WHITE PAPER

Evolving use of digital endpoints in clinical research for congestive heart failure

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CLARIO.

Contents

Evolving landscape

Over the past century, treatment for patients with heart failure (HF) has been primarily guided by the assessment of left ventricular ejection fraction (LVEF). Earliest treatments were developed solely for patients with a reduced ejection fraction (rEF). In the development of ACE inhibitors and beta blocker therapies, change in LVEF served as the primary endpoint for demonstrating efficacy in patients with HF with reduced ejection fraction (HFrEF). In contrast, the treatment for patients with HF with preserved ejection fraction (HFpEF) remained controversial for an extended period of time due to limited data. For the population with HFpEF, LVEF is not an appropriate endpoint, and identification of a validated approach for drug efficacy required additional development time.

In parallel to the advances in pharmacological treatments for HF,[1,2] device-based therapies were also developed that provided additive benefits for the sub-group of patients with HFrEF. The evidence supporting benefits for internal cardio-defibrillators (ICDs) and, soon thereafter, cardiac resynchronization therapy (CRT) devices was robust enough to grant them market approval despite their high costs.

In recent years, the treatment landscape has been further enhanced by the approval of sodium-glucose transporter 2 (SGLT2) inhibitors. The EMPEROR trials demonstrated for the first time that medical therapy could provide benefit not only for patients with HFrEF but also for those with HFpEF.[3,4] Examples of SGLT2 inhibitors include empagliflozin, dapagliflozin, and sotagliflozin.[5,6]

Endpoint assessment

Imaging modalities

The development of various imaging techniques for HF have revolutionized clinical research, offering a nuanced understanding of the condition's complexities. Although standard 2-dimensional and doppler echocardiography have historically been the primary modalities, techniques such as 3-dimensional and strain echocardiography, cardiac magnetic resonance imaging (CMR) and nuclear cardiology have all emerged as additional indispensable assets in the diagnostic armamentarium. Each offers unique early insights into cardiac structure and function. While echocardiography provides real-time assessment of ventricular function and valvular integrity, CMR offers unparalleled tissue characterization and quantification of inflammation and fibrosis. Magnetic resonance spectroscopy (MRS) assesses myocardial energetics by measuring the concentrations of key energy metabolites, especially the phosphocreatine/adenosine triphosphate (PCr/ATP) ratio in the heart. Lower PCr/ATP ratios are associated with worse prognosis in HF.[7,8] MRS can be used to monitor response to metabolic therapies in research settings and may detect energetic abnormalities before structural changes occur.[9] Although it is a powerful research tool for understanding and monitoring heart disease, its clinical use is currently limited to specialized centers and research studies due to its technical complexity, need for specialized equipment and need for expertise.

As highlighted in recent research, no single imaging technique for HF is capable of detecting disease acuity and different patterns of HF pathophysiology.[9,10] The limitations of echocardiography underscores the importance of leveraging complementary diagnostic tools, such as CMR. By providing unparalleled insights into myocardial tissue characterization, inflammation and fibrosis quantification, CMR has emerged as a valuable adjunct to conventional imaging techniques, enabling clinicians to better risk stratify and tailor therapeutic strategies to individual patients' needs.[9,10] As the field continues to evolve, the integration of CMR and other advanced imaging modalities into clinical research and practice is likely to play a pivotal role in redefining our understanding of HF and informing the development of novel, targeted therapies.

The burgeoning interest in positron emission tomography (PET) techniques has also further expanded the diagnostic repertoire for HF, enabling the non-invasive assessment of viability, active inflammation, fibrosis and angiogenesis. As the field continues to evolve, the integration of PET and other advanced imaging modalities into clinical research and practice is poised to revolutionize our understanding of HF, facilitating the development of precision medicine approaches tailored to individual patients' needs.

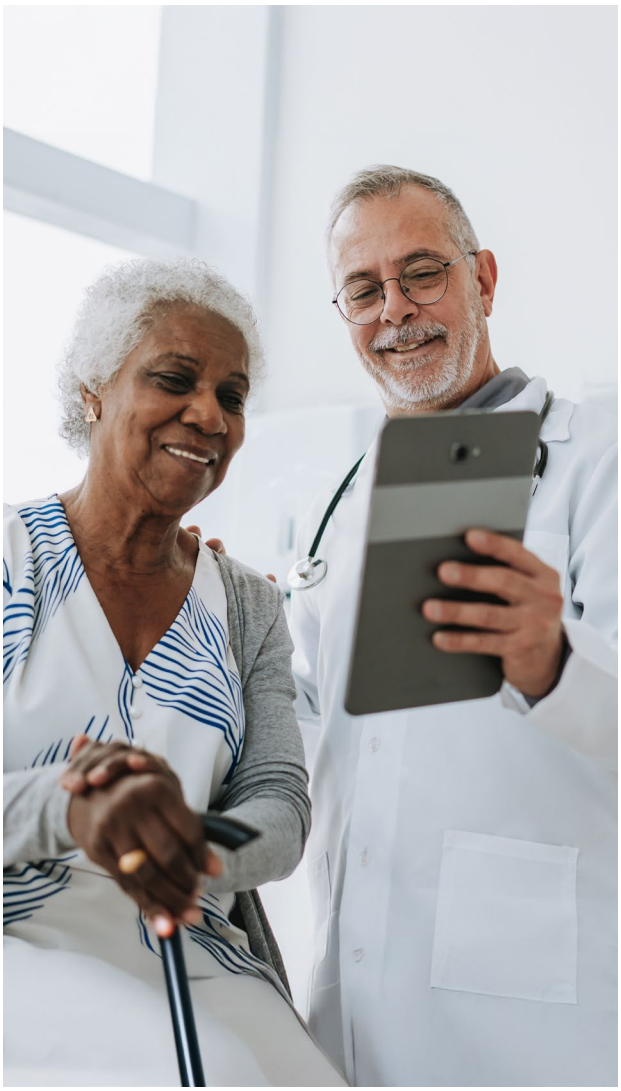

Table 1: Imaging endpoints in HF clinical trials – cardiovascular imaging (CVI)

Imaging modality	Endpoint	Description	Clinical relevance	Example study
Echocardiography (global longitudinal strain [GLS])	GLS, LVEF, myocardial work indices	Strain imaging to detect subclinical dysfunction and remodeling	Predicts outcomes beyond LVEF; monitors therapy effects	Short-term GLS in HFrEF on sacubitril/valsartan[11]: early GLS improvement vs baseline
	GLS prognostic value for heart failure with improved ejection fraction (HfimpEF)	GLS – risk stratification in improved EF patients	Long-term guidance in recovered EF	Prognostic value of GLS in HFimpEF[12]: each 1% increase in GLS leading to a 14% lower risk of CV death/HF admissions
Echocardiography (pressure-strain loop [PSL] + medication)	PSL indices (global work index [GWI], global constructive work [GCW]), GLS	Advanced myocardial work metrics	Evaluates combined angiotensin receptor-neprilysin inhibitor (ARNI) + sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy impact post-myocardial infarction (MI)	LV-PSL for prognosis post-MI[13]: GCW at 6 months predicted MACE (major adverse cardiac events)
Cardiac MRI (late gadolinium enhancement [LGE])	LGE extent, arrhythmic risk, mortality	Inflammation, fibrosis imaging in non-ischemic dilated cardiomyopathy	Guides scarring, arrhythmia prevention and mortality risk	Meta-analysis 2019 (452–874 pts)[14]: LGE predicted CV death/ventricular arrhythmia (VA) events
	LVEF, extracellular volume (ECV), LGE, T1/T2 mapping	Ventricular volumes and myocardial tissue characterization	Detects fibrosis, inflammation, viability in HFpEF and non-ischemic cardiomyopathies	Feasibility study of real-time CMR in HFpEF diagnosis[15]

Table 1: Imaging endpoints in HF clinical trials – cardiovascular imaging (CVI) (continued)

Imaging modality	Endpoint	Description	Clinical relevance	Example study
Coronary computed tomography angiography (CCTA)/computed tomography (CT) imaging	Not specifically for HF; evolving with strain imaging	Emerging CT strain/flow tools	Early research-stage applications in HF phenotyping	—
	Coronary stenosis, plaque burden, calcium scoring	High-resolution 3D imaging of coronary arteries	Identifies ischemic causes of HF, risk stratification	Compared CCTA + fractional flow reserve derived from CT (FFRCT) pathway to traditional testing in coronary artery disease evaluation. PRECISE trial[16]
Single-photon emission computed tomography (SPECT)/PET	Myocardial perfusion, viability and metabolic activity	PET perfusion F-18 tracer showing high accuracy for perfusion and cellular function	Guides revascularization in ischemic HF	Flurpiridaz F-18 PET[17]: FDA approval Sept 2024; sensitivity 63–77%, specificity 66–86%
Multigated acquisition (MUGA)	No major recent HF-specific studies	Historically precise EF quantitation	Superseded by echo/CMR; niche oncology use	—

Clinical events adjudication

The value of centralized adjudication of HF events may vary widely depending on the nature of the study population, phase of the study, nature (e.g., safety vs efficacy) and complexity of the study endpoints, experience of the investigators and experience of the clinical endpoint committee (CEC).[18] In HF trials, showing that new drugs provide significant benefit in objective outcomes, such as cardiac-related death and hospitalization, over existing treatments is often required. To demonstrate these benefits, a cardiovascular outcomes trial (CVOT) is conducted where MACE adjudication is the primary endpoint and centralized adjudication is critical for obtaining accurate and valid outcomes. Therefore, it is important to engage an experienced adjudication provider and committee members and to implement a robust process for event identification and definition, CEC member selection and resolution of discordant assessments, particularly when source documentation is limited.

Electronic clinical outcome assessment (eCOA) endpoints

A new chapter in HF clinical development started at the end of the 2000s when the FDA first laid out its expectations regarding the use of patient-reported outcomes (PROs) in drug development to support labeling claims.[19] Almost simultaneously, the first large-scale outcome studies with patients with HFrEF were initiated using the Kansas City Cardiomyopathy Questionnaire (KCCQ) as a secondary endpoint.[20,21]

Patient-reported outcome measures (PROMs) are frequently the most effective tools for assessing patients' symptoms, functioning and health-related quality of life. PROMs can minimize observer bias, actively involve patients in the research process and provide valuable insights for health service resource planning.[22,23] As for other clinical outcome assessments (COAs), the electronic collection of PROMs – as eCOA – can help to further maximize their potential thanks to higher quality data, faster availability and reduced burden for and better engagement of participants.

Recent regulatory guidance updates from the FDA[24] and EMA[25] further highlight the importance of robust PROMs as endpoints in clinical trials. These changes aim to ensure that new treatments improve not only physician-assessed clinical outcomes but also the perceived quality of life of patients.

In addition, one could observe recent calls for more convergence of PRO use in both clinical trials and routine clinical practice with patients with CVD,[26,27] potentially leading to a more holistic picture of what represents a successful treatment, especially in HF. In this respect, key points of interest in HF include:

- Emphasis on symptom relief: Measures of symptom improvement, such as reductions in shortness of breath and fatigue
- Quality of life evaluations: Assessments of impact on overall well-being and daily living
- Functional capacity assessments: Evaluations of physical abilities, like walking distance or daily activity levels

For example, the 2017 EMA guidance for HF drug development puts an emphasis on functional status as measured via exercise tests plus global clinical evaluations alongside the use of PROs to show an improvement in symptoms and quality of life:[28]

- Functional capacity recommendations include measurements of maximal oxygen consumption (MVO_2) during bicycle- or treadmill-based exercise and a supervised 6-minute walk test (6MWT). In the older adult

population, other functional tests, such as the stair climb test, Short Physical Performance Battery (SPPB) or hand-grip strength assessment can be used.

- Clinical symptoms can be assessed more holistically using the New York Heart Association (NYHA) classification.

Safety assessment: Electrocardiogram (ECG) and arrythmia detection

ECG is a fundamental component of safety assessment across all therapeutic areas, including studies involving patients with established heart disease. In early-phase clinical trials, it is essential to confirm drug safety by demonstrating the absence of any clinically significant effect on the QTc interval. This is typically studied in healthy volunteers.

Evaluating ECGs in patient populations with HF can be especially challenging due to pre-existing cardiac conditions as well as the potential effects of concomitant medications. The absence of a centralized, impartial review of ECGs can result in under-reporting or false-positive reporting of clinically significant events.

Implementing centralized ECG over-read in a clinical study provides an important safeguard. This process helps ensure precision and consistency in interpretation, reduces variability across sites and mitigates the risk of false-positive and false-negative findings. Ultimately, centralized review enhances data integrity and strengthens patient safety monitoring throughout the trial.

In recent years, novel technologies have emerged to enhance arrhythmia monitoring in HF trials, including home-based monitoring systems, mobile cardiac outpatient telemetry (MCOT) and remote ECG solutions. These tools provide continuous or near real-time data, improving the detection of clinically significant events that might otherwise be undetected.

Arrhythmias occur more frequently in patients with HF than in most other cardiology populations,[1,2] making early detection and management during clinical trials essential for patient safety and to identify potential safety signals. Traditional monitoring approaches often rely on intermittent assessments, which can fail to capture transient or asymptomatic episodes. To address this limitation, patient-driven devices such as the KardiaMobile 6-lead home ECG[29] offer a convenient option for recording symptomatic events. These devices empower patients to actively participate in their care while providing investigators with timely, high-quality data.

However, for comprehensive monitoring, especially in high-risk populations, additional strategies such as continuous patch-based recorders or telemetry systems may be warranted.[30,31] These technologies enable

prolonged observation periods and retrospective analysis, supporting a more robust safety framework in HF trials. With some technologies, events are only interpreted retrospectively after the patch recorder is removed and data are downloaded and subsequently analyzed. Other devices allow for transmission of data remotely, enabling some analysis throughout the recording window. These technologies are especially helpful for detecting infrequent events like paroxysmal atrial fibrillation or transient heart block. However, it is important to recognize that, with continuous recordings, a number of normal and asymptomatic arrhythmias, such as premature ventricular beats, bradycardia or low-grade AV block, may be detected. Therefore, it is essential to include a sufficient pre-dose recording period so drug-related events can be clearly distinguished from pre-existing conditions.

If there is an elevated risk of clinically significant arrhythmias, out-of-clinic ECG monitoring with semi-automatic alerts – such as MCOT – is often recommended. MCOT provides continuous monitoring and near real-time transmission of ECG data, enabling early detection of potentially dangerous arrhythmias and timely intervention.

In addition to arrhythmia surveillance, blood pressure (BP) monitoring plays an important role in HF trials. BP assessments are typically performed both in clinical settings and at home to ensure longitudinal safety monitoring.[32] These measurements help identify hemodynamic changes that may signal adverse drug effects or disease progression. Proper and consistent measurement of BP in a clinical study is particularly challenging, and data quality is highly variable. Robust site and participant training on best practice is essential. Additionally, deploying the same model BP cuff across all sites and leveraging technologies that report an average of multiple replicate inflations at each time point can substantially improve precision and accuracy.

Ambulatory blood pressure monitoring (ABPM) is a specialized modality in which a participant wears a BP cuff for 24 hours, with inflations occurring every 20 or 30 minutes. This can be particularly useful in later-phase trials to evaluate diurnal and nocturnal BP patterns,[33] offering insights into circadian variations and treatment impact. However, ABPM is not generally employed to assess pressor effects of HF therapies, as any drug that significantly raises BP would likely be considered unsuitable for further development. Instead, ABPM serves as a complementary tool for understanding long-term BP trends and optimizing patient safety.

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