Enhancing patient-centricity in cardiovascular outcomes: Exploring endpoint strategies with Clinical Outcome Assessments (COAs) in approved drugs for chronic heart failure

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OBJECTIVE

- Regulatory agencies have published guidelines outlining requirements for demonstrating efficacy in chronic heart failure interventions in clinical trials.
- **The FDA grants priority review status for chronic heart failure treatments, whereas the EMA follows a standard review procedure**[1].
- These procedural differences may result in divergence in data requirements for regulatory drug approval, such as the FDA's acceptance of novel endpoints for heart failure, which may not align with EMA standards[2]. Consequently, these variations can lead to **differences in clinical outcome assessment (COA) endpoint strategies between the FDA and EMA**.
- The objective was **to explore and compare FDA and EMA guidelines for chronic heart failure endpoint strategies**, as well as to examine how these recommendations have been implemented drug labels.

METHODS

A search was conducted in April 2024 using Mapi Research Trust's databases: a) PROINSIGHT™, to review EMA and FDA guidelines on chronic heart failure trials and b) PROLABELS™, to capture labels mentioning COAs of EMA- and FDA-approved drugs. This resulted in 2 guidelines (EMA n = 1, FDA n = 1) and 27 labels (EMA n = 8, FDA = 19). Seven FDA labels that included only non-specified endpoint positionings were excluded from analysis.

1) Visited ePROVIDE[3] in April 2024

ePROVIDE™ Online Support for Clinical Outcome Assessments

2) Filtered: Therapeutic Indication for "Chronic Heart Failure" and Health Agency for "EMA" and "FDA"

PROINSIGHT™ Providing Regulatory Insights to Clinical Outcome Assessments

PROLABELS™ Clinical Outcome Labeling Claims Database

FINDINGS

EMA and FDA guidelines related to chronic heart failure were searched for in PROINSIGHT. Primary, secondary, and other endpoints with(out) COA instruments were recommended. PROLABELS was subsequently searched to explore the frequency of each concept of interest associated with the specific COA instrument. Mortality was, for example, recommended and included in 7 EMA and 13 FDA drug labels as primary endpoints. As digital health technologies (DHTs) are not detailed in ePROVIDE databases, they were not included in the analysis.

EMA

Guideline: Clinical investigation of medicinal products in the treatment of chronic heart failure[4]

Primary endpoint recommendations

Concept of interest	Instrument (Type of OA[c])
Mortality	Non-COA
Time to first heart failure hospitalisation	
Functional capacity	6-Minute Walk Test (6-MWT) (PerfO[a])

Secondary endpoint recommendations

Concept of interest	Instrument (Type of OA[c])
Improvement of symptoms	New York Heart Association functional class (NYHA Classification)
Health-related quality of life (HRQoL)	Minnesota Living with Heart Failure Questionnaire (MLHFQ) (PRO[b])
	Kansas City Cardiomyopathy Questionnaire (KCCQ) (PRO[b])

Drug Labels (n= 8)‡

The concept of interests mentioned in the guidelines were included in the labels; however, the recommendations pertaining to endpoint positioning were not strictly adhered to. The 6-MWT and the MLHFQ were absent from all labels. Although not mentioned in the guidelines, Patient Global Impressions scale (PGI), were used in labels.

Primary endpoint concepts (OAs)
- Clinical events (PGI; NYHA), n=1
- Mortality or hospitalisation (Non-COA), n=7

Secondary endpoint concepts (OAs)
- All-cause mortality (Non-COA), n=2
- Symptoms of heart failure (KCCQ), n=2
- Mortality or hospitalisation (Non-COA), n=2
- Renal function (Non-COA), n=2

FDA

Guideline: Treatment for heart failure: endpoints for drug development guidance for industry[5]

Primary endpoint recommendations

Concept of interest	Instrument (Type of OA[c])
Mortality	Non-COA

Secondary endpoint recommendations

Concept of interest	Instrument (Type of OA[c])
Symptoms	Not stated
Exercise capacity	
Functional capacity	
Activities of daily living	Accelerometry data using DHTs

Other endpoint recommendations

Concept of interest	Instrument (Type of OA[c])
Symptoms	KCCQ (PRO[b])
Physical limitation	

Drug Labels (n= 12)‡

The concept of interests mentioned in the guidelines were included in the labels as both primary and secondary endpoints. The KCCQ was not utilised in any label despite being recommended. Most endpoints were either non-COAs or unspecified. Although not mentioned in the guidelines, physician's or patient's global assessment, were used in labels

Primary endpoint concepts (OAs)
- All-cause mortality, hospitalisation or heart failure (Non-COA), n=13
- Exercise capacity (Not stated), n=2
- Health-related quality of life (HRQoL) (Not stated), n=2
- Physical capacity (6-MWT), n=1
- Exercise duration (Not stated), n=1
- Functional status (MLHFQ), n=1

Secondary endpoint concepts (OAs)
- Functional status (NYHA), n=2
- HRQoL (Not stated), n=1
- Mortality (Non-COA), n=2
- Hospitalisation (Non-COA), n=5
- Physician global assessment (Physician's Global Assessment Scale), n=2
- Patient global assessment (Patient's or Subjective Global Assessment Scale), n=2

[a] PerfO = Performance outcomes; [b] PRO = Patient-reported outcomes; [C] OA = Outcome assessment

‡ DHTs are not specified in ePROVIDE databases, including PROLABELS, as it is a COA database, and were subsequently not included in the analysis

KEY TAKEAWAYS

- This work highlights a divergence between heart failure clinical outcomes (mortality and functional capacity assessment) in FDA and EMA guidelines.
- A key difference between the EMA and FDA guideline is that EMA allows a COA, namely, the **6-MWT (PerfO)**, to be placed as primary endpoint and HRQoL COAs such as the **MLHFQ and KCCQ**, as secondary endpoints. FDA takes a different approach and only allows COAs as **'other' endpoints**.
- Another significant takeaway is that the FDA is allowing a **DHT to be considered as an endpoint**.
- Despite misalignment in recommendations, the list and types of COAs mentioned in labeling claims are more convergent between EMA and FDA, showing a **closer agreement with EMA recommendations**.
- One possible explanation for these results are that the FDA's guideline remains a draft guidance document, whereas the EMA's guideline has already been adopted. A second possible reason could be that the FDA has a stricter strategy in accepting instruments for endpoint positions in clinical trials. A third reason could be that endpoints with COAs recommended by EMA and FDA reflect guidance rather than a strict requirement.

REFERENCES

[1] Bayer (2020) *U.S. FDA Grants Priority Review to new drug application for Vericiguat to treat chronic heart failure*. Available at: https://www.bayer.com/media/en-us/us-fda-grants-priority-review-to-new-drug-application-for-vericiguat-to-treat-chronic-heart-failure (Accessed: 01 July 2024).

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