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 evaluated more 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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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 [15–30], 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 [15–30], 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 [15–30], the USA (n = 16 [25%]) [15–30], the UK (n = 16 [25%]) [31–46] and Canada (n = 5 [8%]) [24, 47–50].

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 commonly 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...
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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<br>Study type: Cost utility<br>Model type: Markov model with 1-month cycle lengths<br>Perspective: Payer<br>Time horizon: 10 years<br>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<br>Study type: Cost utility<br>Model type: Alive and dead Markov model, with half-cycle correction and 1-month cycle lengths<br>Perspective: NHS<br>Time horizon: Lifetime<br>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<br>Study type: Cost utility<br>Model type: Markov model<br>Perspective: NHS<br>Time horizon: Lifetime<br>Discount rate: Not reported | QALYs, costs, ICERs                        | Not reported                            | Not reported                         |
| Backhouse et al. [36] UK | Unclear                       | Chronic | Core model/adaptation: Core model<br>Study type: Cost effectiveness<br>Model type: Trial-based analysis<br>Perspective: NHS<br>Time horizon: 5 years<br>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                  |
| 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 |
| 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                           |
| 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 | QALYs, LYG, costs, ICERs, WTP | Sensitivity analysis was not specified but established key model drivers | Hospitalization                          |
|                          |                               |         | 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 |                             |                                      |                                          |
| Lorgelly et al. [42] UK   | NYHA                          | Chronic | Core model/adaptation: Core model | 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 |
|                          |                               |         | 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 |                             |                                      |                                          |
| de Lissovoy et al. [18] USA | NYHA                          | Acute   | Core model/adaptation: Core model | LYG, costs, ICERs | Sensitivity analysis was not specified but established key model drivers | Cost of treatment Long-term survival |
|                          |                               |         | Study type: Cost effectiveness |                             |                                      |                                          |
|                          |                               |         | Model type: Trial-based analysis |                             |                                      |                                          |
|                          |                               |         | Perspective: Hospital |                             |                                      |                                          |
|                          |                               |         | Time horizon: Lifetime |                             |                                      |                                          |
|                          |                               |         | Discount rate: Not reported |                             |                                      |                                          |
| de Lissovoy et al. [60] multi-country | Unclear | Acute   | Core model/adaptation: Core model | Costs, ICERs, WTP | Bootstrap analysis | Long-term survival |
|                          |                               |         | Study type: Cost effectiveness |                             |                                      |                                          |
|                          |                               |         | Model type: Trials-based analysis |                             |                                      |                                          |
|                          |                               |         | Perspective: Third-party payer |                             |                                      |                                          |
|                          |                               |         | Time horizon: Lifetime |                             |                                      |                                          |
|                          |                               |         | Discount rate: Not reported |                             |                                      |                                          |
| 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 |
| 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 |
| 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 |
| 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 | 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 | 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 | 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    | 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      |
| 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  
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 |
| 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
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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%]), HFrEF (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 HFrEF, it was also not possible to conduct any comparison according to publications and their patient

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
subset. 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 | 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 2 0 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 5 0 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 | Measurement and valuation of preference-based outcomes | 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 | Estimating resources and costs | If applicable, describe the population and methods used to elicit preferences for outcomes | 25 | 6 2 30 40 9 3 48 |
| 13a | | 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) | Publication response (%) |
|----------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|
|          |                                           |                                                                                                                                             | 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

| Item no. | Item                                      | Description                                                                                                                                                                                                 | Publication response (n) | Publication response (%) |
|----------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|
|          |                                           |                                                                                                                                             | True | False | Unclear | NA | True | False | Unclear | NA |
| 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

| Item no. | Item                                      | Description                                                                                                                                                                                                 | Publication response (n) | Publication response (%) |
|----------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|
|          |                                           |                                                                                                                                             | True | False | Unclear | NA | True | False | Unclear | NA |
| 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

| Item no. | Item                                      | Description                                                                                                                                                                                                 | Publication response (n) | Publication response (%) |
|----------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|
|          |                                           |                                                                                                                                             | True | False | Unclear | NA | True | False | Unclear | NA |
| 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 |
Cost-Effectiveness Models in Heart Failure

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 number of hospital visits or actual duration of hospital stays. This is a particular consideration in a chronic condition such as HF, where HF is only considered as a single Markov state, or if only one hospitalization can occur within one model cycle.

On the background of these reasons, further investigation is warranted to determine more reliable candidates of disease progression that will facilitate for the likelihood of a patient experiencing a hospitalization event. Although a number of parametric distributional modeling methods are available for modeling survival data beyond the measured period provided by the modeling approach for determining disease status and progression, the use of a hazard function in the modeling approach can also be problematic. Although a number of parametric distributional modeling methods are available for modeling survival data beyond the measured period provided by the modeling approach for determining disease status and progression, the use of a hazard function in the modeling approach can also be problematic.

Table 2 (continued)

| Item no. | Item |
|----------|------|
| 24       | Conflicts of interest |

Description: 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.

| Publication response (n) | Publication response (%) |
|--------------------------|--------------------------|
| True False Unclear NA    | True False Unclear NA    |
| 46 8 1 8 73 13 2 12      | 46 8 1 8 73 13 2 12      |

CHEERS Consolidated Health Economic Evaluation Reporting Standards

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

Ad: A number of parametric distributional modeling methods are available for modeling survival data beyond the measured period provided by the modeling approach for determining disease status and progression, the use of a hazard function in the modeling approach can also be problematic. Although a number of parametric distributional modeling methods are available for modeling survival data beyond the measured period provided by the modeling approach for determining disease status and progression, the use of a hazard function in the modeling approach can also be problematic.
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 [EVPPPI]) 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.

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Author Contributions All authors adhered to the ICMJE authorship criteria. GL Di Tanna and G Globe planned and designed this study. GL Di Tanna, A Bychenkova and F O’Neill conducted the review, screened the studies and extracted the information. All authors were involved in the data analysis and interpretation, initial drafting of the manuscript, and review and final approval of the manuscript for submission.

Compliance with Ethical Standards

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Conflict of interest GL Di Tanna, A Bychenkova, H Wirtz, and G Globe are employees of Amgen and may hold corporate stock in Amgen. H Wirtz also holds corporate stock in Teva Pharmaceuticals Industries Ltd. F O’Neill was an employee of Amgen until April 2018. P Miller has previously consulted for AstraZeneca, GSK, Pfizer, Novartis, Roche, Chiesi, and Bayer. B Ó Hartaigh was an employee of Curo, part of the Envision Pharma Group, when the study was conducted, who was contracted by Amgen to provide editorial support in the preparation of this manuscript.

Statement of human rights and/or animals For this type of study, formal consent is not required.

Data availability Data sharing is not applicable to this article as no datasets were generated or analysed during the current review.

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