

Key considerations for cost-effectiveness modeling in heart failure with left ventricular ejection fraction ≥ 40%

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Introduction

- The treatment landscape for patients with heart failure (HF) with left ventricular ejection fraction (LVEF) ≥ 40% is expanding, now including the use of sodium/glucose cotransporter 2 inhibitors and, subject to marketing authorisation, finerenone
- This has strengthened the need for recognized methods to assess the cost-effectiveness of new interventions
- This study aimed to synthesize the key challenges for economic modeling in HF with LVEF ≥ 40%-and to propose a conceptual model structure with a global focus
- Two approaches were considered to capture disease progression: the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the New York Heart Association (NYHA) classification

Results

Systematic literature review

- In total, 36 health economic models were identified through the SLR; 94% (34) of these utilized a Markov model
- The results of the models were driven by short-term HF events and cardiovascular death based on trial primary endpoints, with disease progression measured with either the KCCQ or the NYHA classification
- The choice of KCCQ clinical summary score or total symptom score to define health states was aligned with the secondary trial outcome in all models
- Models submitted to National Institute for Health and Care Excellence (NICE) used KCCQ exclusively to inform progression-based health states, which was considered appropriate by NICE
- Models submitted to Canada’s Drug Agency—L’Agence des médicaments du Canada (CDA-AMC) included both KCCQ and NYHA structures, but the KCCQ structure received criticism and the NYHA was preferred
- For dapagliflozin and empagliflozin, renal events were captured in submission models by including acute kidney injury or acute renal failure adverse events. A composite renal outcome was collected in the trial for empagliflozin, but it was not used in the submission model because there was no statistically significant treatment benefit.
- There was no precedence for the inclusion of an end-stage kidney disease (ESKD) health state in NICE or CDA-AMC models

Model concept

- The recommended model structure for HF with LVEF ≥ 40% is presented in **Figure 2**, with explanation of the key model features explained in **Table 1**
- Key challenges associated with the development of this cost-effectiveness model and considerations for future models are presented in **Table 2**

Table 1. Key features of the conceptual model

Key feature	Description/rationale
Model type	
Markov model	This modelling approach has been effectively utilized in previously published models and has been consistently accepted by NICE and CDA-AMC
Health states	
KCCQ or NYHA health states	Flexibility to capture HF disease progression using either KCCQ quartiles or NYHA categories allows the health state definition to be selected based on the preferences of the country HTA body using prespecified trial outcomes. KCCQ quartiles were defined using the baseline distribution of patients’ KCCQ scores in the trial, in line with previous NICE models (dapagliflozin and empagliflozin) ^{1,2}
ESKD health state (exploratory)	The ESKD health state captures patients who experienced a sustained decline in eGFR <15 mL/min per 1.73m ² , initiated dialysis, or underwent renal transplantation. These outcomes were captured as part of the secondary renal composite outcome of FINEARTS-HF. This health state potentially allows for patients with high costs and low utilities to be differentially captured. This approach was validated during an advisory board with experts. The health state is exploratory based on the data constraints of capturing renal decline over the trial period
Non-CV and CV death	CV mortality was captured in the primary composite endpoint of FINEARTS-HF, whereas all-cause mortality was a secondary outcome. Both mortality measures are used to calculate non-CV mortality
Disease-specific events	
HF (HHF and UHFV) events	HF events were included in line with their inclusion within the primary composite outcome of FINEARTS-HF. First and subsequent HF events are captured distinctly to reflect possible differences in the treatment effect on first and subsequent events
Renal events	Flexibility is included in the model to capture renal events using a sustained decrease in eGFR ≥50% (to capture the remaining outcome of the composite renal outcome in FINEARTS-HF) and/or including renal-related adverse events

Abbreviations: CDA-AMC, Canada’s Drug Agency—L’Agence des médicaments du Canada; CV, cardiovascular; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization due to heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; SLR, systematic literature review; UHFV, urgent heart failure visit

References: 1. NICE. TA902: dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction; 2023. <https://www.nice.org.uk/guidance/ta902>; 2. NICE. TA929: empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction; 2023. <https://www.nice.org.uk/guidance/ta929>; 3. Vaduganathan M, Neuen BL, McCausland F, et al. Why has it been challenging to modify kidney disease progression in patients with heart failure? J Am Coll Cardiol. 2024;S0735-1097(24)08242-1; 4. Huo X, et al. New York Heart Association Class and Kansas City Cardiomyopathy Questionnaire in Acute Heart Failure. JAMA Netw Open. 2023 Oct 2;6(10):e2339458; 5. Greene SJ, et al. Comparison of New York Heart Association Class and Patient-Reported Outcomes for Heart Failure With Reduced Ejection Fraction. JAMA Cardiol. 2021 May 1;6(5):522-531.

Acknowledgments: The authors would like to thank Chris Wiggins for his contributions to the systematic literature review that informed this research, and Laura Klein and Karl Read for their editorial assistance.

Methods

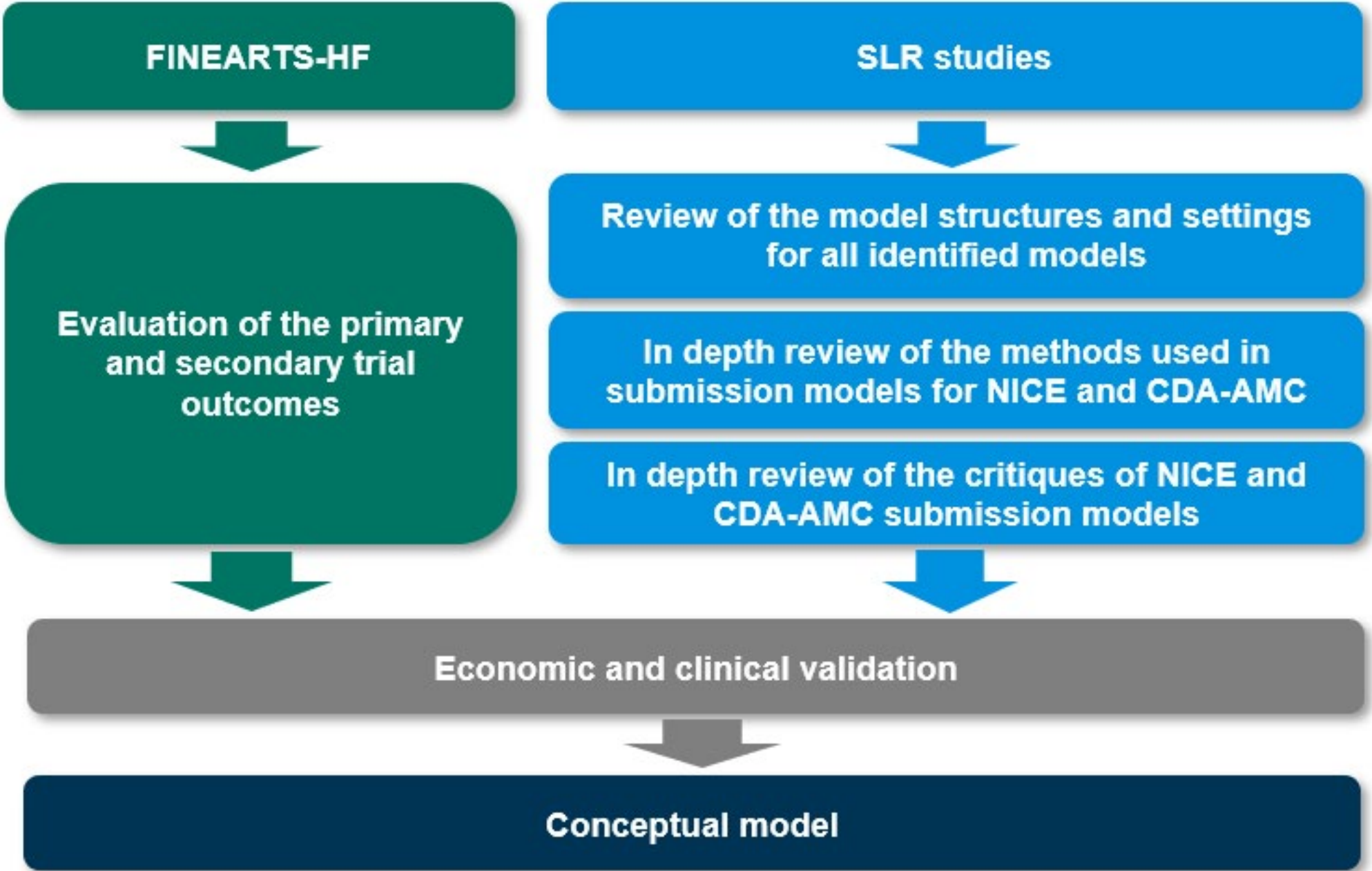
Systematic literature review

- A systematic literature review (SLR) was conducted from 2013 to 14 June 2024 through MEDLINE, Embase, health technology assessment databases, and specified grey literature
- The objective of the SLR was to identify previously conducted health economic models among patients with HF with LVEF ≥40%) and NYHA class II to IV

Model conceptualization

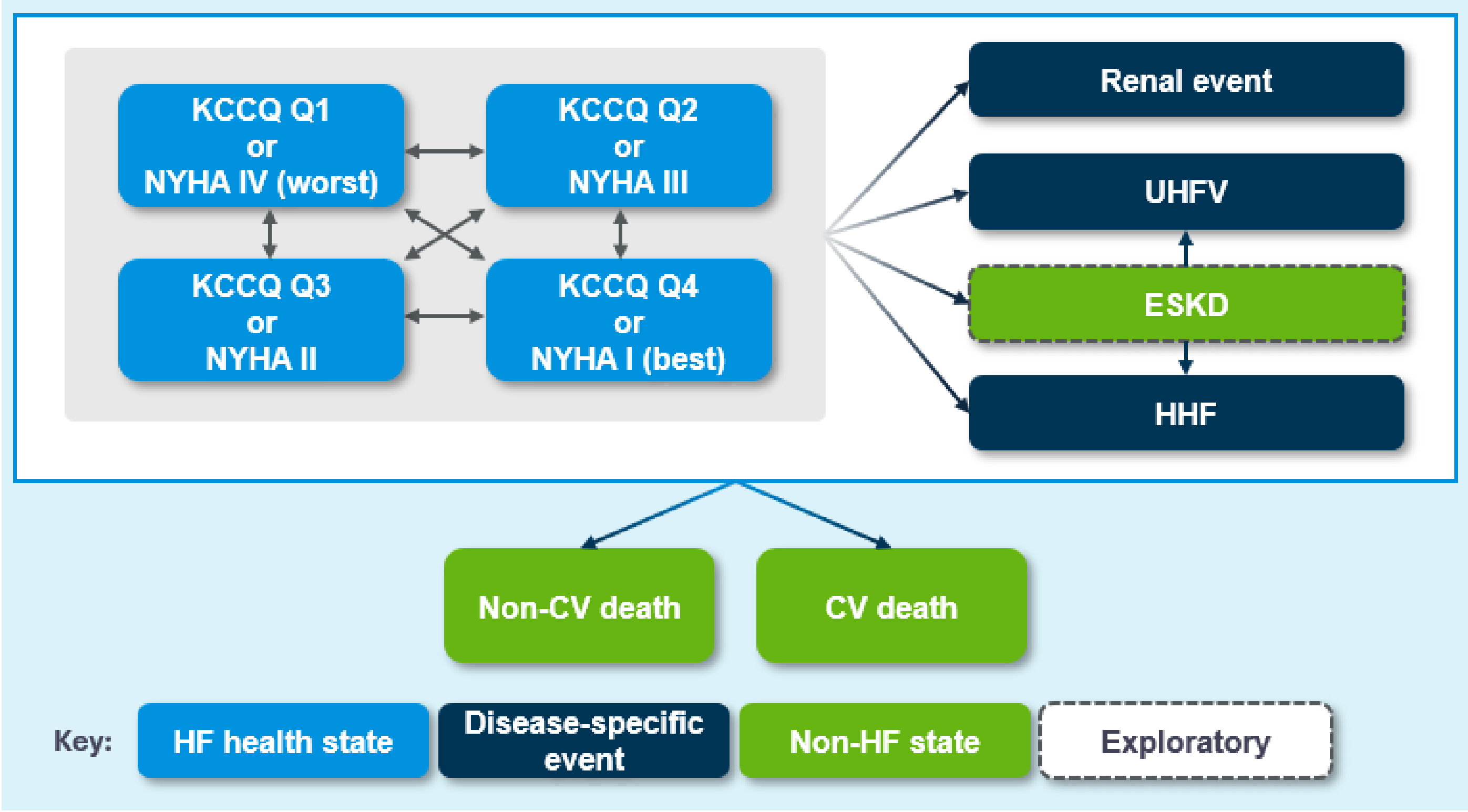
- The conceptual model for HF with LVEF ≥ 40% was based on the studies included in the SLR and FINEARTS-HF, the recent finerenone trial. Economic and clinical expertise was sought to validate the model structure and assumptions. **Figure 1** describes the model conceptualization process

Figure 1. Flow chart of the conceptualization process



Abbreviations: CDA-AMC, Canada’s Drug Agency—L’Agence des médicaments du Canada; NICE, National Institute for Health and Care Excellence; SLR, systematic literature review

Figure 2. Conceptual model for HF with LVEF ≥ 40%



Abbreviations: CV, cardiovascular; ESKD, end-stage kidney disease; HF, heart failure; HF with LVEF ≥ 40%, heart failure with left ventricular ejection fraction of greater than 40%; HHF, hospitalization due to heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; Q, quartile; UHFV, urgent heart failure visit

- In **Figure 2**, the light blue and green health states represent permanent health states. The dark blue health states represent events that occur concurrently to patients’ permanent health state
- Given the global model perspective, the conceptual model was developed to appropriately capture the features expected to be required in different country jurisdictions
- Additionally, the conceptual model was developed with the flexibility to accommodate data from different trials and evidence sources, such as real-world evidence. The model includes the following:
 - Functionality to include or exclude the ESKD health state based on the sufficiency of the renal data available
 - Flexibility for HF events, renal events, and mortality to be linked explicitly to the KCCQ or NYHA health states or directly to the treatment

Table 2. Considerations for future cost-effectiveness models in HF with LVEF ≥ 40%

Key challenges	Description and considerations for future models
Choosing KCCQ or NYHA	Consideration should be given to which measure is more suitable to capture heart failure-related disease progression, taking into account the preference for KCCQ or NYHA in the country jurisdiction and the available data from the clinical trial
Capturing long-term renal outcomes and progression to ESKD	Clinical trials for HF with LVEF ≥ 40% are not designed or equipped to capture the impact of treatment on renal outcomes, creating substantial challenges in accurately capturing renal outcomes in economic models for HF with LVEF ≥ 40%. ³ Previous models have captured renal events as adverse events. This model proposes a more flexible approach, using multiple methods (including an ESKD health state) to explore the impact of renal events and decline on cost-effectiveness. However, these methods remain exploratory because they are subject to the same data limitations. Further data collection and validation of long-term renal outcomes in HF with LVEF ≥ 40% patients is needed to better understand the impact of treatment on renal events over time

Abbreviations: ESKD, end-stage kidney disease; HF, heart failure; HF with LVEF ≥ 40%, heart failure with left ventricular ejection fraction of greater than 40%; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association

Conclusions

- This conceptual model was designed to assess the global cost-effectiveness of emerging therapies in patients with HF with LVEF ≥ 40%
- The model provides a basis for modelling emerging treatments in HF with LVEF ≥ 40% by considering critique of previous models and by introducing flexibility for the definition of disease health states, in addition to exploring novel ways to capture renal outcomes
- However, there is still considerable uncertainty in the long-term renal outcomes of HF with LVEF ≥ 40% patients who are treated with emerging therapies, rendering long term cost-effectiveness estimates uncertain. Future research and data collection in this area would therefore help to improve the robustness of cost-effectiveness estimates for emerging therapies
- Additionally, given the NICE and CDA-AMC specific focus of this research, further study should be done to understand the acceptance of the KCCQ and the NYHA in other national and regional jurisdictions, particularly given the general movement away from using the NYHA due to concerns of its insensitivity to capture changes in patient symptoms^{4,5}

Disclosure: CH, HS and CC are all employees of Putnam, UK, which received funding from Bayer to conduct this research.