SYSTEMATIC REVIEW

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Evaluating Cost-Effectiveness Models for Pharmacologic Interventions in Adults with Heart Failure: A Systematic Literature Review

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Abstract

Background Heart failure (HF) is a well-recognized public health concern and imposes high economic and societal costs. Decision analytic models exist for evaluating the economic ramifications associated with HF. Despite this, studies that appraise these modelling approaches for augmenting best-practice decisions remain scarce.

Objective Our objective was to conduct a systematic literature review (SLR) of published economic models for the management of HF and describe their general and methodological features.

Methods This SLR employed a combination of relevant search terms associated with HF, which were used in a number of databases, including MEDLINE, Embase, the National Health Service Economic Evaluation Database, Cost-Effectiveness Analysis Registry, ScHARR Health Utilities Database and Cochrane Library Database. A number of model features (i.e. model structure, specification, outcomes assessed, scenario and sensitivity analysis, key model drivers) were extracted and subsequently summarized.

Results Of 64 publications retained, a selection of modelling approaches were identified, including Markov ($n = 28$), trial-based analytic ($n = 22$), discrete-event simulation ($n = 6$), survival analytic ($n = 7$) and decision-tree modelling ($n = 1$) approaches. The bulk of publications employed either a cost-utility ($n = 27$) or cost-effectiveness ($n = 36$) analysis and evaluatedmore than one study outcome, which typically included overall costs ($n = 59$), incremental cost-effectiveness ratios ($n = 55$), life-years gained ($n = 48$) and willingness-to-pay thresholds ($n = 37$). Most publications focused on patients with chronic HF ($n = 40$) and used New York Heart Association (NYHA) disease classifications to categorize patients and determine disease severity. Few ($n = 19$) publications documented the use of hospitalization states for modelling patient outcomes and associated costs. A quality assessment of the included publications revealed most articles demonstrated reasonable methodological value.

Conclusions We identified numerous decision analytic modelling approaches for evaluating the cost effectiveness of pharmacologic treatments in HF. A Markov cohort model approach was most commonly used, and most models relied on NYHA classes as a proxy of HF severity, disease progression and prognosis.

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Key Points for Decision Makers

A more comprehensive understanding of the economic models that exist for the management of heart failure is needed.

This systematic literature review identified numerous publications that documented the various decision analytic modelling approaches, with a Markov cohort model the approach most commonly used to assess economic and societal implications in the heart failure setting.

The majority of included studies employed New York Heart Association (NYHA) disease classifications to establish disease severity for modelling purposes.

Further investigation is warranted to help underline the utility of reliable candidates of disease progression and their use in decision analytic models to provide a more precise estimate of the costs incurred while also guiding clinical decision making in the management of heart failure.

1 Introduction

Heart failure (HF) has rapidly become a global health concern, with an estimated 26 million people living with this chronic health condition [1–4]. With the bulk of post-industrial nations experiencing a demographic shift, owing mostly to a dramatic growth in the aging population [5], it is not surprising this epidemiologic transition is expected to lead to an increase in the global prevalence and incidence of HF in coming years [2, 6]. Numerous phenotypes for HF exist and are often defined by left-ventricular ejection fraction function [7]. These typically encompass HF with reduced ejection fraction (HFrEF), which reflects systolic dysfunction indicative of impaired contraction in the left ventricle, and HF with preserved ejection fraction (HFpEF), characterized by abnormal relaxation of the left ventricle [8].

Few treatments specific to patients with HFpEF are available (e.g. diuretics, revascularization for ischaemia, blood pressure control), though evidence indicating improvements in survival based on these pharmacologic therapies within this patient subset is somewhat lacking. A number of pharmacologic treatments are also available for those with HFrEF, including (but not limited to) angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin-II receptor antagonists, mineralocorticoid receptor antagonists and angiotensin receptor inhibitors. Two additional treatments that have recently gained approval for use in the management of HFrEF include sacubitril/valsartan, a first-in-class

angiotensin receptor neprilysin inhibitor, and ivabradine, a hyperpolarization-activated cyclic nucleotide-gated channel blocker. In light of these newly approved treatments and those that currently exist in the HF setting, understanding of the economic implications relative to the cost-effectiveness profiles of these pharmacologic regimens needs to improve.

In 2011, Goehler et al. [9] performed a systematic literature review (SLR) of the extant economic modelling approaches available for HF in an effort to examine their usefulness for evaluating health technologies in HF. Several detailed decision models were identified for assessing the various HF technologies, though the bulk of these models differed considerably according to their modelling complexity, approach and underlying assumptions [9]. The majority of these models further relied on New York Heart Association (NYHA) functional classifications as a proxy of disease extent and severity [9].

We conducted an SLR to evaluate published economic models on pharmacologic treatments that reported on health economic outcomes among adults with HF. In particular, we sought to provide an update of the available literature following the article by Goehler et al. [9], which examined data up to June 2010. We further wanted to examine in detail the core modelling specifications and structures as well as key features that were documented in more recently published economic models in the HF patient population.

2 Methods

2.1 Literature Review

We performed an SLR and identified relevant citations by searching a number of literature databases, including MEDLINE, Embase, the National Health Service Economic Evaluation Database, the Cost-Effectiveness Analysis Registry, the ScHARR Health Utilities Database and Cochrane Library Database using key search terms (Electronic Supplementary Material [ESM] 1). To identify the most up-to-date studies pertinent to current clinical practice, the present SLR aimed to include only data published since 1997 (i.e. up until November 2017). The search strategies were confined to all cost-effectiveness studies conducted in human patients with HF. Principal and practical guidelines advocated by the Cochrane Collaboration Handbook [10] and the Centre for Reviews and Dissemination [11] were also employed (where relevant) in an effort to limit any risk of bias and error.

2.2 Study Eligibility

This SLR utilized the PICOS (Population, Intervention, Comparator, Outcomes, and Study) design criteria for defining relevant inclusion and exclusion terms. In brief, studies

were retained for further analysis if they included adult patients who had HF and were aged ≥ 18 years, provided details related to a pharmacologic treatment for HF and documented any mathematical model of cost-effectiveness specific to patients with HF who received a pharmacologic treatment. We subsequently excluded studies that were observational, experimental, preclinical, pharmacokinetic or pharmacodynamic in nature; a case report or case series (ten or fewer patients); a letter to the editor, opinion piece or review article; or published before 1997.

2.3 Study Selection

The titles and abstracts of all retrieved search records were screened to identify any relevant references for inclusion (as per the National Institute for Health and Care Excellence methods guide [12]). Full publications for all retained records were subsequently examined in detail, with a final list of relevant studies compiled thereafter. Both the search and the screening phases were independently conducted by two trained investigators (AB and FON). Any disagreements were resolved through further discussion or by consensus with a senior investigator (GDT). Figure 1 presents a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram displaying the number of retained studies and a list of excluded studies. In an effort to evaluate the quality

of models retrieved from the study selection process, we reviewed good modelling practice methods and employed the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement checklist [13, 14].

2.4 Data Summary

Data abstracted from the retained publications included study design and population characteristics, model structure and specifications, and specific model outcomes, which are summarized according to the specific research questions, "What is the current availability of cost-effectiveness models for pharmacologic treatments in HF?"; "What are the core model specifications (e.g. types and structures, etc.) of previously published health economic models in HF?"; and "What are the key drivers derived from previously conducted cost-effectiveness analyses in HF?" Data are summarized using text where relevant, or displayed in accompanying tables and figures, as necessary. A brief summary describing the quality of studies based on the CHEERS statement checklist [13] for each research question is also reported. This method aimed to address the appropriateness of the modelling approaches and structures, the quality of reporting, and possible limitations that might have impaired the validity and generalizability of the study findings.

Fig. 1 Flow chart displaying the number of publications included as well as the number of publications that were excluded, with reasons
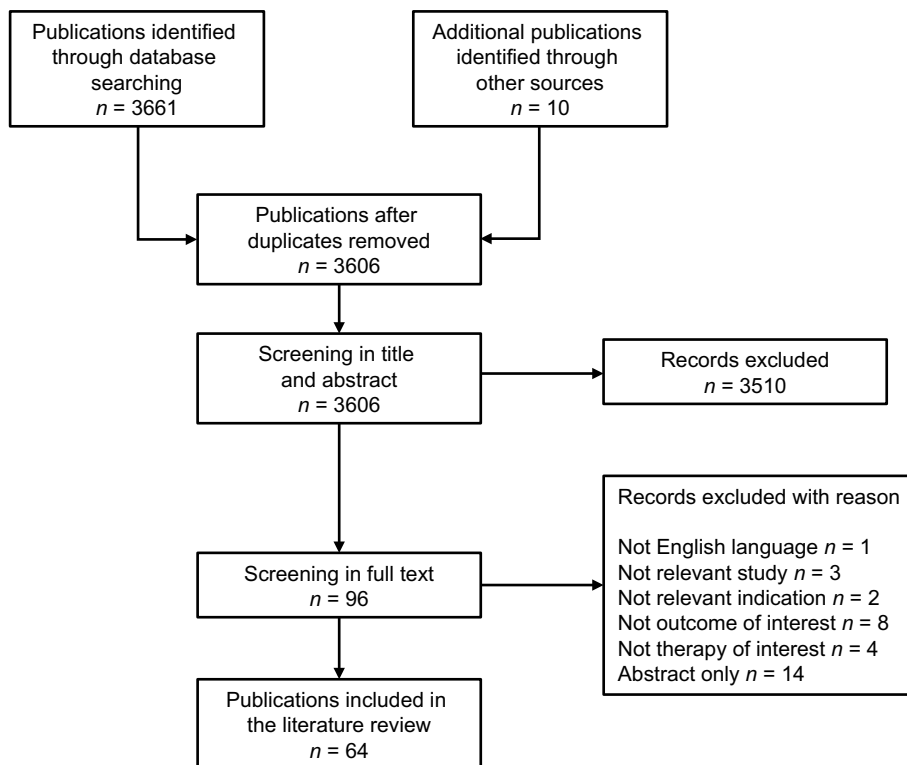
3 Results

3.1 Literature Search

The original SLR search yielded a total of 3671 citations. Of these, 65 were duplicates that were subsequently removed. A further 3510 articles failed to meet the inclusion criteria based on their titles and abstracts at screening, and an additional 32 publications were excluded for specific reasons as outlined in Fig. 1.

3.2 Description of Studies

Overall, 64 articles were suitable for inclusion. The ages of the patient populations ranged from 20 to 93 years. The proportion of men within each patient cohort also varied, with a minimum and maximum of 22 and 89% documented across publications. Altogether, the geographic regions of the populations in the 64 publications encompassed 15 different countries: the most commonly identified nations included the USA ($n = 16$ [25%]) [15–30], the UK ($n = 16$ [25%]) [31–46] and Canada ($n = 5$ [8%]) [24, 47–50]. A total of 48 (75%) publications included in this review reported their source of funding [15, 16, 18, 22, 24–35, 37–42, 44, 45, 47, 48, 50–71]. Of the included publications, the most commonly reported pharmacologic treatments administered to patients with HF included eplerenone ($n = 12$ [19%]), ramipril ($n = 11$ [17%]) enalapril ($n = 8$ [13%]) and ivabradine ($n = 6$ [9%]).

3.3 Overview of Economic Model Structure and Specifications

3.3.1 Markov Model Approach

Most of the publications provided reasonable details in relation to the types of modelling approaches employed (Table 1). The most common modelling approaches used included a Markov cohort model type ($n = 28$ [41%]) [15, 17, 19, 22, 23, 26, 27, 32–34, 38–40, 44, 48, 49, 51, 52, 58, 66–69, 72–76]. Given the versatility of the Markov model approach in adopting different types of health states patients can potentially experience, this method was further categorized into health state classifications. These typically included an "alive or dead" state [17, 19, 32, 33, 39, 51, 67], NYHA disease classification [15, 23, 52, 58, 68], cardiovascular events [22, 26, 27, 38, 44, 48, 66, 72, 74–76] and hospitalization states [27, 49, 66, 72, 74–76]. Specific Markov model structure was unclear in four studies [34, 40, 69, 73]. Seven studies focused on a two-state Markov approach based around the "alive" and "dead" states [17,

19, 32, 33, 39, 51, 67]. Five studies that employed a Markov cohort model approach used the NYHA disease classification system [15, 23, 52, 58, 68]. Three of these studies [23, 52, 58] incorporated five health states: one for each NYHA class and a separate one for death. Another publication [68] used four health states according to each of the NYHA classifications to determine health states. A number of methods were employed for modelling according to the NYHA disease classification system, which were based on classifying patients according to their level of HF severity. Some studies employed a constant movement of patients (i.e. belonging to the same health state within the study timeframe) [23, 52], whereas others provided a greater level of detail surrounding transition probabilities [68]. NYHA classifications were generally derived from trial data or from secondary sources when data were unavailable, which may have influenced the estimation of patient ratios within respective NYHA clusters.

Within nine articles that used the Markov model method, HF was often modelled alongside other cardiovascular health states [15, 27, 32, 34, 38, 66, 72, 74, 76]. Aside from HF, other cardiovascular conditions concurrently modelled included myocardial infarction and post cardiovascular events [34, 76]. Few publications employed hospitalization states with hazard ratios [75] or rate ratios [27] that were applied to transition probabilities in an effort to account for between-treatment effects. One publication [27] adjusted for mortality to increase with age and calibrated mortality rates over the course of the trial to reflect changing probabilities as patients progressed through the model with increasing age. Shorter timeframes of approximately 10 years were implemented in some publications [74], whereas others adopted a lifetime horizon [27, 38, 66, 75, 76]. One study used a random effects meta-analysis to examine the importance of hospitalization as a health state, which was dependent on the number of hospitalizations and death [49]. Other studies associated hospitalization with mortality by implementing survival methods or lifetime tables, linked either directly or independently to hospitalization as a central state of health [75].

3.3.2 Trial-Based Analytic Approach and Event Simulation

A number of the retrieved articles followed a trial-based analytic approach ($n = 22$ [34%]) [16, 18, 21, 24, 25, 28–30, 36, 37, 42, 43, 45, 46, 54–57, 59–62]. Some studies [30] analysed clinical trial data with fractional polynomials and piecewise regression to obtain survival hazard functions over time, adjusting for patient characteristics, whereas others [43] employed the life-table method to calculate a gain in life-years, estimating the probability of death using the relative risk of treatment versus placebo from trial data. Certain publications [46, 56] extrapolated clinical trial data within

Table 1 Overview of economic models reported in publications

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Erhardt et al. [63] Sweden	NYHA	Unclear	*Core model/adaptation:* Adaptation; *Study type:* Cost effectiveness; *Model type:* 'Real-world' partition survival analysis; *Perspective:* Third-party payer; *Time horizon:* 3.8 years; *Discount rate:* 5% for both costs and health outcomes	LYG, costs, ICERs, WTP	OWSA; the key model drivers were varied to establish their effect on the outcome	Hospital costs; Number of rehospitalizations for HF
Schadlich et al. [70] Germany	NYHA	Unclear	*Core model/adaptation:* Core model; *Study type:* Cost effectiveness; *Model type:* Partition survival model; *Perspective:* Payer; *Time horizon:* 3.8 years; *Discount rate:* 5% for costs	LYG, costs, ICERs	DSA; Weibull estimation of survival probability and LYG	Treatment duration; Number of rehospitalizations per patient; Inpatient treatment for decompensated HF
Anderson et al. [53] South Africa	NYHA	Unclear	*Core model/adaptation:* Adaptation; *Study type:* Cost utility; *Model type:* Partition survival model; *Perspective:* Third-party payer; *Time horizon:* 3.8 years; *Discount rate:* 0%, 5% and 10% for costs. 5% for health outcomes	LYG, costs, ICERs	Analysis established best- and worst-case scenarios	Treatment duration
Hart et al. [65] Spain	NYHA	Unclear	*Core model/adaptation:* Adaptation; *Study type:* Cost effectiveness; *Model type:* Area under the survival curve analysis of survival and rehospitalization probability; *Perspective:* Payer; *Time horizon:* 3.8 years; *Discount rate:* 6% for both costs and health outcomes	LYG, costs, ICERs	Establishes the effect of additional costs and non-hospital costs on the ICER for the intervention	Treatment duration; Length of hospital stay

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Ademi et al. [51] Australia	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Markov model with four transition states with 1-year cycle lengths *Perspective:* Payer *Time horizon:* 10 years *Discount rate:* 5% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Univariate analysis	Efficacy measures (predominantly those regarding CV mortality) Drug cost
Ademi et al. [52] Australia	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Five-health-state Markov model with 1-year cycle lengths *Perspective:* Payer *Time horizon:* 10 years *Discount rate:* 5% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Scenario analysis	Number of hospitalizations
Lee et al. [41] UK and Spain	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Discrete-event simulation model determining risk of hospitalization for HF, new-onset of AF, AEs, treatment discontinuation, and mortality *Perspective:* Payers *Time horizon:* Lifetime *Discount rate:* 3.5% for health outcomes for the UK model and 3% for the Spanish model	QALYs, LYG, costs, ICERs, WTP	DSA and PSA	Drug cost Cost of disease management and monitoring Number of hospitalizations

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Thanh et al. [50] Canada	Unclear	Unclear	*Core model/adaptation:* Adaptation *Study type:* Cost utility *Model type:* Discrete-event simulation model of hospitalizations, AEs, AF, device implantation, discontinuation, and death *Perspective:* Healthcare *Time horizon:* Lifetime *Discount rate:* 3% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Scenario analysis and OWSA	Drug cost Scale parameters of Weibull distributions estimating time to event of device implantation CV hospitalization for patients receiving intervention
CADTH [47] Canada	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Discrete-event simulation model of hospitalization, AEs, discontinuation, and AF, resulting in either mortality or device implantation *Perspective:* Ministry of Health (governmental) *Time horizon:* Lifetime *Discount rate:* 5% for both costs and health outcomes	QALYs, LYG, costs, ICERs	DSA and PSA	Not reported
SMC [35] Scotland	Unclear	Unclear	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Discrete-event simulation model *Perspective:* NHS *Time horizon:* Lifetime *Discount rate:* Not reported	QALYs, costs, ICERs	Scenario analysis	Mortality

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
AWMSG [31] Wales	Unclear	Unclear	*Core model/adaptation:* Core model; *Study type:* Cost utility; *Model type:* Discrete-event simulation model; *Perspective:* NHS; *Time horizon:* Lifetime; *Discount rate:* 3.5% on both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	OWSA	Distribution parameters for CV mortality; Number of HF hospitalizations; Utility decrements associated with age
Weintraub et al. [29] USA	Unclear	Unclear	*Core model/adaptation:* Core model; *Study type:* Cost utility; *Model type:* Trial- and registry-based analysis; *Perspective:* Societal; *Time horizon:* 16 months; *Discount rate:* 3% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Bootstrap analysis	Age; Use of blocker treatment after AMI; Use of life-saving interventions
de Pouvourville et al. [61] France	Unclear	Unclear	*Core model/adaptation:* Adaptation; *Study type:* Cost utility; *Model type:* Trial- and registry-based analysis; *Perspective:* Partially societal; *Time horizon:* 16 months; *Discount rate:* 5% for both costs and health outcomes	QALYs, LYG, costs, ICERs	PSA	Long-term survival
Zhang et al. [30] USA	Unclear	Unclear	*Core model/adaptation:* Adaptation; *Study type:* Cost utility; *Model type:* Trial-based analysis; *Perspective:* Societal; *Time horizon:* 16 months; *Discount rate:* 3% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Not reported	Post-trial costs

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
McKenna et al. [44] UK	Unclear	Unclear	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Markov model with 1-year cycle lengths *Perspective:* NHS *Time horizon:* Lifetime *Discount rate:* 3.5% for both costs and health outcomes	QALYs, costs, ICERs, WTP	Sensitivity analysis was not specified but established key model drivers	Treatment efficacy
Ollendorf et al. [25] USA	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* Payers *Time horizon:* Lifetime *Discount rate:* Not reported	QALYs, costs, ICERs, WTP, VBP	Sensitivity analysis was not specified but established key model drivers	Assumed duration of improved outcomes with the intervention (sacubitril/valsartan)
King et al. [23] USA	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Markov model using NYHA disease classification and death to establish health states with 3-month cycle lengths *Perspective:* Third-party payer *Time horizon:* Lifetime *Discount rate:* 3% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	DSA and PSA	Probability of CV death
Sandhu et al. [27] USA	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Markov model of hospitalization reasons, ED visit for HF and death, with 1-month cycle lengths *Perspective:* Societal *Time horizon:* Lifetime *Discount rate:* 3% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Sensitivity analysis was not specified but established key model drivers	Survival

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Ramos et al. [69] Netherlands	NYHA	Chronic	*Core model/adaptation:* Adaptation; *Study type:* Cost utility; *Model type:* Markov model with a half-cycle correction and 1-month cycle lengths; *Perspective:* Societal; *Time horizon:* Lifetime; *Discount rate:* 4% for costs and 1.5% for health outcomes	QALYs, LYG, costs, ICERs, WTP	Scenario analysis	Hospitalization; Mortality
van der Pol et al. [75] Netherlands	NYHA	Chronic	*Core model/adaptation:* Core model; *Study type:* Cost utility; *Model type:* Markov model with four health states and 1-month cycle lengths; *Perspective:* Healthcare payer; *Time horizon:* Lifetime; *Discount rate:* 4% for costs and 1.5% for health outcomes	QALYs, LYG, costs, ICERs, WTP, VBP	Univariate analysis	Risk of death; Utility of patients who are not hospitalized; QALYs
NICE [32] England	NYHA	Chronic	*Core model/adaptation:* Core model; *Study type:* Cost utility; *Model type:* Markov model with a half-cycle correction and 1-month cycle lengths; *Perspective:* NHS; *Time horizon:* Lifetime; *Discount rate:* 3.5% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Sensitivity analysis was not specified but established key model drivers	Treatment effect; The constant term in the statistical model of all-cause mortality
SMC [33] Scotland	NYHA	Chronic	*Core model/adaptation:* Core model; *Study type:* Cost utility; *Model type:* Two-state, alive and dead, Markov model; *Perspective:* NHS; *Time horizon:* Lifetime; *Discount rate:* Not reported	QALYs, costs, ICERs	A range of sensitivity analyses and scenario analysis	Survival estimates; Duration of treatment effect; Time horizon

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
ICER [15] USA	NYHA	Chronic	*Core model/adaptation:* Core model. *Study type:* Cost utility. *Model type:* Markov model with 1-month cycle lengths. *Perspective:* Third-party payer. *Time horizon:* Lifetime. *Discount rate:* 3% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP, VBP	Sensitivity analysis was not specified but established key model drivers	Duration of treatment effect. Price of drug
Varney [46] UK	NYHA	Chronic	*Core model/adaptation:* Core model. *Study type:* Cost effectiveness. *Model type:* Trial-based analysis. *Perspective:* NHS. *Time horizon:* 5 years. *Discount rate:* 6% for both costs and health outcomes	LYG, costs, ICERs	Sensitivity analysis was not specified but established key model drivers	Annual rate of hospitalization
Ekman et al. [62] Sweden	NYHA	Chronic	*Core model/adaptation:* Core model. *Study type:* Cost effectiveness. *Model type:* Trial-based analysis. *Perspective:* Societal. *Time horizon:* 2.3 years. *Discount rate:* 3% for both costs and health outcomes. Costs occurring within the context of the clinical trial have not been discounted	LYG, costs, ICERs, WTP	OWSA	Cost of life-years gained
Polistena et al. [73] Italy	NYHA	Chronic	*Core model/adaptation:* Adaptation. *Study type:* Cost effectiveness. *Model type:* Markov model. *Perspective:* NHS. *Time horizon and discount rate:* Not reported	QALYs, LYG, costs, ICERs, WTP	PSA	Not reported

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Kansal et al. [22] USA	NYHA	Chronic	*Core model/adaptation:* Core model; *Study type:* Cost utility; *Model type:* Markov model with 1-month cycle lengths; *Perspective:* Payer; *Time horizon:* 10 years; *Discount rate:* Not reported	QALYs, LYG, costs, ICERs, WTP	PSA	Time horizon; Treatment effect on HF hospitalization and mortality
Edwards et al. [39] England	NYHA	Chronic	*Core model/adaptation:* Core model; *Study type:* Cost utility; *Model type:* Alive and dead Markov model, with half-cycle correction and 1-month cycle lengths; *Perspective:* NHS; *Time horizon:* Lifetime; *Discount rate:* 3.5% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	DSA and PSA	Treatment effect
SMC [34] Scotland	NYHA	Chronic	*Core model/adaptation:* Core model; *Study type:* Cost utility; *Model type:* Markov model; *Perspective:* NHS; *Time horizon:* Lifetime; *Discount rate:* Not reported	QALYs, costs, ICERs	Not reported	Not reported
Backhouse et al. [36] UK	Unclear	Chronic	*Core model/adaptation:* Core model; *Study type:* Cost effectiveness; *Model type:* Trial-based analysis; *Perspective:* NHS; *Time horizon:* 5 years; *Discount rate:* 6% for both costs and health outcomes	LYG, costs, ICERs	Sensitivity analysis was not specified but established key model drivers	Long-term survival

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Malik et al. [43] UK	Unclear	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness and cost consequence *Model type:* Trial-based analysis *Perspective:* NHS *Time horizon:* Lifetime *Discount rate:* 6% for both costs and health outcomes	ICERs, WTP	OWSA	Cost of drug
Lamy et al. [24] USA and Canada	Unclear	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* Third-party payer *Time horizon:* 4.5 years *Discount rate:* 3% for costs	Costs, ICERs, WTP	Not reported	Not reported
Bjorholt et al. [54] Sweden	Unclear	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* Societal *Time horizon:* 4.5 years *Discount rate:* 3% for both costs and health outcomes	LYG, costs, ICERs, WTP	Not specified	Not reported
Beard et al. [37] UK	Unclear	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* NHS *Time horizon:* 5 years *Discount rate:* 6% for both costs and health outcomes	LYG, costs, ICERs, WTP	Not specified	Not reported

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Grover et al. [48] Canada	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Markov model with 1-year cycle lengths *Perspective:* NHS *Time horizon:* Lifetime *Discount rate:* 3% for both costs and health outcomes	QALYs, LYG, ICERs	Not reported	Long-term survival
Colombo et al. [57] Italy	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trials-based analysis *Perspective:* NHS *Time horizon:* 2 years *Discount rate:* 3% for both costs and health outcomes	LYG, costs, ICERs	Sensitivity analysis was not specified but established key model drivers	Hospital admissions
Angus et al. [16] USA	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* Societal *Time horizon:* 18 months *Discount rate:* 3% for both costs and health outcomes	LYG, costs, ICERs, WTP	Sensitivity analysis was not specified but established key model drivers	Cost of drug Cost of hospital stay
Borghi et al. [55] multi-country	Killip	Mixed	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* Third-party payer *Time horizon:* 12 months *Discount rate:* Not reported	Costs, ICERs, WTP	Not specified	Not reported

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Pradelli et al. [68] Italy	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Markov model using NYHA disease classification and death to establish health states with 1-month cycle lengths *Perspective:* NHS *Time horizon:* 10 years *Discount rate:* 3.5% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Sensitivity analysis was not specified but established key model drivers	Hospitalization
Lorgelly et al. [42] UK	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* NHS *Time horizon:* 3 years *Discount rate:* 3.5% for both costs and health outcomes	LYG, costs, ICERs, WTP	Sensitivity analysis was not specified but established key model drivers	Cost of statin treatment, hospitalizations and procedures for major CV events
de Lissovoy et al. [18] USA	NYHA	Acute	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* Hospital *Time horizon:* Lifetime *Discount rate:* Not reported	LYG, costs, ICERs	Sensitivity analysis was not specified but established key model drivers	Cost of treatment Long-term survival
de Lissovoy et al. [60] multi-country	Unclear	Acute	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trials-based analysis *Perspective:* Third-party payer *Time horizon:* Lifetime *Discount rate:* Not reported	Costs, ICERs, WTP	Bootstrap analysis	Long-term survival

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Cleland et al. [56] multi-country	Unclear	Mixed	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trials-based analysis *Perspective:* Third-party payer *Time horizon:* 4 years *Discount rate:* 3% for both costs and health outcomes	LYG, ICERs, WTP	Sensitivity analysis was not specified but established key model drivers	Long-term survival Hospitalization
Sculpher et al. [45] UK	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* NHS *Time horizon:* 4 years *Discount rate:* 6% for costs and 2% for health outcomes	LYG, costs, ICERs, WTP	Sensitivity analysis was not specified but established key model drivers	Risk of death Hospitalization
Delea et al. [19] USA	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Six-state Markov model with 1-month cycle lengths *Perspective:* Not reported *Time horizon:* Lifetime *Discount rate:* 3% for both costs and health outcomes	LYG, costs, ICERs	Not specified	Not reported
Rosen et al. [26] USA	Unclear	Chronic	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Markov model with 1-year cycle lengths *Perspective:* Payer *Time horizon:* Lifetime *Discount rate:* 3% for both costs and health outcomes	LYG, costs, ICERs, WTP	OWSA	Hazard ratios for RCA, CHF, and MI

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Inomata et al. [66] Japan	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Four-state Markov model with 1-month cycle length *Perspective:* Payer *Time horizon:* Lifetime *Discount rate:* 3% for both costs and health outcomes	LYG, costs	Not specified	Not reported
Gregory et al. [21] USA	Unclear	Unclear	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial- and registry-based data analyses *Perspective:* Not reported *Time horizon:* Lifetime *Discount rate:* 5% for both costs and health outcomes	LYG, costs, ICERs	Sensitivity analysis was not specified but established key model drivers	Price of drug Relative mortality risk
Barry [72] Ireland	Unclear	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Markov model *Perspective:* Healthcare *Time horizon:* 10 years *Discount rate:* 5% for costs and 1.5% for health outcomes	ICERs	OWSA	Price of drug
Cowper et al. [58] multi-country	Unclear	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Markov model using NYHA disease classification and death to establish health states with 6-month cycle lengths *Perspective:* Societal, Medicare, hospital, physician, and patient *Time horizon:* 5 years *Discount rate:* 3% for both costs and health outcomes	Costs	OWSA	Clinical efficacy of beta-blockers

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Glick et al. [64] multi-country	NYHA	Mixed	*Core model/adaptation:* Core model *Study type:* Cost utility *Model type:* Decision analytic model *Perspective:* Payers *Time horizon:* Not reported *Discount rate:* 3% for both costs and health outcomes	QALYs, costs	OWSA	HF classification
Caro et al. [77] multi-country	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Discrete-event simulation *Perspective:* Payer *Time horizon:* 2 years *Discount rate:* 3% for both health costs and outcomes	Costs	Not specified	Not reported
Gerhard et al. [20] USA	NYHA	Unclear	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Decision-tree model *Perspective:* Not reported *Time horizon:* 6 months *Discount rate:* Not reported	LYG, costs, ICERs	Not reported	Not reported
Dasbach et al. [59] multi-country	NYHA	Unclear	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Trial-based analysis *Perspective:* Third-party payer *Time horizon:* Not reported *Discount rate:* 3% for both costs and health outcomes	Costs, WTP	Sensitivity analysis was not specified but established key model drivers	Overall survival Resource data

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Levy et al. [49] Canada	Unclear	Unclear	*Core model/adaptation:* Adaptation; *Study type:* Cost effectiveness; *Model type:* 5-state Markov model with 1-month cycle lengths; *Perspective:* Payer; *Time horizon:* 20 years; *Discount rate:* 3% for both costs and health outcomes	LYG, costs, ICERs	PSA	Discount rate; Choice of out-of-hospital mortality rate
McMurray et al. [78] NA	Unclear	Unclear	*Core model/adaptation:* Not reported; *Study type:* Cost effectiveness; *Model type:* Survival analysis; *Perspective and time horizon:* Not reported; *Discount rate:* 6% for both costs and health outcomes	LYG, costs, ICERs	Not specified	Not reported
Van Genugten et al. [71] Netherlands	Unclear	Unclear	*Core model/adaptation:* Core model; *Study type:* Cost effectiveness; *Model type:* Survival analysis; *Perspective:* Not reported; *Time horizon:* Lifetime; *Discount rate:* 4% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	OWSA and PSA	Not reported
Cowie et al. [38] UK	NYHA	Chronic	*Core model/adaptation:* Core model; *Study type:* Cost utility; *Model type:* Markov model with 1-year cycle lengths; *Perspective:* Payer; *Time horizon:* Lifetime; *Discount rate:* 4% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Not specified	Not reported

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Tilson et al. [74] Ireland	Unclear	Unclear	*Core model/adaptation:* Adaptation; *Study type:* Cost effectiveness; *Model type:* Markov model; *Perspective:* Payer; *Time horizon:* 10 years; *Discount rate:* 5% for both costs and health outcomes	ICERs	Not specified	Not reported
Kourlaba et al. [67] Greece	NYHA	Chronic	*Core model/adaptation:* Adaptation; *Study type:* Cost effectiveness; *Model type:* Two-state, alive and dead, Markov model; *Perspective:* Third-party payer; *Time horizon:* Lifetime; *Discount rate:* 3.5% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	Scenario analysis	Not reported
Banka et al. [17] USA	NYHA	Unclear	*Core model/adaptation:* Not reported; *Study type:* Cost effectiveness; *Model type:* Two-state, alive and dead, Markov model; *Perspective:* Single payer and healthcare; *Time horizon:* Lifetime; *Discount rate:* 3.5% for both costs and health outcomes	QALYs, LYG, costs, ICERs	Sensitivity analysis was not specified but established key model drivers	Probability of death; Hospitalization; Total costs; Length of HF treatment's risk reduction on mortality and hospitalization
Yao et al. [76] multi-country	NYHA	Chronic	*Core model/adaptation:* Core model; *Study type:* Cost effectiveness; *Model type:* Markov model with 1-month cycle lengths; *Perspective:* Payer, NHS; *Time horizon:* Lifetime; *Discount rate:* 4% for both costs and health outcomes	QALYs, LYG, costs, ICERs, VBP	Scenario analysis	Not reported

Table 1 (continued)

Study, country	Disease classification system	HF type	Model specifications	Modelling outcomes assessed	Type of scenario/sensitivity analysis	Key model drivers
Griffiths et al. [40] UK	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost effectiveness *Model type:* Two-state Markov model, with 1-month cycle lengths *Perspective:* NHS *Time horizon:* Lifetime *Discount rate:* 4% for both costs and health outcomes	QALYs, LYG, costs, ICERs, WTP	DSA and PSA	Treatment effect
Vera-Llonch et al. [28] USA	NYHA	Chronic	*Core model/adaptation:* Core model *Study type:* Cost minimization *Model type:* Trial-based analysis *Perspective, time horizon, discount rate:* NA	Costs	Not specified	Not reported

AE adverse event, *AF* atrial fibrillation, *AMI* acute myocardial infarction, *CHF* chronic heart failure, *CV* cardiovascular, *DSA* deterministic sensitivity analysis, *ED* emergency department, *HF* heart failure, *ICER* incremental cost-effectiveness ratio, *LYG* life-years gained, *MI* myocardial infarction, *NA* not applicable, *NHS* National Health Service, *NYHA* New York Heart Association, *OWSA* one-way sensitivity analysis, *PSA* probabilistic sensitivity analysis, *QALYs* quality-adjusted life-years, *RCA* root cause analysis, *VBP* value-based pricing, *WTP* willingness to pay

the post-observational period, with others [16] assuming that the treatment efficacy for intervention and placebo declined at the same rate. One publication [30] described the uncertainty for life expectancy values, which was estimated using three external sources. However, given the disparity in population outcomes that were derived from the external sources, these results were considered conservative only [43]. Other approaches that were utilized included a discrete-event simulation ($n = 6$ [9%]) [31, 35, 41, 47, 50, 77]. Two of these studies were derived from health technology assessments [31, 47]. All six articles relied on the use of clinical trial data [31, 35, 41, 47, 50, 77], some of which underlined a shorter trial duration [31, 41, 50] as these trials were terminated early because of the favourable treatment efficacy of the intervention, which in turn, may have influenced model assumptions regarding the initial long-term efficacy assigned to the treatments involved.

3.3.3 Partition-Type Survival Modelling

Some articles used a real-world partition-type survival analysis ($n = 5$ [8%]) [53, 63–65, 70] to evaluate the cost effectiveness of a specific intervention. All publications used the area between Kaplan–Meier curves or time-to-failure survival modelling to estimate differences in life-years gained, hospitalizations and other outcomes between treatment arms. Some indicated that trial data may have underestimated the economic benefit of the intervention by omitting non–study-related physician appointments and laboratory tests [63, 70]. Information regarding hospital length-of-stay statistics [63, 65] or estimated survival rates for the various treatment groups [63] were absent from a number of publications. Most often, differences between treatment arms were captured by the disparity in area under the curves for the probability of first hospitalization as well as the number of life-years gained. Two other publications also used survival analytic models for assessment but did not describe their approach to model structure and specifications [71, 78].

3.3.4 Decision Tree Modelling

One publication based their model on the use of a decision tree approach [20]. The absence of Markov nodes made it challenging to assess the overall economic impact, given this study only included a shorter timeline (i.e. maximum duration of 6 months), offering limited insight into the long-term economic implications associated with HF.

3.4 Health States, Utilities, and Resource Information

All study types implemented either a cost-utility ($n = 27$ [42%]) or cost-effectiveness approach ($n = 36$ [56%]), with

the exception of one publication that used a cost-minimization method [28]. Time horizons tended to vary in duration across publications, ranging from 12 months to a lifetime horizon (Table 1). Most of the models included a health system perspective, with models in a further nine publications based on a societal perspective. The applied discount rates were typically in the range of 3–6%, depending on where the publication originated (Table 1). A total of 19 studies included information outlining hospitalization states for modelling patient outcomes and associated costs (Fig. 2). The majority ($n = 14$ [22%]) of these health-state types were generally classified as hospitalization.

3.5 Modelling Outcomes and Sensitivity Analyses

The bulk of the publications assessed more than one type of study outcome (Table 1). These typically included overall costs ($n = 59$ [92%]), incremental cost-effectiveness ratios (ICERs) ($n = 55$ [86%]), life-years gained ($n = 48$ [75%]) and willingness-to-pay (WTP) thresholds ($n = 37$ [58%]). Figure 3 displays the range of ICERs and WTP thresholds that were obtained according to study outcomes and regions assessed across the retrieved articles. The majority of analyses were evaluated from a US and UK healthcare perspective and used a drug versus placebo approach to establish cost effectiveness. ICERs captured within the UK were typically below the classic threshold of £20,000 per quality-adjusted life-year (QALY), with similar observations found according to US thresholds (i.e. most below \$US50,000 per QALY). Overall, within the included studies, active treatments (drug vs. drug) yielded higher ICERs than drug versus placebo comparisons (Fig. 3). There were many contributing factors, due to marginal utility gains and higher prices, driving ICER values upwards. It is fair to say that the value of an ICER would be expected to drop with
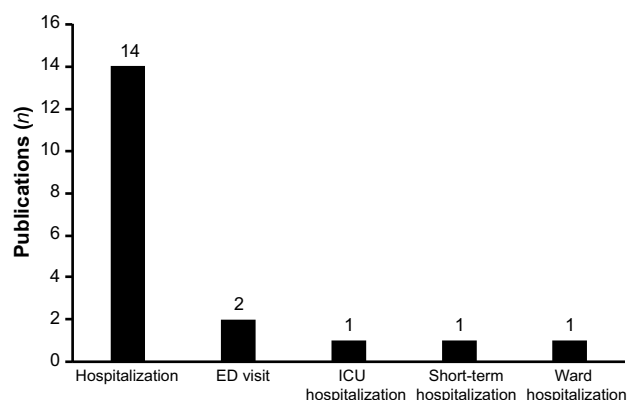

Fig. 2 Hospitalization states utilized by a selection of retrieved studies during model construction for evaluating patient outcomes and associated costs. *ED* emergency department, *ICU* intensive care unit
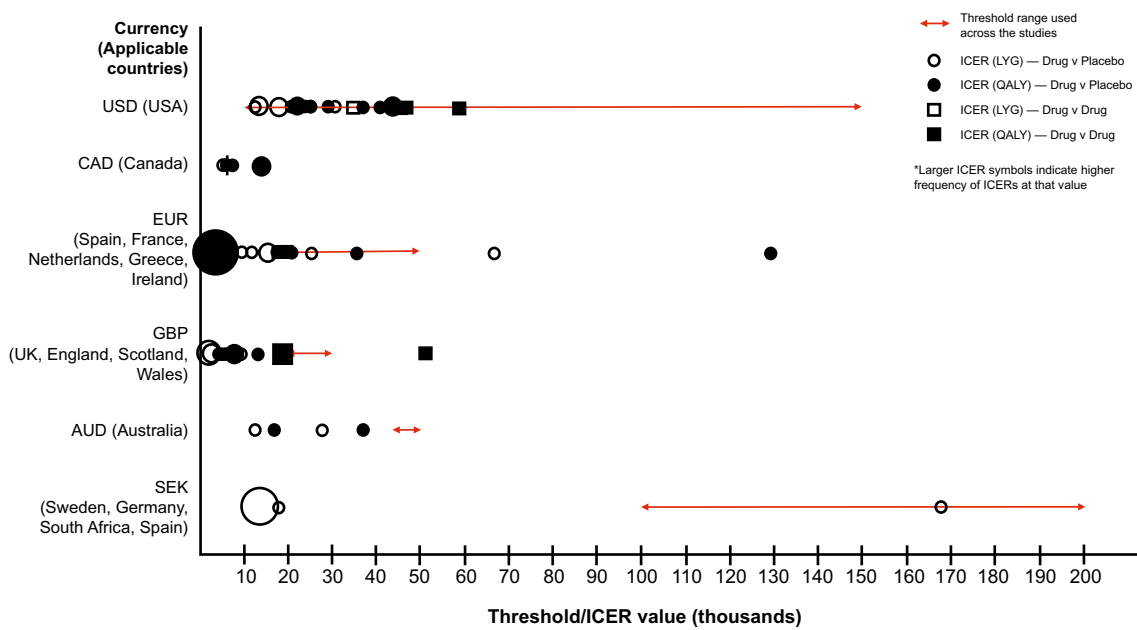
Fig. 3 Frequency and range of incremental cost-effectiveness ratios and willingness-to-pay thresholds according to study outcomes derived from retrieved articles and regions. *AUD* Australian dollar, *CAD* Canadian dollar, *EUR* Euro, *GBP* British pound, *ICER* incremental cost-effectiveness ratio, *LYG* life-years gained, *QALY* quality-adjusted life-year, *SEK* Swedish krona, *USD* United States dollar

the introduction of new drugs to the market; however, ICER values for drug versus placebo were generally less than drug versus drug comparisons. ICERs also varied widely across countries, partly due to varying approaches within modelling structures and specifications as well as the use and consideration of costs, patient utilities and health gains employed (Fig. 3). Other outcomes that were frequently evaluated included QALYs (*n* = 32 [50%]), with fewer publications (*n* = 4 [6%]) appearing to focus on value-based pricing as a study outcome (Table 1).

A modest number of the retrieved publications performed scenario (*n* = 4 [6%]) [52, 53, 67, 69] and sensitivity analyses, particularly deterministic sensitivity analysis (*n* = 19 [30%]) [23, 26, 31, 39–41, 43, 47, 50, 51, 58, 62–65, 70–72, 75] or probabilistic sensitivity analysis (*n* = 12 [19%]) [22, 23, 29, 39–41, 47, 49, 60, 61, 71, 73]. Although the types of sensitivity analyses were not specified in the remainder of the included publications, most studies were capable of establishing key model drivers. Several components that emerged as key model drivers included the probability of death/survival (*n* = 19 [30%]) [17, 18, 21, 23, 27, 32, 33, 35, 36, 45, 48, 49, 51, 56, 59–61, 69, 75], (re)hospitalizations (*n* = 15 [23%]) [17, 31, 41, 42, 45, 46, 50, 52, 56, 57, 63, 65, 68–70], treatment efficacy duration (*n* = 12 [19%]) [15, 17, 22, 32, 33, 39, 40, 44, 53, 58, 65, 70] and cost of treatment (*n* = 9 [14%]) [15, 16, 18, 21, 41, 43, 50, 51, 72].

3.6 Modelling Disease Type and Classifications

The majority of published models (40 publications [64%]) [15, 16, 19, 22–28, 32–34, 36–43, 45–48, 51, 52, 54, 57, 58, 62, 66–69, 72, 73, 75–77] focused on patient populations that presented with chronic HF, with only two (3%) [18, 60] and three studies (5%) [55, 56, 64] conducting their economic assessment according to patients with acute HF or a mixture of both HF types, respectively (Table 1). Descriptions of patient HF types were unclear in the remaining 19 publications (28%). With the majority of economic models specific to chronic HF, unsurprisingly, these findings were largely similar to the trends (i.e. for model specifications and structure) documented for the overall number of publications (Table 1). Comparison of the acute HF publications with the overall review findings was not feasible given the paucity of studies that focused solely on acute HF. Likewise, studies in this review that focused on acute and chronic HF (i.e. mixed) concurrently for economic evaluation were also limited. Additional subsets of HF assessed within the retained articles were examined; they included HFrEF (*n* = 45 [70%]), HFpEF (*n* = 6 [9%]) and both mixed HF subtypes (*n* = 2 [3%]), with the remainder of publications (*n* = 11 [17%]) not reporting a specific HF subtype. Given the lack of differentiation across papers and how they defined patients with HFrEF and HFpEF, it was also not possible to conduct any comparison according to publications and their patient

subsets. A total of 41 publications (64%) [15–17, 19, 20, 22, 23, 25, 27, 28, 32–34, 38–42, 45–48, 51–53, 57, 59, 60, 62–70, 73, 75–77] used the NYHA disease classification system to categorize patients and determine the severity of HF, of which 34 (83%) [15–17, 19, 22, 23, 25, 27, 28, 32–34, 38–42, 45–47, 51, 52, 57, 59, 62, 64, 66–69, 73, 75–77] focused on patients assigned to NYHA classifications II–III. The observed model structures and specifications within these publications were similar to those found according to the overall number of HF publications (Table 1). Only one publication (2%) [55] employed the Killip classification system, and definitions of disease classification were unclear in the remainder (*n* = 22 [34%]) (Table 1).

3.7 Quality of Available Publications

In total, 63 publications (98%) were eligible for quality assessment using the CHEERS checklist (Table 2). One study was omitted from quality assessment as only the abstract was presented in English [73]. The majority of checklist items according to the six main category domains were shown to be documented within publications, and most of the included articles demonstrated reasonable methodological quality (Table 2). However, some of the publications only reported on certain items, including "measurement of effectiveness" of data (*n* = 31 [49%] for both sub-items), "measurement and valuation of performance-based outcomes" (*n* = 25 [40%]), information regarding "estimation of resources and costs" (*n* = 22 [35%] for item A; *n* = 35 [55%] for item B), as well as "characterizing uncertainty" (*n* = 22 [35%] for item A; *n* = 36 [56%] for item B) and "heterogeneity" (*n* = 38 [60%]) (Table 2).

4 Discussion

In this review, we sought to describe the methodological components currently available for use in the economic evaluation of HF, with the intention of guiding future decision analytic models aimed at assessing the cost effectiveness of treatment strategies in the field of HF management. We identified 64 modelling studies, most of which displayed suitable methodological quality. The retrieved models typically employed a Markov or trial-based analytic approach and displayed sufficient details about model perspectives and discount rates. Several recurring outcomes appeared to be commonly assessed within each model, including total costs, ICERs, life-years gained, WTP and QALYs.

Some variability in model structure was evident across the retrieved publications because of the disparity in choice of time horizons used, which ranged from 12 months to a lifetime. We observed a trend away from cost-effectiveness analysis carried out using clinical trial data (or extrapolations

from these) towards a modelling-based approach using, for example, Markov modelling. Less than half (i.e. 41%) of the retrieved publications specified their use of deterministic sensitivity/scenario analysis and/or probabilistic sensitivity analysis [79]. We consider this finding a missed opportunity to assess in detail the parameter uncertainty and the impact of key variables in the cost-effectiveness profiles. Further, although this review identified a number of decision analytic models in the HF setting, collectively, the variability that existed across these models rendered it a challenge to perform a more comprehensive comparison of the retrieved findings. Varying degrees of severity were also found for hospitalization and/or cardiovascular outcomes that were modelled across treatment arms. Some studies tended to use hazard ratios and probabilities from clinical trial data in an effort to estimate the relative probability of HF and hospitalization between treatments. In one publication [39], regression equations employed clinical trial data to determine the treatment effect, whereas other studies used statistical distributions along with survival curves to define clinical efficacies, outcomes and death. Moreover, the rate of survival was frequently derived using time-constant probabilities that differed across treatment arms, health states and/or time horizons [32, 34]. Other studies tended to calculate mortality as a function of age and sex [68] or by use of survival tables [75]. The complexity of these different methodologies underlines the importance of exploring the most suitable modelling approaches, depending on the research question at hand, for appropriately and reliably conducting economic assessments in the management of HF.

Most studies employed NYHA disease classifications for establishing disease severity among patients for modelling purposes. Yet, it remains questionable whether the predominant use of this instrument (as observed in this review) is appropriate, given limitations around reproducibility, reliability, and clinician's interpretation of what construes "normal" in patients who present with HF [80–82]. Although NYHA functional classification represents a useful clinical measure for defining patient-relevant disease status, alternative classifications may need to be developed to reliably assess disease progression. Our observations support the views of Goehler et al. [9], who documented that most prior models exclusively used NYHA classification as a function of defining disease status, progression and prognosis. From a modelling perspective, the heterogeneity in profiles of patients with HF indicate that sole use of the NYHA instrument to measure disease status is insufficient. Moreover, there is some debate as to how individual clinicians employ the NYHA classifications for evaluating HF severity among patients, with their approaches often considered unclear [82]. Additionally, novel approaches, such as those that implement machine-learning algorithms, would likely extend our understanding of how to select the most suitable

Table 2 Overview of the quality of included publications according to the CHEERS checklist

Item no.	Item	Description	Publication response (n)[a]				Publication response (%)[b]			
			True	False	Unclear	NA	True	False	Unclear	NA
Title and abstract										
1	Title	Identify the study as an economic evaluation, or use more specific terms such as 'cost-effectiveness analysis', and describe the interventions compared	63[a]	0	0	0	100	0	0	0
2	Abstract	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions	54	1	0	8	86	2	0	12
Introduction										
3	Background and objectives	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	63	0	0	0	100	0	0	0
Methods										
4	Target population and subgroups	Describe characteristics of the base-case population and subgroups analysed, including why they were chosen	62	0	1	0	98	0	2	0
5	Setting and location	State relevant aspects of the system(s) in which the decision(s) need(s) to be made	60	0	3	0	95	0	5	0
6	Study perspective	Describe the perspective of the study and relate this to the costs being evaluated	58	0	5	0	92	0	8	0
7	Comparators	Describe the interventions or strategies being compared and state why they were chosen	63	0	0	0	100	0	0	0
8	Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate	63	0	0	0	100	0	0	0
9	Discount rate	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	57	6	0	0	91	9	0	0
10	Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	63	0	0	0	100	0	0	0
11a	Measurement of effectiveness	Single-study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical-effectiveness data	31	0	0	32	49	0	0	51
11b		Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical-effectiveness data	31	1	0	31	49	2	0	49
12	Measurement and valuation of preference-based outcomes	If applicable, describe the population and methods used to elicit preferences for outcomes	25	6	2	30	40	9	3	48
13a	Estimating resources and costs	Single-study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	22	1	0	40	35	2	0	63
13b		Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	35	0	5	23	55	0	8	37

Table 2 (continued)

Item no.	Item	Description	Publication response (n)[a]				Publication response (%)[b]			
			True	False	Unclear	NA	True	False	Unclear	NA
14	Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs, if necessary. Describe methods for converting costs into a common currency base and the exchange rate	56	1	6	0	89	2	9	0
15	Choice of model	Describe and give reasons for the specific type of decision analytic model used. Providing a figure to show model structure is strongly recommended	56	7	0	0	89	11	0	0
16	Assumptions	Describe all structural or other assumptions underpinning the decision analytic model	58	0	5	0	92	0	8	0
17	Analytic methods	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g. half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	51	3	9	0	81	5	14	0
Results										
18	Study parameters	Report the values, ranges, references and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended	55	1	7	0	87	2	11	0
19	Incremental costs and outcomes	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios	61	0	2	0	97	0	3	0
20a	Characterizing uncertainty	Single-study-based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective)	22	0	1	40	35	0	2	63
20b		Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions	36	3	1	23	56	5	2	37
21	Characterizing heterogeneity	If applicable, report differences in costs, outcomes or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information	38	15	10	0	60	24	16	0
Discussion										
22	Study findings, limitations, generalizability, and current knowledge	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge	54	3	6	0	86	5	9	0
Other										
23	Source of funding	Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other nonmonetary sources of support	46	11	0	6	73	17	0	10

Table 2 (continued)

Item no.	Item	Description	Publication response (n)[a]				Publication response (%)[b]			
			True	False	Unclear	NA	True	False	Unclear	NA
24	Conflicts of interest	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations	46	8	1	8	73	13	2	12

CHEERS Consolidated Health Economic Evaluation Reporting Standards

[a]Total *n* assessed by checklist was 63; one publication was unavailable in English [73]

[b]The publication number (*n* = 63) included in this quality assessment was used as the denominator for completeness of study information

candidate predictors in HF [83, 84], through identifying important clusters of risk factors that would facilitate our approach to quantifying disease status in the management and evaluation of HF.

Not all retrieved publications reported details on hospitalizations (e.g. as a health state) when evaluating the costs associated with HF. Of the few studies that provided sufficient information, the majority were classified as general hospitalization. Of those few publications that defined a specific hospitalization type for determining health states, two were classed as emergency department visits, one specified an intensive care unit visit; and two other publications specified a short-term and a ward hospitalization, respectively. Indicators of (re)hospitalization can provide crucial information beyond classification instruments and offer further details about the patient profile, thus proving useful to the modeller when attempting to evaluate the economic and societal implications in HF. Nevertheless, the use of generalized indicators for hospitalization in a model structure should be given careful consideration, alongside any potential for bias or skewing. For example, if hospitalization is only considered as a single Markov state, or if only one hospitalization can occur within one model cycle, a skewing in observations and related costs could occur depending on the actual type and number of hospital visit(s) or actual duration of hospital stays. This is a particular consideration in a chronic condition such as HF, where frequent rehospitalizations are very common [1, 8]. Although both hospitalization and NYHA disease classifications may offer a more comprehensive assessment of disease status when combined, additional research is undoubtedly needed to help further underline the utility of both measures and their reliability to act as surrogates of HF when attempting to capture disease status, progression and prognosis.

On the background of these reasons, further investigation is warranted to determine more reliable candidates of disease progression that will facilitate forthcoming development of decision analytic models. At minimum, these measures are expected to be readily accessible, straightforward to quantify and have the capacity to provide added value to a model over and above existing parameters (i.e. NYHA class and hospitalization) [32]. Depending on the availability of data and outcomes to be modelled, regression equation modelling such as Poisson and negative binomial regression models could potentially enhance the modelling approach for determining the likelihood that a patient might experience a hospitalization event. Although a number of parametric distributions estimating survival data beyond the measured period provide plausible estimates and an alternative to the Cox model, they do compromise on their restrictions on the shape of the hazard function, often causing an over-estimation in the treatment effect [32]. To overcome this problem, it is

worth considering more flexible parametric models such as restricted cubic splines to enable modelling of the baseline hazard. This approach offers advantages of greater flexibility in the shape of the hazard function, particularly when compared with the parametric modelling approach.

4.1 Limitations

Some limitations inherent to this review need to be emphasized. It was not our intention to offer a comprehensive evaluation of the results of the retrieved studies but rather to provide an overview of similar model features that were employed. It should be borne in mind that each publication differs according to their overall aims, target population considered, health procedures assessed and accessibility to study data. To this end, advocating an optimal modelling approach for use in the HF setting was beyond the scope of this review. Exploring the various economic models according to HF patient subsets, particularly those who presented with either HFrEF or HFpEF, was challenging given the disparity in study sample classifications observed across the retrieved articles. Hence, disentangling the similarities in model structures to identify clear trends in specifics of methodology is beyond the scope of our analysis. In addition, how to best identify key model drivers and specifications according to HF subtypes warrants further investigation. Indeed, we encourage health economics modellers involved in HF treatment assessments to perform value of information analyses (at least expected value of perfect information [EVPI] and expected value of perfect parameter information [EVPPI]) to better evaluate the value of the expected benefit of further investigating uncertain parameters in the decision model [85]. Only models derived from full-text publications were included, and we did not seek direct communication with the corresponding authors of these articles. On this basis, our understanding of the retrieved models is expected to be limited, particularly considering each publication seldom displays all available information because of publication constraints typically administered by journals. As such, we cannot discount the possibility that certain model elements of interest (e.g. as documented in technical modelling reports) may have been overlooked by the present review. We employed a study inclusion window of 20 years for the current analysis. As such, we cannot discount the possibility that other studies deemed suitable for inclusion into this SLR have since been published.

5 Conclusion

Numerous decision analytic modelling approaches for evaluating the cost effectiveness of HF treatments have been adopted, with a Markov cohort model proving to be the most commonly used approach. The majority of the models tended to differ in structure as well as health states and frequently relied upon the use of NYHA disease classification as a surrogate of disease severity, progression and prognosis. Recognizing alternative and more succinct approaches for the purpose of defining an optimal model structure would undoubtedly permit for a more precise estimation of the associated costs incurred, while facilitating clinical decision making in the management of HF.

Compliance with Ethical Standards

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