trial (ongoing)	AUGMENT-HF demonstrated that alginate-hydrogel injection with standard medical therapy improves exercise capacity, symptoms, and clinical status of patients with advanced HF more than standard medical therapy alone	CorMatrix-ECM epicardial patch trial and VentriGel injectable trial are both ongoing phase I trials

Ad5.hAC6, Adenovirus 5 encoding adenylyl cyclase 6; AGENT-HF, **A**AV1-CMV-Serca2a **Gen**e **T**herapy Trial in **H**eart **F**ailure; Allogeneic MPC, allogeneic mesenchymal precursor cell; AUGMENT-HF, Randomized, Controlled Study to Evaluate Algisyl-LVR as a Method of Left Ventricular Augmentation for Heart Failure; CHART-1, **C**ongestive **H**eart Failure C**a**rdiopoietic **R**egenerative **T**herapy; CUPID 2, Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease; DREAM-HF, A **D**ouble-blind, **R**andomized, Sham-procedure-controlled, Parallel-group **E**fficacy and Safety Study of **A**llogeneic **M**esenchymal Precursor Cells (CEP-41750) in Patients With Chronic **H**eart **F**ailure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology; ECM, extracellular matrix; EF, ejection fraction; HF, heart failure; IMPACT-CABG, **Imp**lantation of **A**utologous **C**D133$^+$ S**t**em Cells in Patients Undergoing **CABG**; LV, left ventricular; LVEDV, LV end-diastolic volume; MPC, mesenchymal precursor cell; REGENERATE-AMI, Randomised Controlled Clinical Trial of the Use of Autologous Bone Marrow Derived Progenitor Cells to Salvage Myocardium in Patients With Acute Anterior Myocardial Infarction; STOP-HF, **S**tromal Cell-Derived Factor-1 Plasmid **T**reatment f**o**r **P**atients With **H**eart **F**ailure.

the need for donor cells. An optimal therapy may in fact combine progenitor cells with bioactive scaffolds to enhance engraftment and proreparative effects.

Although clinical translation is less complicated with acellular biomaterials, additional research is needed. First, the optimal biomaterial for cardiac therapy is not established. Second, biomaterials can be delivered as an injectable or an epicardial patch. Injectable agents are advantageous because they are amenable to less invasive approaches, but delivery is less controlled and the risk of systemic embolization is high.[77] Use of biomaterials as a patch over an injured region is more invasive, but there is no embolization risk and the implant targets the epicardium, which is emerging as a key anatomic regenerative niche.[78] Finally, more rigorous clinical trials are needed to substantiate the beneficial effects of acellular scaffold therapy previously demonstrated in preclinical studies.

Toward optimal disease management: biomarker-guided HF management

Although a number of emerging HF biomarkers, such as high-sensitivity troponins, soluble toll-like receptor 2 (myocardial stretch/remodelling), galectin 3 (inflammation), and cystatin C (renal function) have the potential for refining prognosis and providing targets for management, the best-studied biomarkers in HF are the NPs.[79] Although NPs have had a well-established role in the evaluation of patients with symptoms of HF, measurement of NPs is now accepted to have additional value in the management of HF. Moreover, serial measures of both B-type natriuretic peptide (BNP) and its amino terminal propeptide cleavage equivalent (N-terminal proBNP [NT-proBNP]) provide incremental improvements in prognostication over a single-point measurement with respect to death or worsening HF.

Notably, NP measurement may inform the response to a broad range of medical therapies for HF. Most HF drugs, CRT, and exercise training lower concentrations of NPs in parallel with the benefit of such therapies. One notable exception is the effect of neprilysin inhibition (in the form of sacubitril/valsartan). BNP is a substrate of neprilysin, and inhibition with sacubitril/valsartan will raise levels of BNP, whereas NT-proBNP (whose metabolism is independent of neprilysin) levels fall on treatment.[80]

To the extent that changes in NPs have prognostic meaning, there has been interest in serial measurement of these peptides not only to longitudinally assess risk but also to serve as a "guide" for HF therapy. The theory underpinning a "guided" approach is that achievement of target HF therapy combined with a reduction in NP concentrations is superior to standard HF care alone without consideration of NP levels. Although this might allow for a more personalized approach to HF care, the rationale for this approach extends beyond the concept of precision care. It is well established that doses of HF therapies achieved in real-world settings are far lower than those used in clinical trials. Reasons for the underachievement of medical therapy are numerous but include the inability to recognize risk and tailor therapy accordingly as well as clinician inertia with respect to adding and titrating medications.[81] Thus this NP-guided approach might facilitate better outcomes than a "1 size fits all" approach to HF care.

Most data regarding the role of NP-guided HF care have been obtained from studies of patients with chronic ambulatory HFrEF. However, some data do suggest the potential utility of using BNP or NT-proBNP as a target for therapy in acute HF. In this setting, concentrations of BNP and NT-proBNP primarily reflect severity of congestion; lack of reduction in NPs after diuresis in hospitalized patients with HF strongly predicts the likelihood of recurrent HF events, including rehospitalization or death. As such, serial measurement of NP levels is now embraced as a strategy to help guide suitability for hospital discharge in acute HF.[82]

In the setting of chronic HF, trends in NP levels also reveal the severity of myocardial remodelling, valvular regurgitation, and atrial arrhythmias.[83] Each of these abnormalities have therapeutic interventions. To this end, a number of relatively small underpowered trials with a broad heterogeneity of designs have explored whether BNP- or NT-proBNP–guided medical therapy for chronic HFrEF might reduce the incidence of events. General findings from NP-guided therapy trials suggest that this approach is well tolerated and more often result in greater uptitration of medical therapy compared with usual care.[84] Although this strategy may be promising, a recent NT-proBNP–guided trial for HFrEF management was halted for lack of efficacy,[18] although full results are not yet available.

Understanding the results of NP-guided therapy trials is complex, and biomarker strategy trials may be beset by numerous challenges (Table 4). For example, in earlier studies, BNP or NT-proBNP targets for care were inappropriately high, leading to undertreatment in the guided-therapy arm. In other studies, care in the "usual care" arm was more aggressive than true "standard of care," leading to overachievement in management compared with what might have been expected outside of a clinical trial.

Studies that have triangulated the correct NP target, more aggressive care in the guided-therapy arm, and significant differences in achieved NP levels with guided therapy have typically realized a benefit from this approach. For example, in the ProBNP Outpatient Tailored Chronic HF Therapy (PROTECT) trial,[92] NT-proBNP–guided therapy with a target value of 1000 pg/mL was associated with more aggressive medical therapy and more significant NT-proBNP lowering compared with usual care. In PROTECT, NT-proBNP–guided care was associated with a 56% reduction in CV events and greater improvement in patient-reported quality of life.[85]

Toward optimal disease management: an evolving framework for RM in HF

RM refers to enhanced patient surveillance, either through structured telecommunications support (human to human or human to machine) or telemonitoring using external or internal sensors. Cardiac implantable electronic devices (CIEDs) process electrical signals, with algorithms based on sensing (night heart rate, heart rate variability, atrial and ventricular tachyarrhythmia detection), pacing, and intrathoracic impedance. Most strategies have focused on averting hospitalizations by predicting worsening HF ("crisis detection") while supporting disease management. Early studies were heterogeneous in methodological quality, sample size, population, intervention, and control group care,[86] with

Table 4. Challenges in natriuretic peptide–guided strategy trials

Challenge	Potential consequence
High natriuretic peptide target	Undertreatment in guided-therapy arm
Unblinded design	Knowledge of treatment assignment may lead to differences in clinician behaviour in "usual care" arm (including overtreatment relative to true standard of care) vs overtreatment in guided-therapy arm
Inability to receive natriuretic peptide results in a timely fashion during office encounters	Treatment decisions may be made without knowledge of biomarker results
Lack of response to elevated natriuretic peptide result in the guided-therapy arm	Undertreatment of higher-risk patients with higher risk for adverse outcomes

meta-analyses suggesting reduced mortality and hospitalizations.[86] Numerous subsequent large multicentre randomized controlled trials have demonstrated no benefit (Table 5).[87-93]

Failings to date are unsurprising given the heterogeneity of HF and manifestations of acute decompensation. For example, only a minority of patients have substantial weight gain before decompensation, and monitoring based on weight alone is ineffective.[94] Weight gain is typically preceded by several weeks of reducing intrathoracic impedance and increasing pulmonary artery diastolic and right ventricular pressure, potentially offering a more precise monitoring signal.[95] However, impedance-based monitoring alone has failed to improve outcomes in multiple clinical trials (Table 5).[90,92] CIED algorithms have combined impedance, sensing, and pacing variables into composite HF risk scores with little improvement.[96] Such approaches are inherently limited by reliance on electrical signals that characterize only a proportion of the disease pathway.

Crisis detection strategies effectively "test" patients repeatedly for impending decompensation. However, using single thresholds in fluctuant biological measures limits accuracy. Combining this with complex substrate, limited test performance, and long test to decompensation times inevitably generates low positive predictive values and numerous false-positive alerts. Moreover, the entire paradigm of physiological monitoring requires actionable effective therapies to either avert decompensation or maintain clinical stability. A huge challenge for all "crisis detection" strategies is the lack of effective therapies for AHF.

Clinical trials in HF have focused on harder morbidity and mortality end points (Table 5). RM did significantly improve quality of life in **C**ardioMEMS **H**eart Sensor **A**llows **M**onitoring of **P**ressure to **I**mprove **O**utcomes in **N**YHA Class III Heart Failure Patients (CHAMPION),[93] **B**etter **E**ffectiveness **A**fter **T**ransition-**H**eart **F**ailure (BEAT-HF),[88] and **T**elemedical **I**nterventional **M**onitoring in **H**eart **F**ailure (TIM-HF),[89] although the magnitude of improvement was modest. Although there is a need to integrate both quantity and quality of health in outcome assessment, the patient experience must also be valued in relation to opportunity costs. It is essential that incremental benefit be demonstrated using accepted metrics such as quality-adjusted life-years. This will most likely be driven by a combination of reduced hospitalizations and improved quality of life, emphasizing the need for novel end points. Economic analyses of RM have suffered from limited methodological quality, heterogeneity in populations and interventions, and poorly described costs.[97] For affordable implementation of RM strategies, careful consideration must be given to the resources required: Who bears responsibility for monitoring and acting on the data? What is the acceptable time frame in which to act? What are the medicolegal implications of RM?

Monitoring requires either single or multiple signals strongly associated with the underlying disease process. Direct cardiac pressure monitoring is the most promising of the former. Over 6 months, continuous pulmonary artery pressure monitoring was associated with fewer HF-related hospitalizations and improved quality of life in the CHAMPION trial.[93] Monitored patients received 0.88 additional medication changes monthly, largely diuretics or vasodilators. Although changes dropped sharply after the initial study phase, the intervention was found to be cost-effective,[98] and preliminary real-world experience suggests that this approach to ambulatory hemodynamic monitoring reduces HF hospitalization and related costs.[99]

Dynamic interaction between multiple signals may further refine the patient trajectory. Multidimensional strategies should integrate many biological variables with more sophisticated scales, rate of change measures, and individualized thresholds. These should be coupled with advanced analytics, machine learning and "N-of-1" meta-analytic and multilevel modelling approaches to characterize patient phenotypes.

RM is a complex intervention, involving complex interactions between system components and those delivering or receiving care, targeting diverse outcomes, and requiring flexibility and tailoring of the intervention. As such, effectiveness, cost-effectiveness, and implementation all require equally rigorous evaluation before routine integration into clinical practice.

Promising interventions for acute HF

The past few years have witnessed the assessment of multiple interventions for the treatment of AHF. Although promising AHF therapies have recently been characterized by disappointing results in large-scale outcome trials, it is worth highlighting the novel strategies under evaluation. Although there is overlap, these therapeutic approaches have targeted volume removal and renal function, vasodilation, or cardiac performance.

Mechanical ultrafiltration (UF) is the most direct method for volume removal, with many theoretical advantages over the more commonly used diuretics, including the removal of isotonic fluid compared with hypotonic fluid with diuretic agents. This excess removal of sodium, possibly associated with less neurohormonal activation, has provided biological plausibility for the improved outcomes observed in some early UF studies.[100] A report from the prematurely terminated **A**quapheresis **V**ersus **I**ntravenous **D**iuretics and Hospitalization for **H**eart **F**ailure (AVOID-HF) trial suggested that patients hospitalized for HF treated with adjustable UF had a trend toward a longer time to a first HF event and fewer HF events overall[101]; however, other randomized trials have failed to show any advantage of UF.[26] Other ongoing trials will test

Table 5. Landmark randomized clinical trials of remote monitoring in heart failure

Study	Measure	Population	Follow-up	Primary end point	Secondary end points	Quality of life
TELE-HF 2010[87]	Telephone-based interactive voice response system	N = 1653 Recent HF hospitalization	180 d	Death and all-cause readmission, 52.3% vs 51.5%; $P = 0.75$	Death, 11.1% vs 11.4%; $P = 0.88$ Hospitalization: HF, 27.5% vs 27.0%; $P = 0.81$ Any, 49.3% vs 47.4%; $P = 0.45$	Not assessed
BEAT-HF 2016[88]	BP, heart rate, weight, symptoms	N = 1437 HF hospitalization	180 d	All-cause readmission, 50.8% vs 49.2%; $P = 0.74$	Death, 14.9% vs 14.0%; $P = 0.34$	MLHFQ 32.6 vs 28.5; $P = 0.02$
TIM-HF 2011[89]	3-lead ECG, BP, weight	N = 710 NYHA II-III EF $\leq$ 35% with HFH or EF $\leq$ 25%	Median, 26 mo	Death, 8.4% vs 8.7% per 100 person-years HR, 0.97 (0.67-1.41); $P = 0.87$	Hospitalization: HF, 0.84 (0.60-1.18); $P = 0.32$ CV cause, 1.07 (0.84-1.35); $P = 0.58$ Any, 1.12 (0.91-1.37); $P = 0.29$	SF-36 physical 54.3 vs 49.9; $P = 0.01$ NYHA class, no difference PHQ-9, no difference
DOT-HF 2011[90]	Impedance audible alert	N = 335 NYHA II-IV, EF $\leq$ 35% CRT-D, ICD	Median, 14.5 mo	Death and HF hospitalization, 29% vs 20% HR, 1.52 (0.97-2.37); $P = 0.06$	Death, 1.24 (0.63-2.44); $P = 0.54$ HFH, 1.79 (1.08-2.95); $P = 0.02$ Outpatient visit 250 vs 84; $P < 0.0001$	Not assessed
IN-TIME 2014[91]	Multiparametric	N = 664 NYHA II-III, EF $\leq$ 35% CRT-D, ICD	1 y	Composite clinical score, 18.9% vs 27.2% Worsened score, OR, 0.63 (0.43-0.90)	Death, 3.0% vs 8.2%; $P = 0.004$ HFH, 13.2% vs 14.2%; $P = 0.38$	NYHA class, no difference Patient global assessment, no difference
OptiLink-HF 2016[92]	Impedance	N = 1002 NYHA II-III, EF $\leq$ 35% HFH < 12 mo	1.9 y	Death or CV hospitalization, 45.0% vs 48.1% HR, 0.87 (0.72-1.04); $P = 0.13$	Death, 0.89 (0.62-1.28); $P = 0.52$ Hospitalization: HF, 0.87 (0.67-1.12); $P = 0.28$ CV, 0.89 (0.73-1.08); $P = 0.22$	Not assessed
CHAMPION 2011[93]	CardioMEMS pulmonary artery pressure	N = 550 NYHA III, any EF Previous HFH	6 mo	HF hospitalization, 0.32 vs 0.44 HR, 0.72 (0.60-0.85); $P = 0.0002$	DAOH, 174.4 vs 172.1; $P = 0.02$	MLHFQ, 45 vs 51; $P = 0.02$
REM-HF ESC 2016	Multiparametric	N = 1650 NYHA II-IV CRT-D, ICD, CRT-P	Mean, 2.8 y	Death or CV hospitalization, 42.4% vs 40.8% HR, 1.01 (0.87-1.18); $P = 0.87$	Not yet reported	Not yet reported

BEAT-HF, **B**etter **E**ffectiveness **A**fter **T**ransition-**H**eart **F**ailure; BP, blood pressure; CHAMPION, **C**ardioMEMS **H**eart **S**ensor **A**llows **M**onitoring of **P**ressure to **I**mprove **O**utcomes in **N**YHA Class III Patients; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; CV, cardiovascular; DAOH, days alive out of hospital; DOT-HF, **D**iagnostic **O**utcome **T**rial in **H**eart **F**ailure; ECG, electrocardiogram; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; HFH, HF hospitalization; HR, hazard ratio; ICD, implantable cardioverter device; IN-TIME, Implant-Based Multiparameter Telemonitoring of Patients With Heart Failure; MLHFQ, Minnesota Living With Heart Failure Questionnaire; NYHA, New York Heart Association; OR, odds ratio; PHQ-9, Patient Health Questionnaire 9; REM-HF, Remote Management of Heart Failure Using Implantable Electronic Devices; SF-36, 36-item Short Form; TELE-HF, Telemonitoring to Improve Heart Failure Outcomes; TIM-HF, **T**elemedical **I**nterventional **M**onitoring in **H**eart **F**ailure.

this concept more fully (ClinicalTrials.gov: NCT02846337 and NCT02769351).

A number of novel approaches to vasodilation therapy have been developed for AHF. TRV027, a "biased" ligand of the angiotensin II type 1 receptor (AT1R), selectively antagonizes the negative effects of angiotensin II while preserving the potential procontractility effects of AT1R stimulation. In the phase II **B**iased **L**igand of the **A**ngiotensin Receptor **S**tudy in **A**cute **H**eart **F**ailure (BLAST-AHF) study,[102] 621 patients hospitalized for AHF were randomized to different doses of TRV027. It did not confer any benefit over placebo at any dose regarding the primary composite end point or any of the individual components. However, the approach of using biased ligands is intriguing and may provide future directions for AHF therapies.

Ularitide is the synthetic form of urodilatin, a human NP that is generated by differential processing of pro−atrial NP in distal renal tubule cells and appears to be involved in sodium homeostasis. Ularitide exerts vasodilatory, diuretic, and natriuretic actions through the same pathways as the other NPs, nesiritide (B-type NP) and cenderitide (an A-type NP).[103] Small hemodynamic studies demonstrated beneficial effects of ularitide in reducing pulmonary capillary wedge pressure and systemic vascular resistance, with commensurate increases in cardiac index and decreases in blood pressure, consistent with its mechanism as a vasodilator.[104] The **Tr**ial of **U**laritide's **E**fficacy and Safety in Patients With **A**cute **H**eart **F**ailure (TRUE-AHF) trial evaluated the effect of a 48-hour infusion of ularitide compared with placebo in 2157 patients with AHF.[22] Neither of the 2 primary end points (CV death or the clinical composite over the initial 48 hours) was improved.

Serelaxin is a recombinant form of human relaxin-2, a hormone that is believed to play a central role in maternal adaptations to pregnancy, improving vascular compliance and renal function while providing end organ protection.[105] Mechanistic studies confirmed its beneficial hemodynamic effects of reducing wedge pressure and systemic and pulmonary vascular resistance.[105] The first phase III trial of serelaxin, Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF),[106] met its primary end point of demonstrating significant improvement in dyspnea during the first 5 days in patients admitted with AHF, dyspnea, mild to moderate renal dysfunction, and normal to elevated systolic blood pressures treated with a 48-hour infusion of serelaxin compared with placebo, as well as a reduction in all-cause mortality at 180 days. The second phase III trial, serelaxin, RELAX-AHF-2, randomized 6545 patients with AHF to either 48-hour infusions of serelaxin or placebo. As recently reported,[107] serelaxin-treated patients had no improvement in either primary end point (180-day CV mortality or worsening HF through day 5) or in in any secondary end point.

For decades, investigators have attempted to develop therapies that improve cardiac performance without the deleterious effects of current inotropic agents. One of these approaches has been the development of nitroxyl donors. In preclinical models, these agents have positive inotropic, lusitropic, and vasodilator effects that are cyclic adenosine monophosphate independent.[108] Early dose finding studies have supported the vasodilating effects of these agents, although demonstrating direct myocardial effects has been confounded by this vasodilation. This approach is currently under investigation with the nitroxyl donor BMS-986231 in the Evaluate the Safety and Efficacy of 48-hour Infusions of HNO (Nitroxyl) Donor in Hospitalized Patients with Heart Failure (STANDUP AHF) study (ClinicalTrials.gov: NCT03016325), enrolling patients admitted for AHF.

Another recent approach to improve cardiac performance is the development of cardiac myosin activators. Omecamtiv mecarbil is a selective cardiac myosin activator that enhances myocardial performance with no increase in intracellular calcium transients and myocardial oxygen demand.[109] As discussed earlier, this agent is being evaluated in the setting of chronic HF in the GALACTIC-HF trial. In the setting of AHF, the **A**cute **T**reatment with **O**mecamtiv **M**ecarbil to **I**ncrease **C**ontractility in **A**cute **H**eart **F**ailure (ATOMIC-AHF) was a phase II dose-finding study in patients admitted with AHF, dyspnea, and reduced EF who were randomized to a 48-hour infusion of 1 of multiple omecamtiv mecarbil doses or placebo.[110] The primary end point of dyspnea relief from an individual omecamtiv mecarbil dose compared with placebo was not achieved, but there was significant improvement in dyspnea in the high-dose group compared with its paired placebo group.

Despite disappointing results in the recent major outcomes trials in patients with AHF, there have been many interesting and compelling approaches in development for the treatment of these patients. To date, it is unclear whether the failure of some potential AHF therapies relates to the heterogeneous populations studied, the choice of clinical end points, or the time horizon over which the intervention is made and outcomes are assessed. Although AHF may represent a severe manifestation of a chronic and deteriorating physiological state, it is possible that the use of biomarkers and RM strategies to intervene earlier, before the onset of overt signs or symptoms, may yield more meaningful clinical benefits.

Conclusions

Comprehensive and highly personalized HF care will leverage advances in precision diagnosis, drug development, device technology, and, possibly, regenerative medicine. Further, developments in disease-monitoring strategies and identification of appropriate interventions in response to changes in clinical course will afford new opportunities to change the trajectory of illness and improve prognosis. Despite the gaps in knowledge and challenges in application of emerging therapies, the future of HF care is exciting and full of promise.

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