Cost-Effectiveness of Heart Failure (HF) Treatments– A Targeted Literature Review (TLR)

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BACKGROUND & OBJECTIVES

- The worldwide prevalence of HF was estimated to be 64.3 million cases (8.5 per 1,000 inhabitants) in 2017[1].
- Patients with HF may have been treated with chronic pharmacological treatments along with cardiac implantable electronic devices (implantable cardioverter-defibrillator [ICD], cardiac resynchronization therapy [CRT], and ventricular assisted device)[2].
- This study aimed to assess the health economic evidence of chronic heart failure (CHF) treatments through a TLR.

METHODS

Eligibility criteria

- A literature search was conducted in EMBASE, MEDLINE, EconLit, NHS EED and HTA databases.
- Modelling studies assessing the cost-effectiveness of pharmacological treatment and medical devices in CHF were included (limits: 2011-2021 and English language).
- Key countries of interest were UK, US, Japan, Australia, Germany, China, and France.

RESULTS

Overview of included studies

- The title and abstract of 2,668 abstracts were screened and 22 papers (Table 1) were included in the review.
- Eighteen studies assessed the cost-effectiveness of pharmacological treatments: sacubitril/valsartan (n=8), dapagliflozin (n=5), empagliflozin (n=1), ivabradine (n=3), and vericiguat (n=1); and four studies assessed cost-effectiveness of medical devices (ICD / CRT pacemakers [CRT-P], CRT defibrillator [CRT-D], Baroreflex activation therapy [BAT], and cardiac contractility modulation [CCM]).
- Cost-effectiveness studies were based in US (n=8), UK (n=4), Germany (n=3), Australia (n=3), China (n=2) or multiple countries (n=2).
- Eleven studies included patients with left ventricular ejection fraction (LVEF) ≤40%, eight studies with LVEF ≤35%, one study with LVEF ≤45% and one study with LVEF 25%-45%. Except for three studies, all studies included patients with NYHA classes II-IV; two studies included NYHA class III and one included all NYHA classes.

Cost-effectiveness analysis results

- Compared to standard of care, all active treatments were reported as cost-effective at the specific willingness to pay thresholds for each country, except in one study, ICD, CRT-P and CRT-D were found to be cost-effective only in specific patient sub-groups.
- Across the studies, relative-risk for hospitalization and death, cost of treatment, utility values, time horizon and age of patients were identified as key model drivers.

Model approach and technical specification

- Markov models were the most common modelling technique (n=18), followed by risk equations (n=4).
- Eight studies categorized patients based on the New York heart association (NYHA) classification, four studies used disease classifications based on diabetes status and Kansas City Cardiomyopathy Questionnaire Score (KCCQ).

Model inputs

- Clinical inputs for NYHA progression, hospitalization and mortality were derived from RCTs (CARE-HF, DAPA-HF, PARADIGM-HF, SHIFT, FIX-HF) or published literature.
  - NYHA progression: the majority (5/8) of studies which categorized patients by NYHA classification assumed the same NYHA progression probabilities between the intervention and comparator.
  - Hospitalization: HF hospitalization and/or all-cause hospitalization were captured across majority of the studies. Hospitalization probabilities were assumed to be constant across time horizon in most (17/22) studies.
  - Mortality: All-cause mortality and cardiovascular (CV) were captured across majority of the studies.
- Utility inputs were also derived from RCTs (CARE-HF, DAPA-HF, PARADIGM-HF, SHIFT, FIX-HF and VICTORIA) or published literature.
- Resource use and costs included the cost of drug acquisition, routine management of HF (including costs of visits to physician, medication, and rehabilitation), HF and non-HF hospitalization. In studies assessing cost-effectiveness of medical device, costs of initial implant operation and replacement, and battery replacement were also included.

Table 1. Summary of included cost-effectiveness studies

Author, Year	Country -perspective	Intervention vs comparator	Time horizon, cycle length	Input source	NYHA class, LVEF	Model design	Health states	Approach/tool used for utility	ICER
Sandhu 2016 [3]	US - Societal	Sacubitril–valsartan vs Lisinopril	Lifetime, 1 month	PARADIGM-HF	II-IV, ≤40%	Markov model	2 HS: alive or dead	EQ-5D	$47,053
King 2016 [4]	US - Medicare	Sacubitril–valsartan vs Enalapril	Lifetime, 3 months	PARADIGM-HF	II-IV, ≤35%	Markov model	5 HS: NYHA class I, II, III, and IV and death	EQ-5D	$50,959
McMurray 2018 [5]	UK, Denmark, Colombia – Public healthcare	Sacubitril–valsartan vs Enalapril	Lifetime, 1 month	PARADIGM-HF	II-IV, ≤40%	Markov model	2 HS: alive or dead	EQ-5D	UK: £17,134; Denmark: €22,620; Colombia: €11,200;
Chin 2020 [6]	Australia – Public healthcare	Sacubitril–valsartan vs Enalapril	20 years, 1 year	PARADIGM-HF	II-IV, ≤35%	Markov model	2 HS: alive (with HFREF) and Dead	EQ-5D	$40,513 (AUD)
Zueger 2018 [7]	US - Medicare	Sacubitril–valsartan vs Enalapril	5 years, 1 month	PARADIGM-HF	II-IV, ≤40%	Markov model	5 HS: NYHA class I, II, III, and IV and death	EQ-5D	$143,891
van der Pol 2019 [8]	Germany- Statutory Health Insurance	Sacubitril–valsartan vs Enalapril	30 years, 1 month	PARADIGM-HF	II-IV, ≤40%	Markov model	4 HS: outpatient treated HFrEF, hospital admissions to a general ward, hospital admissions including a stay at the ICU, death	EQ-5D	€19,300
Gaziano 2016 [9]	US - Medicare	Sacubitril–valsartan vs Enalapril	30 years, 1 month	PARADIGM-HF	II-IV, ≤40%	Markov model	2 HS: alive or dead	EQ-5D	$45,017
Wu 2020 [10]	China – patient	Sacubitril–valsartan vs Enalapril	10 years, 1 month	PARADIGM-HF	II-IV, ≤40%	Markov model	5 HS: NYHA class I, II, III, and IV and death	EQ-5D	$2,481
Savira 2021 [11]	Australia – Public healthcare	Dapagliflozin + SoC vs SoC	Lifetime, 1 year	DAPA-HF	II-IV, ≤40%	Markov model	3 HS: 'alive and event-free', 'alive after non-fatal hospitalisation for heart failure' and 'dead'	EQ-5D	$12,842 (AUD)
Parizo 2021 [12]	US - Medicare	Dapagliflozin vs SoC	Lifetime, 1 month	DAPA-HF	II-IV, ≤40%	Markov model	6 HS: patients on dapagliflozin, patients on SoC, left ventricular assist device, heart transplant, non-CV death, CV death	KCCQ-->EQ-5D	$83,650
Isaza 2021 [13]	US - Medicare	Dapagliflozin + GDMT vs GDMT	Lifetime, 1 month	DAPA-HF	II-IV, ≤40%	Markov model	5 HS: no event, HF hospitalization, urgent care, incident diabetes, death	KCCQ-->EQ-5D	$68,300
McEwan 2020 [14]	UK, Germany, Spain – Public healthcare	Dapagliflozin + SoC vs SoC	Lifetime, 1 month	DAPA-HF	II-IV, ≤40%	Markov model	5 HS: 4 subgroups per KCCQ score and dead	KCCQ-->EQ-5D	UK: £5,822; Germany: €5,379; Spain: €9,406
Yao 2020 [15]	China – Public healthcare	Dapagliflozin + SoC vs SoC	15 years, 3 months	DAPA-HF	II-IV, ≤40%	Markov model	5 HS: NYHA class I, II, III, and IV and death	EQ-5D	$3,828
Adena 2019 [16]	Australia – Public healthcare	Ivabradine + SoC vs SoC	Lifetime, 6 months	SHIFT	II-IV, ≤35%	Markov model	5 HS: stable HF; HF hospitalisation; HF death; non-HF CV death; and non-CV death.	EQ-5D	$14,905 (AUD)
Griffiths 2014 [17]	UK – Public healthcare	Ivabradine + SoC vs SoC	Lifetime, 1 month	SHIFT	II-IV, ≤35%	Risk equations	5 subgroups: NYHA class I, II, III, and IV and death	EQ-5D	Baseline heart rate ≥75 bpm: £8,498; baseline heart rate ≥70 bpm: £13,764
Kansal 2016 [18]	US - Medicare	Ivabradine + background therapy vs Background therapy	10 years, 1 month	SHIFT	II-IV, ≤35%	Markov model	11 HS: 10 mutually exclusive hospitalization and death	EQ-5D	$24,920
Alsumali 2021 [19]	US - Medicare	Vericiguat + SoC vs SoC	30 years, 1 month	VICTORIA	II-IV, ≤45%	Markov model	4 HS: alive prior to HF hospitalization, alive during HF hospitalization , alive post HF hospitalization , death	EQ-5D-5L	$82,448
Kansal 2019 [20]	UK – Public healthcare	Empagliflozin + SoC vs SoC	Lifetime, NR	EMPA-REG OUTCOME	NR, NR	Risk equations	10 CV and renal events including stroke, HF hospitalization, and CV death	EQ-5D	£4,083
Borisenko 2018 [21]	Germany - Statutory Health Insurance	BAT vs OMT	Lifetime, 1 month	CARE-HF	III, ≤35%	Decision tree + Markov model	5 HS: NYHA class I, II, III, and IV and death.	EQ-5D	€27,951
Witte 2019 [22]	UK – Public healthcare	CCM + SoC vs SoC	Lifetime, 1 month	FIX-HF Phase 1 FIX-HF Phase 2 FIX-HF-5C	III, 25-45%	Risk equations	4 subgroups: NYHA functional classes I& II, III, IV, and death	MLWHFQ-->EQ-5D	£22,988
Mealing 2016 [23]	UK – Public healthcare	ICD, CRT-P or CRT-D vs medical therapy	Lifetime, 1 month	Meta-Analysis	I-IV ≤35%	Risk equations	3 outcomes: all-cause mortality, all-cause hospitalization, HRQoL	EQ-5D	- CRT-D is cost-effective in 10 of 24 subgroups; - ICD is cost-effective in all non-NYHA IV patients with QRS < 120 ms and for NYHA I/II non-LBBB morphology patients with 120 ms<QRS <149 ms - CRT-P is cost-effective in all NYHA III/IV patients with QRS>120ms
Hadwinger 2021 [24]	Germany- Statutory Health Insurance	CRT-D + OMT vs CRT-P + OMT	20 years, 1 month	Meta-Analysis and CARE-HF	II-IV, ≤35%	Markov model	6 HS: stable (by NYHA class I, II, III, IV), hospital and death.	EQ-5D	€24,659

Abbreviations: BAT: baroreflex activation therapy; CCM: cardiac contractility modulation, CRT-D: cardiac resynchronization therapy defibrillator/biventricular defibrillator, CRT-P: cardiac resynchronization therapy pacemakers/ biventricular pacemaker, CV: cardiovascular, GDMT: guideline-directed medical therapy, HS: health state, HF: heart failure, HFrEF: heart failure with reduce ejection fraction, ICD: implantable cardioverter-defibrillator, ICER: incremental cost-effectiveness ratio, ICU: intensive care unit, KCCQ: Kansas City Cardiomyopathy Questionnaire Score, MLWHFQ: Minnesota living with heart failure questionnaire, NR: not reported; NYHA: New York Heart Association, OMT: optimal medical therapy, SoC: standard of care.

CONCLUSIONS

- Results of this TLR can be useful for physicians and other decision-makers to prescribe appropriate treatments for CHF.
- Evidence on the cost-effectiveness of medical devices is limited, suggesting an unmet need for an appropriate and economic treatment option in patients uncontrolled on pharmacological therapy.
- Some studies included in this review used the NYHA classification as a proxy for disease severity, however; the use of this instrument has been questioned given limitations around its reproducibility, reliability, and clinician's interpretation of what construes "normal" in patients who present with HF. [14]

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