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# Standardized and hierarchically classified heart failure and complementary disease monitoring outcome measures: European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart)

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## Aims

The lack of standardized definitions for heart failure outcome measures limits the ability to reliably assess the effectiveness of heart failure therapies. The European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart) aimed to produce a catalogue of internationally endorsed data definitions for heart failure outcome measures.

## Methods and results

Following the EuroHeart methods for the development of cardiovascular data standards, a working group was formed of representatives from the European Society of Cardiology Heart Failure Association and other leading heart failure experts. A systematic review of observational and randomized clinical trials identified current outcome measures, which was supplemented by clinical practice guidelines and existing registries for contemporary definitions. A modified Delphi process was employed to gain consensus for variable inclusion and whether collection should be mandatory (Level 1) or optional (Level 2) within EuroHeart. In addition, a set of complementary outcome measures were identified by the

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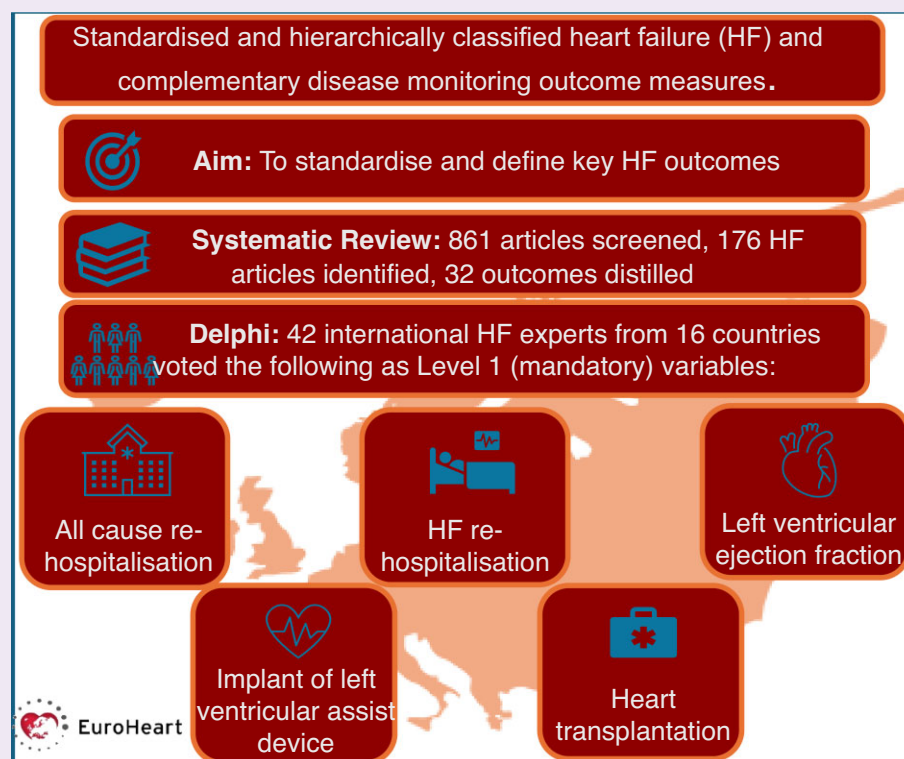
working group as of scientific and clinical importance for longitudinal monitoring for people with heart failure. Five Level 1 and two Level 2 outcome measures were selected and defined, alongside five complementary monitoring outcomes for patients with heart failure.

## Conclusion

We present a structured, hierarchical catalogue of internationally endorsed heart failure outcome measures. This will facilitate quality improvement, high quality observational research, registry-based trials, and post-market surveillance of medical devices.

## Graphical Abstract

Standardized and hierarchically classified heart failure and complementary disease monitoring outcome measures. HF, heart failure.



## Keywords

Outcomes definitions • Heart failure • EuroHeart • Quality of care



for inclusion as a Level 2 variable was at least 75% of participants selecting for the variable either as Level 1 or Level 2. The results of the poll were presented and discussed among the working group during an online meeting held on 28 October 2023. Participants were invited to provide feedback during voting and there was a proposal made by the experts that additional variables to monitor disease progression and response to therapy over time would be valuable. This resulted in a re-vote on the complementary variables by means of an online poll. The agreed list of variables and their definitions were then reviewed by the working group for ratification.

## Hierarchical grading

The working group classified outcome measures as Level 1 that should be collected for all participants, and Level 2 that may be selected by participating centres depending on their own requirements.

## Implementation and application

The final set of Level 1 heart failure outcome measures will be programmed into the EuroHeart IT system by the EuroHeart Registry Technology Group. Data recorded on the IT platform will have an associated date of outcome occurrence and outcome multiplicity is allowed (except for the occurrence and date of death). The expected target population will be patients hospitalized after an index presentation of heart failure or after an outpatient visit for heart failure at a participating centre in EuroHeart countries. Data reporting and its statistical analysis will be in accordance with a statistical analysis plan.

## Patient involvement

Patients were not invited to the vote on the candidate list of variables as per their request as they advised us that the process was too technical. The results of the poll have been presented to the ESC patient forum, which support this work.

## Results

The systematic review retrieved 4728 studies, of which 861 (18%) met the inclusion criteria. Of these, 176 (20%) studies concerned heart failure. The potentially relevant outcome measures were extracted by members of the Data Science Group and were supplemented by those used in existing registries. In total, 34 candidate outcomes measures for heart failure were presented to the working group for independent voting. The final set of outcome measures was selected after a series of meetings and online polls between 16 July and 28 October 2023.

## Hierarchical outcomes

### Level 1 (mandatory) outcome measures

There were five outcome measures specific to heart failure that were deemed mandatory to collect and defined as Level 1 by the working group. These were in addition to the EuroHeart generic Level 1 cardiovascular outcome measures.

These were: (i) capture of left ventricular ejection fraction as a percentage. Where this is not possible, the category reported should be according to ESC guidance,<sup>16</sup> (ii) all-cause hospitalization, (iii) heart failure hospitalization, (iv) implantation of left ventricular assist device, and (v) heart transplantation (Figure 1 and Table 1).

### Level 2 (optional) outcome measures

There were two outcome measures that were deemed optional to collect and defined as Level 2 by the working group (Figure 1 and Table 1).

These were device implantation that included: transvenous pacemakers; leadless pacemakers; transvenous; subcutaneous implantable

cardioverter defibrillators; implantable cardioverter defibrillators; cardiac resynchronization therapy—pacemaker; and cardiac resynchronization therapy—defibrillator and resuscitated ventricular arrhythmia.

## Complementary monitoring outcome measures

The working group proposed additional heart failure outcome measures that may be used for monitoring patients with heart failure, supplementary to the Level 1 and Level 2 heart failure outcome measures. These were: (i) concurrent presence of atrial fibrillation (AF), classified as first diagnosed AF, paroxysmal, persistent or permanent as defined by ESC guidelines<sup>17</sup>; (ii) N-terminal brain natriuretic peptide levels (NT-proBNP); (iii) estimated glomerular filtration rate (eGFR); (iv) change in left ventricular ejection fraction [i.e. the difference in the left ventricular ejection fraction (%) be measurement using the same imaging modality for calculating left ventricular ejection fraction]; and (v) New York Heart Association class (NYHA) (Figure 2 and Table 1).

## Discussion

Through a structured and collaborative international expert-led process, we have identified and defined a catalogue of hierarchical outcome measures for patients with heart failure, including a complementary suite of monitoring variables. These will be used to measure the clinical outcomes for participants in EuroHeart and have wider utility for randomized clinical trials, prospective observational cohorts, and clinical registries outside EuroHeart.

The identification and optimal clinical management of heart failure is critical, given the increasing prevalence of heart failure and represents a significant health burden across Europe.<sup>3</sup> Recent advances in guideline directed care have been associated with improved symptoms, better quality of life, reduced all-cause mortality, and fewer heart failure readmissions.<sup>18,19</sup> Nonetheless, translating clinical guidelines into real world practice can be challenging. Indeed, previous work has shown that provision of guideline directed care for heart failure is variable between and within the European countries and this can be associated with adverse outcomes.<sup>20,21</sup> One possible cause for this could be variability in defining key outcome measures<sup>4</sup> which can impact heart failure hospitalization rates.<sup>22</sup>

The EuroHeart heart failure outcome measures build upon existing cardiovascular outcomes relevant to patients with heart failure, including those by the ARC.<sup>5,7</sup> There are similarities between these outcomes set: like ARC, all-cause, and cardiovascular-specific mortality were included as mandatory variables within EuroHeart. These are important safety outcomes that are necessary for regulatory approval of device and pharmacological interventions within cardiology.<sup>1</sup> Similarly, all-cause and heart failure hospitalizations were included, and are predictors of mortality and disease severity.<sup>23</sup> They are also important for patients,<sup>23</sup> and health services,<sup>20</sup> and in research are often components of a composite outcome.<sup>24</sup> Left ventricular assist device and heart transplantation likewise was included within both EuroHeart and ARC given their importance in advanced disease management and increasing within Europe.<sup>1,2</sup>

Both organizations provide similar definitions for heart failure hospitalization, with emphasis on the admission to hospital being attributed primarily to heart failure and that the hospitalization must exceed 24 h or cross a calendar day. For worsening heart failure to be defined as an outcome measure, both organizations agree upon the requisite for clinical, biomarker and radiological markers, and augmentation of medical therapy from baseline.

Categorizing and defining heart failure outcomes in hierarchical fashion is a hallmark feature of EuroHeart data standards,<sup>8–11</sup> which

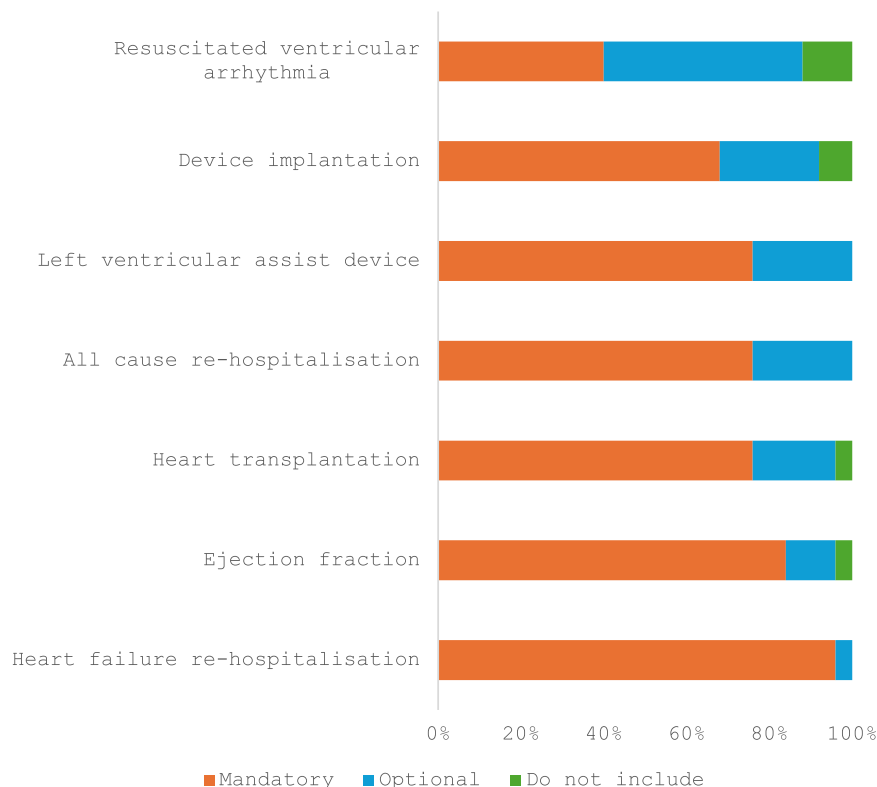
**Table 1** Level 1 and 2 heart failure outcome measures and definitions

Heart failure: Level 1 variables	
All-cause rehospitalization	Unscheduled hospitalization for any cause, defined as a being admitted for more than 24 h or past a calendar day. <sup>a,b</sup>
Heart failure rehospitalization	Hospital admission primarily related to heart failure (HF). Heart failure is a clinical syndrome characterized by typical symptoms (e.g. dyspnoea) and/or signs (e.g. ankle swelling), caused by a structural and/or functional cardiac abnormality (e.g. left ventricular hypertrophy or impairment), and associated with elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion from a cardiogenic origin at rest or with exercise. Unplanned HF hospitalization is defined as a patient requiring an unscheduled hospital admission for a <i>primary diagnosis</i> of HF with a length of stay that either exceeds 24 h or crosses a calendar day (if hospital admission and discharge times are unavailable). To satisfy the criteria for a HF hospitalization, the patient must be admitted primarily for HF with signs, symptoms, and diagnostic testing results identical to those already described above. The patient must also require treatment for HF such as significant augmentation of oral diuretics, intravenous diuretics, or mechanical or surgical intervention for HF. <sup>a-d</sup>
Left ventricular ejection fraction	Let ventricular ejection fraction, ideally measured with echocardiography.
Heart transplantation	Receipt of surgery in which a failing, diseased heart is replaced with a healthier donor heart. <sup>e</sup>
Left ventricular assist device	Implant of a left ventricular assist device (LVAD).
<b>Heart failure: level 2 variables</b>	
Device implantation	Implantation of: <ul style="list-style-type: none"> <li>• Transvenous permanent pacemaker is an electronic device that is implanted in the subcutaneous tissue and gives the heart an electrical stimulation through transvenous wires.</li> <li>• Leadless pacemaker is an electronic device that is implanted directly into the right ventricle.</li> <li>• Transvenous implantable cardioverter defibrillator (ICD) is a device that is used to correct abnormal heartbeat through transvenous wires.</li> <li>• Subcutaneous ICD is an ICD with a pre-sternal lead and is positioned between the latissimus dorsi and serratus muscle within the subcutaneous tissue.</li> <li>• Extravascular ICD is an ICD with a substernal lead and the device in the subcutaneous tissue of the lateral thorax.</li> <li>• Cardiac resynchronization therapy (CRT) device and pacemaker (CRT-P) is defined as a biventricular pacemaker that sends electrical stimulation to both ventricles.</li> <li>• CRT-D is a biventricular pacemaker and defibrillator.<sup>f,g</sup></li> </ul>
Resuscitated ventricular tachyarrhythmia	The patient was successfully resuscitated and had return of spontaneous circulation from a ventricular tachyarrhythmia.
NYHA class	NYHA class I: no limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea. NYHA class II: slight limitation of physical activity. The patient is comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnoea. NYHA class III: marked limitation of physical activity. The patient is comfortable at rest. Less than ordinary activity causes fatigue, palpitations, or dyspnoea. NYHA class IV: inability to carry on any physical activity without discomfort. Heart failure symptoms are present even at rest or with minimal exertion. <sup>c,h</sup>
Change in left ventricular ejection fraction	Left ventricular ejection fraction, ideally measured with echocardiography.
Atrial fibrillation	Patient has a concurrent diagnosis of any type of atrial fibrillation with heart failure. Atrial fibrillation is defined as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. The minimum duration of an ECG tracing of atrial fibrillation required to establish the diagnosis of clinical atrial fibrillation is at least 30 s, or the entire 12-lead ECG. Atrial flutter is defined as a supraventricular tachyarrhythmia with coordinated but overly rapid atrial electrical activation, usually with some degree of atrioventricular (AV) node conduction block. The minimum duration of an ECG tracing of atrial flutter required to establish the diagnosis of clinical atrial flutter is at least 30 s, or the entire 12-lead ECG. <sup>i</sup>
NT-proBNP (ng/L)	Serum NT-proBNP in ng/L.
Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m <sup>2</sup> )	Estimated glomerular filtration rate (eGFR) in mL/min/1.73 m <sup>2</sup> .

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**Figure 1** Distribution of votes for Level 1 and Level 2 heart failure outcome measures. Level 1 variable: Mandatory; Level 2 variable: Optional. A total of twenty-five international heart failure experts voted on the above outcome measures. Device implantation refers to leadless, single and dual chamber pacemakers, subcutaneous, extracardiac and subcutaneous defibrillators and cardiac resynchronisation therapies.

differs from previous work on heart failure outcomes set out by the ARC.<sup>5</sup> Previous studies on heart failure have graded outcomes hierarchically based on their importance to both clinicians and regulators, which reflects an ambition from researchers and regulators to adopt a more pragmatic approach to analysis within research.<sup>25,26</sup>

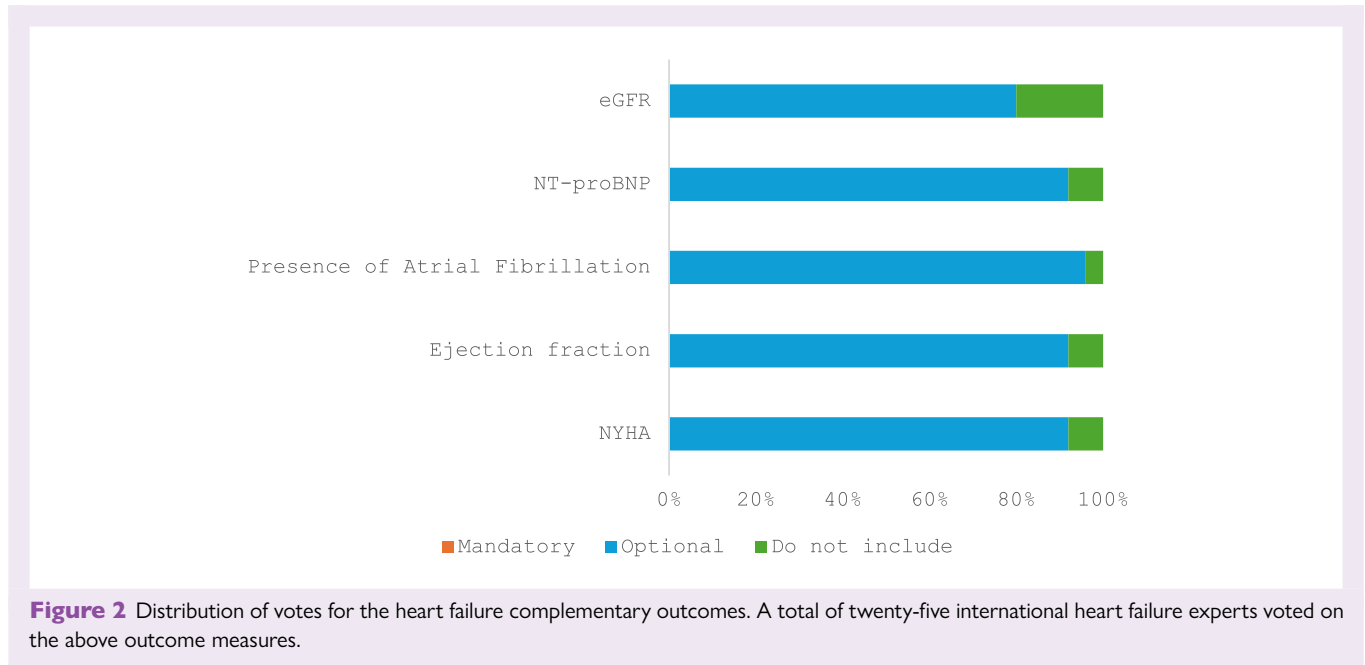
In contrast to ARC, recording left ventricular ejection fraction is a Level 1 outcome in EuroHeart. Current guidelines stratify heart failure according to left ventricular ejection fraction categories due to differences in the benefit of heart failure therapies and the association of worsening outcomes with declining left ventricular ejection fraction.<sup>16,21</sup> However, heart failure with recovery or improvement in ejection fraction is increasingly recognized after implementing guideline-directed therapy and is associated with better long term outcomes.<sup>27</sup> Therefore, the working group agreed that left ventricular ejection fraction should be included both as a stand-alone variable and a variable that can be used for monitoring heart failure.

We also define complementary outcomes that may be used for the longitudinal evaluation of patients with heart failure, beyond traditional 'hard' outcomes.<sup>28</sup> These variables are either mechanistic or surrogate outcomes that, if collected prospectively could form the basis of further research. For example, the Valsartan Heart Failure Trial (Val-HeFT) investigated left ventricular ejection fraction as a surrogate outcome in patients with an ejection fraction below 35% that were randomized to valsartan or placebo. Compared to placebo, patients taking valsartan demonstrated an improvement in left ventric-

ular ejection fraction, improved survival at 12 months and decreased NT-proBNP level.<sup>27</sup> Given the advances in optimal medical therapy in heart failure, monitoring the left ventricular ejection fraction as well as other complementary variables could form the basis of observational research in real world settings. The working group emphasized the need for consistency in the method of measurement, for example serial echocardiogram scans.

The relationship between atrial fibrillation and heart failure is complex, because AF can be either the cause or consequence of heart failure.<sup>29</sup> Studies have shown that catheter ablation in patients with symptomatic paroxysmal or persistent AF in the context of severe left ventricular systolic dysfunction improves outcomes compared to medical therapy alone.<sup>30,31</sup> This highlights the importance of recognizing and considering AF as a potentially therapeutic target in heart failure in contemporary registries or a surrogate marker for deterioration in heart failure.<sup>32</sup> Other outcomes such as eGFR was included given renal impairment is well known to be greatly associated with mortality in patients with heart failure<sup>33</sup> and its prominence as a renal outcome in contemporary heart failure trials.<sup>34,35</sup>

EuroHeart aims to reduce the burden of cardiovascular disease across Europe. The publication of these variables and their definitions will allow us to better understand the outcomes for people with heart failure. They will be integrated with the existing registries,<sup>8-11</sup> and incorporated into the EuroHeart IT platform. This will allow the patterns of clinical care and outcomes of patients to be evaluated



longitudinally across Europe, and provide a platform for international quality improvement to address any unwarranted variation in care,<sup>3,16</sup> and facilitate quality benchmarking.<sup>36</sup> It is therefore important to health care providers, funders, and patients to integrate and optimize provision of guideline-indicated care, whilst monitoring outcomes for patients. By harmonizing data collection from distinct European heart failure registries into an international collaboration together, EuroHeart can better inform and improve cardiovascular care continuously.<sup>37</sup> Integral to this process, however, is the adoption of a catalogue of standardized definitions of cardiovascular outcome measures that allows for research to be more externally generalizable and potentially more efficient in its delivery.<sup>4,37</sup>

We used a robust methodology and harnessed the expertise of a wide range of international experts in heart failure to identify and define these variables. However, we recognize the limitations of this work. Although the outcome measures and their definitions were distilled from a systematic review, the final selection of outcomes were agreed upon by consensus of the international experts within the working group and are therefore subject to selection bias. Nevertheless, the experts that composed the working group were taken from a broad range of countries with a wealth of experience and knowledge within registry work and trials. Furthermore, these definitions were endorsed by the ESC Patient Forum as well as the ESC Committee for Young Cardiovascular Professional that provided an additional layer of validity in our findings. Although the importance of patient reported outcomes measures (PROMs) and experiences (PREMs) is increasingly recognised,<sup>38,39</sup> our remit for this project was limited to clinical outcomes, which was decided by international consensus of the working group. A further project involving PROMs use within heart failure and other cardiovascular conditions is anticipated.

## Conclusion

This document provides a structured, hierarchical catalogue of heart failure outcome measures that are internationally endorsed that includes complementary outcomes. For EuroHeart, this will facilitate quality improvement, prospective observational research, randomized

clinical trials and post-market surveillance of medical devices across Europe.

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