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Clinical and cost-effectiveness of left ventricular assist devices as destination therapy for advanced heart failure: systematic review and economic evaluation

Sophie Beese, Tuba S Avşar, Malcolm Price, David Quinn, Hoong S Lim, Janine Dretzke, Chidubem O Ogwulu, Pelham Barton, Louise Jackson and David Moore

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Abstract

Clinical and cost-effectiveness of left ventricular assist devices as destination therapy for advanced heart failure: systematic review and economic evaluation

Sophie Beese[1†] Tuba S Avşar[1,2†] Malcolm Price[1] David Quinn[3] Hoong S Lim[3] Janine Dretzke[1] Chidubem O Ogwulu[1] Pelham Barton[1] Louise Jackson[1] and David Moore[1*]

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Background: Selected patients with advanced heart failure ineligible for heart transplantation could benefit from left ventricular assist device therapy as 'destination therapy'. There is evidence of the efficacy of destination therapy; however, it is not currently commissioned within the United Kingdom National Health Service due to the lack of economic evidence.

Objective: What is the clinical and cost-effectiveness of a left ventricular assist device compared to medical management for patients with advanced heart failure ineligible for heart transplantation (destination therapy)?

Methods: A systematic review of evidence on the clinical and cost-effectiveness of left ventricular assist devices as destination therapy was undertaken including, where feasible, a network meta-analysis to provide an indirect estimate of the relative effectiveness of currently available left ventricular assist devices compared to medical management. For the systematic reviews, data sources searched (up to 11 January 2022) were Cochrane CENTRAL, MEDLINE and EMBASE via Ovid for primary studies, and Epistemonikos and Cochrane Database of Systematic Reviews for relevant systematic reviews. Trial registers were also searched, along with data and reports from intervention-specific registries. Economic studies were identified in EconLit, CEA registry and the NHS Economic Evaluation Database (NHS EED). The searches were supplemented by checking reference lists of included studies. An economic model (Markov) was developed to estimate the cost-effectiveness of left ventricular assist devices compared to medical management from the United Kingdom National Health Service/personal social service perspective. Deterministic and probabilistic sensitivity analyses were conducted to explore uncertainties. Where possible, all analyses focused on the only currently available left ventricular assist device (HeartMate 3™, Abbott, Chicago, IL, USA) in the United Kingdom.

Results: The clinical effectiveness review included 134 studies (240 articles). There were no studies directly comparing HeartMate 3 and medical management (a randomised trial is ongoing). The currently available left ventricular assist device improves patient survival and reduces stroke rates and complications compared to earlier devices and relative to medical management. For example, survival at 24 months is 77% with the HeartMate 3 device compared to 59% with the HeartMate II (MOMENTUM 3 trial). An indirect comparison demonstrated a reduction in mortality compared to medical management [relative risk of death 0.25 (95% confidence interval 0.13 to 0.47); 24 months; this study].

The cost-effectiveness review included 5 cost analyses and 14 economic evaluations covering different generations of devices and with different perspectives. The reported incremental costs per quality-adjusted life-year gained compared to medical management were lower for later generations of devices [as low as £46,207 (2019 prices; United Kingdom perspective; time horizon at least 5 years)].

The economic evaluation used different approaches to obtain the relative effects of current left ventricular assist devices compared to medical management from the United Kingdom National Health Service/personal social service perspective. All gave similar incremental cost-effectiveness ratios of £53,496–58,244 per quality-adjusted life-year gained – lifetime horizon. Model outputs were sensitive to parameter estimates relating to medical management. The findings did not materially differ on exploratory subgroup analyses based on the severity of heart failure.

Limitations: There was no direct evidence comparing the clinical effectiveness of HeartMate 3 to medical management. Indirect comparisons made were based on limited data from heterogeneous studies regarding the severity of heart failure (Interagency Registry for Mechanically Assisted Circulatory Support score distribution) and possible for survival only. Furthermore, the cost of medical management of advanced heart failure in the United Kingdom is not clear.

Conclusions: Using cost-effectiveness criteria applied in the United Kingdom, left ventricular assist devices compared to medical management for patients with advanced heart failure ineligible for heart transplant may not be cost-effective. When available, data from the ongoing evaluation of HeartMate 3 compared to medical management can be used to update cost-effectiveness estimates. An audit of the costs of medical management in the United Kingdom is required to further decrease uncertainty in the economic evaluation.

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Glossary

Bridge to candidacy A patient too unwell to be a candidate for a therapy, but the bridge carries them to a state of being eligible.

Bridge to transplant Such therapy preserves someone's health well enough and long enough that they are able to receive a transplant after spending time waiting for an organ to become available.

Cost-effectiveness acceptability curve The cost-effectiveness acceptability curve is a graph summarising the impact of uncertainty on the result of an economic evaluation, frequently expressed as an incremental cost-effectiveness ratio in relation to possible values of the cost-effectiveness threshold.

Destination therapy When recovery from heart failure is not possible and patients are ineligible for a heart transplant, the therapies used are considered as destination therapy. Left ventricular assist devices can be given as a destination therapy as can medical management alone. As such, destination therapy is not an alternative to a heart transplant or therapy while awaiting a heart transplant because the patient being ineligible for a heart transplant defines it.

Heart failure Heart failure is a chronic, progressive condition in which the heart muscle is unable to pump enough blood to meet the body's needs for blood and oxygen.

Incremental cost-effectiveness ratio An incremental cost-effectiveness ratio is a summary measure representing the economic value of an intervention, compared with an alternative (comparator).

Left ventricular assist device A left ventricular assist device is a mechanical pump that is implanted in patients with heart failure. It helps the bottom left chamber of the heart (left ventricle) pump blood out of the heart to the aorta and the rest of the body.

Medical management In this report, medical management refers to the range of medical therapies employed to treat patients with heart failure before, or in the absence of, a surgical intervention, such as a left ventricular assist device or heart transplant.

New York Heart Association Functional Classification The New York Heart Association Functional Classification provides a simple way of classifying the extent of heart failure.

Quality-adjusted life-year A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One quality-adjusted life-year is equal to 1 year of life in perfect health.

List of abbreviations

AHF	advanced heart failure
AR	aortic regurgitation
BMI	body mass index
BNP	B-type natriuretic peptide
BTC	bridge to candidacy
BTT	bridge to transplant
CE	Conformité Européenne
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CUA	cost–utility analysis
DT	destination therapy
EF	ejection fraction
ESC	European Society of Cardiology
EQ-5D	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
EUROMACS	European Registry for Patients with Mechanical Circulatory Support
EVPI	expected value of perfect information
FDA	Food and Drug Administration
GI	gastrointestinal
GIB	gastrointestinal bleeding
HM3	HeartMate 3
HR	hazard ratio
HRAEs	haemocompatibility-related adverse events
HT	heart transplant
HTA	Health Technology Assessment
HVAD	HeartWare ventricular assist device
ICD	implantable cardioverter defibrillator
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IMACS	International Registry for Mechanically Assisted Circulation
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IRR	incidence rate ratio
KCCQ	Kansas City cardiomyopathy questionnaire
LV	left ventricle
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LY	life years
MCSDs	mechanical circulatory support devices
MLHFQ	Minnesota living with heart failure questionnaire
MM	medical management
mRS	modified Rankin Scale
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
NMA	network meta-analysis
NYHA	New York Heart Association
PE	pump exchange
PI	pump infection
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	personal social services
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial

REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
RHF	right heart failure
RR	relative risk
RVAD	right ventricular assist device
SF-12	Short Form questionnaire-12 items
SF-36	Short Form questionnaire-36 items
TIA	transient ischaemic attack
VAD	ventricular assist device
VAS	visual analogue scale
VoI	Value of Information
WTP	willingness to pay
XVE	extended vented electric

Plain language summary

The majority of patients with advanced heart failure would be unsuitable for heart transplantation due to their age and comorbidities but selected patients could benefit from a left ventricular assist device. Left ventricular assist device therapy for such patients is known as 'destination therapy'. This is a long-term therapy that involves implanting a battery-powered pump to support the patient's heart.

The purpose of this project was to collect and assess the research evidence on the effectiveness of left ventricular assist devices when used for destination therapy, and to estimate value for money compared to medical management from the United Kingdom National Health Service/personal social service perspective.

This research identified that the currently available left ventricular assist device improves patient survival as well as reducing stroke rates and complications compared to earlier devices and relative to medical management. However, there is uncertainty in the evidence due to the absence of studies directly comparing the current device to medical therapy alone. An ongoing clinical trial is currently assessing this. It also means there is uncertainty about whether left ventricular assist devices could provide value for money as determined currently for the United Kingdom National Health Service.

Scientific summary

Background

Heart failure is a debilitating, progressive syndrome characterised by the inability of the heart to pump blood around the body. Pharmacological treatments are used as first-line treatment but may eventually become less effective and left ventricular assist devices (LVADs) or heart transplant (HT) are considered. LVADs are frequently used as bridge to transplant (BTT) or bridge to candidacy (BTC). However, some patients are ineligible for HT and either continue on medical management (MM) or could have a LVAD implanted as 'destination therapy' (DT). LVAD as DT is not currently commissioned within the United Kingdom National Health Service (UK NHS). The costs of LVADs are high, especially when compared to the alternative MM, but may also offer significant benefit in terms of survival. It is important to determine whether LVADs are both clinically and cost-effective as DT to inform decision-making from the UK NHS/personal social service (PSS) perspective on their potential as long-term treatment for advanced heart failure patients ineligible for HT.

Aims and objectives

What is the clinical and cost-effectiveness of a LVAD compared to MM for advanced heart failure (AHF) patients ineligible for HT (DT)?

The specific objectives to address this aim were to undertake:

- a systematic review of available evidence on the clinical effectiveness of a LVAD as DT, including a network meta-analysis (NMA) to provide an indirect estimate of the relative effectiveness of currently available LVADs compared to MM;
- a systematic review of available economic evidence on the use of a LVAD as DT; and
- the development of an economic model to estimate the cost-effectiveness of a LVAD compared to MM from the UK NHS/PSS perspective.

Due to the withdrawal of the HeartWare ventricular assist device (HVAD) during the undertaking of this research, the analyses primarily focus on the HeartMate 3™ (Abbott, Chicago, IL, USA) device, the only LVAD available in the UK at this time.

Methods

Systematic review of clinical effectiveness

A systematic review was undertaken of all LVADs as DT and reporting followed the general principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review was registered on PROSPERO (CRD42020158987).

Eligibility criteria

Studies of patients over 16 years of age with AHF who received any type of LVAD as DT were included. The review considered all devices, but the analysis focused on the HM3 device due to the recent withdrawal of the HeartWare HVAD (Medtronic, Dublin, Republic of Ireland). Eligible comparators (where relevant) were MM and other LVADs. Outcomes were survival, quality of life (QoL), hospitalisations, major events, complications and functional status.

Study designs eligible were any clinical trial (whether randomised, non-randomised or single arm), observational studies (cohort, case-controls and case series) and reports from patient registries [e.g. INTERMACS, International Registry for Mechanically Assisted Circulation (IMACS)]. Studies were eligible if 50 or more DT patients were included. Systematic reviews were included and used to identify any additional potentially relevant primary studies.

Searches and study selection

Databases were searched from inception to 20 May 2020, with an updated search on 11 January 2022. Databases searched included Cochrane Library (CENTRAL), MEDLINE and EMBASE via Ovid, Epistemonikos, Cochrane Library of Systematic Reviews and World Health Organization (WHO) clinical trials portal (for ongoing studies). There were no restrictions by language or date of publication.

Two reviewers independently undertook title and abstract screening and full-text selection via Covidence (Veritas Health Innovation, Melbourne, VIC, Australia). Disagreements were resolved by a third reviewer or consensus and reasons for exclusion were recorded.

Risk of bias, data extraction and synthesis

Quality assessment and data extraction were completed by one reviewer and checked by a second. Appropriate risk-of-bias tools dependent upon study design were applied.

A hierarchical approach to synthesis was undertaken to avoid double-counting of studies with overlapping patient data and to manage the large volume of evidence. Randomised controlled trials (RCTs) and controlled non-randomised trials were considered in the first instance. Registry reports and uncontrolled observational studies were used to supplement findings for all outcomes. Data were tabulated and analysed in a narrative approach by device, and forest plots without summary estimates were presented (and where appropriate the feasibility of meta-analysis was considered).

A network meta-analysis was considered for the main outcomes to produce an indirect comparison of the HM3 device (across LVAD generations) to MM, but only carried out for survival.

Systematic review of cost-effectiveness

A systematic review of the cost-effectiveness of LVADs was carried out utilising the same search strategy, and at the same time as the clinical effectiveness review, with the addition of three further specialist economics database searches in EconLit, Cost-Effectiveness Analysis (CEA) registry and the NHS Economic Evaluation Database (NHS EED). Appropriate risk-of-bias tools were applied and a narrative synthesis was undertaken.

Economic evaluation

The systematic reviews' findings were used to inform the development of a cost–utility analysis (CUA), from the NHS/PSS perspective, using a Markov model with a lifetime horizon and 1-month cycles. Along with evidence from the reviews, the model was informed by guidance from clinical specialists, patients and commissioners. All costs used were in 2019 prices, and a discount rate of 3.5% was applied as per the national UK guidelines. To produce the base case, mortality risks for MM and LVAD arms required some assumptions and several methods for estimating the risks were identified. Two of these were primarily utilised: non-comparative net weight estimates and comparative estimates mapped to LVAD data from the recent relevant HM3 trial (MOMENTUM).

The analysis was repeated incorporating a small probability of LVAD DT recipients transitioning to HT eligibility. The potential impacts of the severity of heart failure on cost-effectiveness were explored by considering subgroupings of profiles based on the INTERMACS classification. Uncertainty was explored via both deterministic and probabilistic sensitivity analyses, paying specific attention to the life expectancy and ongoing costs.

Results

Systematic review of clinical effectiveness

There were 240 articles from 134 studies included in the clinical effectiveness review (5 randomised trials, 1 non-randomised trial, 86 observational studies, reports from 5 registries, 5 ongoing studies and 32 systematic reviews). Of the six trials that were included, only one of these assessed the HM3 and this was in comparison to the previous generation HeartMate II device (MOMENTUM RCT). The majority of HM3 data comes from this trial, with minimal additional data contributions from registry reports or observational studies of single cohorts. The MOMENTUM study was considered as having some concerns regarding risk of bias; however, this was primarily due to the per-protocol analysis for the DT participants and most other domains were considered low risk.

There were 624 DT patients in the MOMENTUM 3 trial in total, with a mean age of 63 [standard deviation (SD) 12], 82.2% male and 52.1% INTERMACS level 3.

At the longest follow-up point (24 months) survival was 76.7% in HM3 DT patients compared to 59% in HeartMate II patients. Clear and significant improvements in QoL from baseline were reported at 12 months and maintained at 24 months in the HM3 group; however, this was similar in the HeartMate II group. Major events and complications were present in both groups by the 24-month follow-up. There were eight stroke events per 100 patient-years in the HM3, as well as one pump thrombosis event and 70 bleeding events per 100 patient-years. These were all lower than that of the HeartMate II group. Rehospitalisations were also significantly lower in HM3 patients.

While some reports included HM3 patients, there were no HM3 specific data reported in any patient registry reports. One observational study reported that HM3 patients (n = 15) had 0 pump thrombosis events in 24 months of follow-up.

While it was not the focus due to withdrawal, survival levels were lower in the HeartWare HVAD trials when compared to the HM3 in the MOMENTUM trial and there were concerns with the stroke rates reported in the evidence.

Risk of bias across the included trials varied with all but two studies reporting an overall high risk of bias or with some concerns for at least one outcome.

The evidence contained within the remaining trials, observational studies and registry reports mostly relate to devices other than HM3. This evidence is summarised in the main part of this report.

Indirect comparison of HeartMate 3 and medical management

As there were no studies directly comparing HM3 and MM, indirect comparisons of the trial data were required utilising MM data from the older REMATCH trial (the first RCT comparing the first-generation HeartMate device to MM). Data were available to link through available studies for the survival outcome only. The network meta-analysis demonstrated a reduction in the risk of mortality, relative risk of death of 0.25 [95% confidence interval (CI) 0.13 to 0.47] 24 months, with the HM3 compared to MM.

Systematic review of cost-effectiveness

There were 19 studies reported in 20 articles included in the cost-effectiveness review: 5 cost analyses and 14 economic evaluations. Nine studies were US-based and four were UK-based. Most of the studies aimed to compare the health and cost outcomes of LVADs with MM. Most economic evaluations (n = 12) used a CUA approach and only two conducted a CEA. Markov-based modelling was applied in eight studies. The perspective, where stated, was the service provider in most studies. Healthcare resource use was usually estimated based on small numbers of patients from a single centre, which resulted in variability.

In the studies comparing LVAD with MM for DT patients, the incremental cost per quality-adjusted life-year (QALY) gained estimates ranged between £46,207 and £238,401 in 2019 prices over a time horizon of 5 years or longer and from different perspectives. The overall quality of the studies was considered poor to moderate. Some limitations were limited consideration of uncertainty, insufficient time horizon and lack of consideration of some key complications and cost components. Only one study looked at the impact of disease severity on cost-effectiveness. More recent evaluations tended to have lower estimates of incremental cost-effectiveness, presumably reflecting better clinical outcomes of more recent devices. Two recent studies estimated the cost-effectiveness from a UK perspective, deriving incremental cost-effectiveness ratios of £47,361 and £46,207 per QALY gained for the HeartWare device (device withdrawn in 2021) and the HM3 device, respectively compared to MM.

Economic evaluation

The economic evaluation found similar results for each base case:

- Non-comparative net weight estimates approach: LVAD would produce an additional 2.86 QALYs per person, increase life expectancy by 3.73 years and the incremental cost to the NHS would be £152,735 per person. Incremental cost-effectiveness ratio (ICER): £53,496.
- Comparative estimates mapped to LVAD in MOMENTUM approach: LVAD would produce an additional 2.51 QALYs per person, increase life expectancy by 3.06 years and the incremental cost to the NHS would be £146,275 per person. ICER: £58,244.

At a willingness to pay threshold of £50,000 per QALY gained, LVADs would not be considered cost-effective compared to MM for AHF patients ineligible for HT. The same applied when severity weighted ICER estimates based on QALY shortfall methods were used. The deterministic sensitivity analysis showed that inclusion of the probability of becoming eligible for a HT did not change these findings. Furthermore, the findings did not differ in subgroup analyses based on severity of heart failure. Model outputs were most sensitive to estimates related to outpatient costs for both LVAD and MM.

Conclusions

LVADs have significantly improved over time and the currently available HM3 LVAD is considered clinically effective in patients with end-stage heart failure ineligible for transplant, offering survival of over 75% at 2 years of follow-up with reduced complications and major events in comparison to older devices. However, the device compared to MM may not be considered cost-effective when using methods of defining this for end of life in the UK.

Future research

Currently, no RCT has been published that compares the HM3 device to MM; however, there is an ongoing trial (SweVAD) comparing the two, which is due to complete final study follow-up in December 2023. This randomised trial, undertaken in Sweden, should allow for relative effects to be determined between the two interventions. This will ultimately enable more robust data to be used to update the current model, rather than relying upon indirect comparisons with wide uncertainty.

However, further issues around the true cost of MM are still present due to the lack of recent data on these costs in the UK. An audit of MM costs in DT patients in the UK would address this.

Issues also persist in developing reliable subgroup analyses based on severity profiles to aid identification of whether a LVAD is (more) cost-effective for some groups of DT patients. Future trials and other studies should report results by patient severity profiles (e.g. INTERMACS classification), and if registry/observational studies then also by device implanted.

Study registration

This study is registered as PROSPERO CRD42020158987.

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Chapter 1 Background

Introduction

Heart failure (HF) is a condition in which the heart does not pump blood properly around the body, limiting an individual's quality of life (QoL) and reducing length of life. This chapter describes the definition, epidemiology, causes, classification and management of HF.

Definition and classification of heart failure

HF has been defined both as a 'syndrome recognised clinically by a constellation of symptoms and signs produced by complex circulatory and neurohormonal responses to cardiac dysfunction' and as 'a disease characterised by a decline in the heart's ability to pump blood around a person's body at normal filling pressures to meet its metabolic needs.'[1] These definitions describe the clinical presentation as well as the pathophysiological process.[2] Symptoms of HF typically include shortness of breath during exertion and/or fatigue, signs of fluid retention, such as ankle swelling, and fluid in the lungs. Some patients with HF also suffer from heart rhythm abnormalities that can result in sudden death. Over time, most patients with HF experience deterioration in symptoms and hence require hospital treatment, despite medications.

In advanced stages, patients may suffer from shortness of breath at rest or minimal exertion, cachexia and muscular deconditioning, refractory fluid overload and even kidney and liver failure, a condition sometimes known as end-stage or advanced HF (AHF).[3] For consistency in this report, we will use the term AHF to describe this condition of severe HF symptoms despite conventional HF medications. The New York Heart Association (NYHA) classification system is widely used to classify the severity of symptoms related to HF. The NYHA classification has four levels of increasing severity from Class I to IV (*Table 1*). Patients with AHF suffer from NYHA Class III or IV symptoms.

Patients with HF have severely reduced QoL, especially AHF based on a number of questionnaires that measure QoL [EuroQol-5 Dimensions (EQ-5D), Short Form questionnaire-12 items (SF-12), Short Form questionnaire-36 items (SF-36), Minnesota Living with Heart Failure Questionnaire (MLHFQ), Kansas City Cardiomyopathy Questionnaire (KCCQ)].[4,5] QoL can be improved by medical therapy that improves HF.[6–16]

Epidemiology of heart failure

Heart failure prevalence varies widely depending on definitions from an estimated 23 million people worldwide (USA 6 million, Europe 15 million).[17,18] It affects between 1% and 2% of adults in industrialised populations.[19] In the UK, as many as 920,000 people are living with HF with an incidence of 37.5 and 23 per 100,000 person-years for men and women, respectively.[20] The prevalence increases with age (*Table 2*), almost doubling with each decade after 65 years. The calculated lifetime risk of developing HF is 20%.[21] HF-related hospital admission rates in England have increased by 5% over the last 10 years and are estimated to increase by about 50% in the next 25 years. Nearly half of the patients admitted with HF had severe symptoms (NYHA Class III or IV). Despite advances in medical therapy, 1-year mortality remains high at about 32% in patients admitted with HF.[22]

Data on the prevalence of AHF in the UK are lacking. A survey of European countries suggested that about 10% of all patients with HF may meet the criteria for AHF.[23] The Olmsted County (MN, USA) cohort study showed that about 14% of patients with HF met the European Society of Cardiology (ESC)

TABLE 1 New York Heart Association classification of grades of heart failure

NYHA class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnoea.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

TABLE 2 Increasing prevalence of heart failure with age[3]

Age bracket (years)	Prevalence
65–74	1 in 35
75–84	1 in 15
> 85	1 in 7

criteria for AHF with an annual rate of about 33 per 100,000 and 420 per 100,000 for the under 65 and 65–79 age groups, respectively.[24]

Aetiology and pathophysiology of heart failure

Any structural or physiological conditions that affect the ventricular function can cause HF. In the UK, ischaemic heart disease is the major cause of HF, but other causes include dilated cardiomyopathy, which may be familial (genetic) or caused by myocarditis, cardiotoxic drugs or hypertension and valvular heart disease.[25]

Historically, descriptions of HF pathophysiology have centred on the left ventricle (LV) as this heart chamber is the most commonly affected, particularly in ischaemic heart disease. Myocardial injury results in a drop in LV function and activation of the neurohormonal system. The latter contributes to salt and water retention and progressive remodelling of the heart. Fibrosis, muscle wall thinning and increased sphericity associated with LV remodelling, often accompanied by functional mitral regurgitation, further compromise myocardial efficiency and drive the downward spiral towards end-stage or advanced AHF. Myocardial fibrosis and remodelling provide the substrate for both atrial and ventricular arrhythmias, which may worsen HF symptoms and result in sudden death.

Diagnosis of heart failure and advanced heart failure

Heart failure is a clinical diagnosis, based on patient history, physical examination and investigations, such as electrocardiography, measurement of B-type natriuretic peptide (BNP) and echocardiography. The echocardiogram is used to assess heart function [by measuring ejection fraction (EF)] and also to identify possible causes or associated features, such as mitral regurgitation. Other investigations, such as chest radiography, may also detect features to support the diagnosis of cardiomegaly, pulmonary congestion and pleural fluid accumulation, but may also exclude other differential diagnoses. Cardiac

magnetic resonance imaging is increasingly used to assess the heart and identify the cause of HF. In general, BNP and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) are raised in patients with HF and the concentrations increases with the severity of symptoms.[26]

The ESC first defined AHF in a statement in 2007.[27] The position statement was updated in 2018 and the criteria for AHF were defined. The American College of Cardiology and Heart Failure Society of America have also defined AHF (*Table 3*). These definitions of AHF are conceptually very similar – severe symptoms in association with signs of congestion, poor perfusion and hospitalisations attributable to severe cardiac dysfunction despite medical therapy. One-year mortality in patients with AHF may be close to 50% in patients with all the characteristics of AHF.[24]

Recognising the significant heterogeneity in patients with AHF, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles were introduced to better describe the clinical characteristics in patients with NYHA Class III and IV HF (*Table 4*). The INTERMACS profiles have been widely adopted to describe the characteristics of patients with AHF undergoing assessment of heart transplantation or left ventricular assist device (LVAD) therapy.

Health economics

Currency and inflation adjusted cost for hospitalisation is highest in the USA ($125,000/patient/year), while in Europe HF inpatient costs vary from $5000 to $18,000 (2016 prices) with most costs

TABLE 3 European Society of Cardiology definition of AHF

All the following criteria must be present despite optimal guideline-directed treatment

1. Severe and persistent symptoms of HF [NYHA Class III (advanced) or IV].
2. Severe cardiac dysfunction defined by a reduced LVEF ≤ 30%, isolated RV failure or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-pro-BNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HfpEF and HfmrEF.
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing > 1 unplanned visit or hospitalisation in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWTD (< 300 m) or mixed venous oxygen tension (pVO_2) (< 12–14 ml/kg/minute), estimated to be of cardiac origin.

6MWTD, six-minute walking test distance.

TABLE 4 Interagency Registry for Mechanically Assisted Circulatory Support classification of AHF

NYHA class III/IV	INTERMACS class	Description
IV	1	Crash and burn (cardiogenic shock)
IV	2	Deteriorating on inotropes
IV	3	Stable IVI inotropes dependent
IV	4	At home resting symptoms on oral therapy
IV	5	Comfortable at rest but symptoms with minimal activities of daily living (housebound)
III	6	Walking wounded with activities of daily living possible but meaningful activity hampered
III	7	Advanced class III

(50–90%) derived from hospitalisations.[28,29] It usually accounts for 1–2% of a nation's health budget.[29] Health economics indicate that the cost to the NHS is £0.75B annually (approximately 4% of the NHS budget) and continues to rise, largely related to the high prevalence of cardiovascular diseases in older age groups coupled with ageing of the population. Newer medications (angiotensin receptor blocker-neprilysin inhibitors and sodium-glucose cotransporter inhibitors) and interventions (ablations, mitral valve interventions and implantable pulmonary artery pressure monitors) add to the increasing costs of HF therapy.

Medical and electrical device therapy of heart failure

Left ventricular ejection fraction has been a central inclusion criterion over the many decades of clinical trials in HF and has shaped clinical guidelines to this day. Largely based on the LVEF thresholds used in the trials, HF has been categorised into three categories: HF with reduced EF (HfrEF), HF with mid-range EF (HfmrEF) and HF with preserved EF (HfpEF) (*Table 5*). This review will focus on HfrEF, as LVADs are generally not recommended in patients with HfmrEF or HfpEF.

Neurohormonal antagonists, beta-blockers and mineralocorticoid antagonists have well-established benefits in patients with HfrEF and remain the first-line therapy in this group of patients. More recently, the sodium-glucose cotransporter inhibitors have also proven to benefit patients with HfrEF and are likely to form another pillar of HF therapy. Other drugs of benefit in some patients with HfrEF are ivabradine and hydralazine-nitrate combination (*Figure 1*). Loop and thiazide diuretics are routinely used to control congestive symptoms. Treatment options in HfpEF are limited.

Progression in HF is associated with deterioration in kidney function, low blood pressure and fluid overload, often necessitating a dose reduction in HF medications and an escalation in diuretic doses. Low cardiac output is also common at this stage, and inotropes such as dobutamine are used. These are features of AHF that herald HF prioritisation and death.

Implantable electrical devices such as implantable cardioverter defibrillators (ICDs) and biventricular pacemakers [also known as cardiac resynchronisation therapy (CRT)] are commonly used in patients with HfrEF. The latter benefit a specific subset of patients with HfrEF and left bundle branch block, with no benefit or even detrimental effect in patients with narrower QRS complexes. ICDs reduce the risk of sudden arrhythmic deaths, but do not prevent deterioration in cardiac function and death from pump failure in AHF. Shocks from ICDs are recognised indicators of poor prognosis in patients with HF. Heart transplantation or a LVAD may be considered in selected patients in whom these therapies fail.

Heart transplantation

Access to heart transplantation is limited by the shortage of suitable organ donors. In the last 10 years, the number of heart transplants (HTs) performed in the UK has dropped from a peak of almost 200 per year in 2016–8 to about 160 per year in the 2020–1 financial year, even with the adoption of donation after circulatory death heart transplantation.[30] This shortage of suitable donor organs has led to the

TABLE 5 Classification of heart failure by ejection fraction

HfrEF	HfmrEF	HfpEF
Symptoms ± signs LVEF ≤ 40%	Symptoms ± signs LVEF 41–49%	Symptoms ± signs LVEF ≥ 50% Objective evidence of cardiac abnormalities

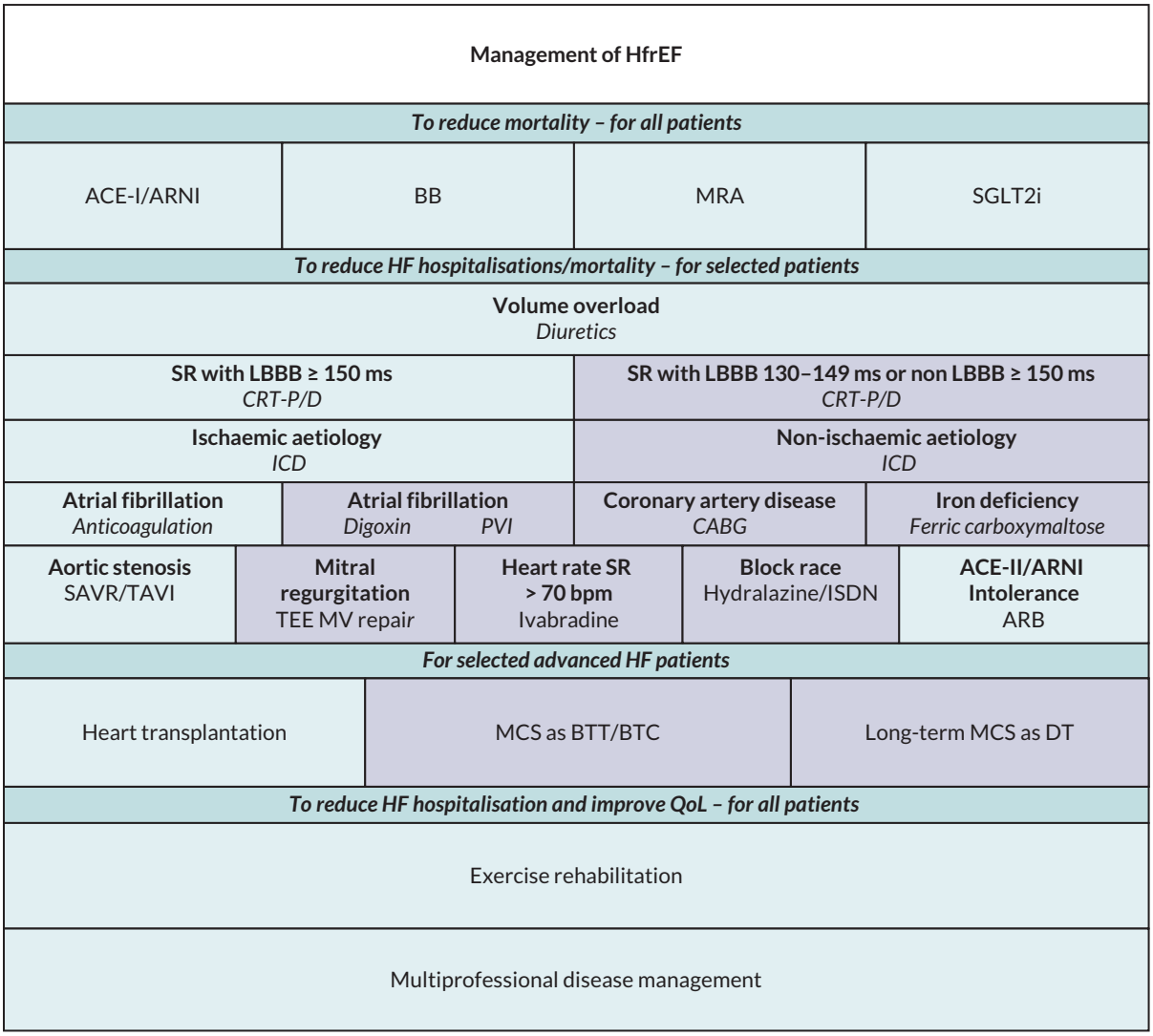


FIGURE 1 European Society of Cardiology guidelines for the management of patients with HfrEF. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; BB, Beta blockers; BTC, bridge to candidacy; BTT, bridge to transplantation; CABG, coronary artery bypass graft; CRT-P/D, cardiac resynchronization therapy with pacemaker/defibrillator; LBBB, left bundle branch block; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonists; MV, mitral valve; PVI, pulmonary vein isolation; SAVR, surgical aortic valve replacement; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SR, sinus rhythm; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography.

selection of potential recipients who are most likely to benefit from transplantation based on a range of criteria including age and comorbidities. In selected patients, heart transplantation is a very effective treatment. In the UK, the median survival from heart transplantation now exceeds 10 years. However, the rigorous selection process effectively excludes the majority of patients with AHF.

Mechanical circulatory support devices

Mechanical circulatory support devices (MCSDs) have increasingly been used in the last decade to support patients with worsening HF. These MCSDs may be categorised into temporary (or short-term) and durable (or long-term) devices. The former are largely extracorporeal devices and patients are managed in hospital (often in a high-dependency or intensive care environment), while patients with the latter may be discharged home on the device. Most of the durable MCSDs used in the UK are LVADs. Total artificial hearts and biventricular assist devices will not be discussed in this review.

The terminology in left ventricular assist device therapy

Historically, the nomenclature of LVAD therapy is closely linked to candidacy or eligibility for heart transplantation and treatment intent:

1. Bridge to candidacy (BTC) refers to LVAD therapy in patients with a contraindication to heart transplantation that is potentially reversible with LVAD therapy, such as renal dysfunction or pulmonary hypertension due to left heart disease. Patients would be expected to become candidates for heart transplantation following reversal of the contraindication by LVAD therapy. Thus, the intention of LVAD therapy is to reverse the contraindication to allow heart transplantation.
2. Bridge to transplantation (BTT) refers to LVAD therapy in patients who are eligible candidates for heart transplantation but may be deteriorating on medical therapy on the waiting lists. Progression of HF while on the waiting list may result in multiorgan failure to the extent that they may no longer be suitable candidates for heart transplantation. This may result in death. The treatment objectives of BTT are to stabilise and prevent death in patients on the waiting list for heart transplantation and optimise the outcome of heart transplantation.
3. Destination therapy (DT) refers to LVAD therapy in patients who are not eligible for heart transplantation due to established contraindication(s) that are not amenable to correction by LVAD. The objective of the LVAD as DT is to provide symptomatic and prognostic benefits to patients with AHF who are at high risk of mortality on medical therapy and not suitable for heart transplantation. In an INTERMACS report, contraindications to heart transplantation included advanced age, renal dysfunction, chronic lung disease or high body mass index (BMI). Despite the initial treatment intent, approximately 10% of patients originally considered unsuitable for heart transplantation and selected for DT subsequently improved sufficiently (e.g. improvement in frailty) to undergo transplantation after 2 years of LVAD therapy.[31]

Evolution of left ventricular assist devices

Left ventricular assist devices have evolved considerably over the last few decades. The first generation of LVADs were pulsatile devices. These pulsatile devices were large devices due to the need for pumping chambers. The poor durability of first-generation pulsatile devices limited longer-term outcomes, with survival limited to < 2 years in the majority of patients. The high device failure rates led to the development of non-pulsatile continuous flow LVADs.

The second-generation LVADs are non-pulsatile axial flow devices. These axial flow LVADs are significantly smaller than the first-generation pulsatile pumps, which simplified device implantation considerably. In addition to the reduction in implant-related morbidity, axial flow LVADs were also associated with improved durability and significantly improved longer-term outcomes. One of the most commonly used axial flow LVADs was the HeartMate II™ LVAD (Abbott, Chicago, IL, USA). These improvements led to greater adoption and acceptance of LVAD therapy. In the USA, LVAD implant rates increased exponentially with the introduction of the second-generation axial flow LVADs. Despite the improved durability, pump thrombosis and bleeding complicated longer-term support with second-generation LVADs.

The third-generation LVADs are centrifugal flow devices. The HeartWare™ ventricular assist device (HVAD™, Medtronic, Dublin, Republic of Ireland) is a small intrapericardial centrifugal flow pump. Promising early results led to approval for clinical use, although pump thrombosis and neurological complications were concerning. The risks of neurological complications and device failure became increasingly evident with widespread use and the device was withdrawn worldwide in June 2021.[32] At present, there are no new implants of the HeartWare HVAD, although some patients continue to be supported in the UK.

The HeartMate 3™ (HM3) LVAD (Abbott, Chicago, IL, USA) was introduced in 2015 in the UK. The HM3 LVAD is a centrifugal flow device with a number of design features to improve ‘haemocompatibility’

and reduce the risk of complications such as pump thrombosis. Clinical studies confirmed a significantly lower risk of pump thrombosis compared to HeartMate II, and an ongoing randomised trial is evaluating reduced antithrombotic therapy with HM3.[33] HM3 is now the only LVAD in use in the UK following the withdrawal of the HeartWare HVAD.

Description of continuous flow left ventricular assist devices

Continuous flow devices are so called because they generate flow throughout the cardiac cycle. In centrifugal devices, blood is drawn via the inflow cannula in the LV by an impeller within the pump and delivers the blood into the aorta via the outflow graft. The outflow of the pump is arranged perpendicularly to the inflow cannula. Flow can be changed by adjusting the pump speed (revolutions per minute) via the system controller. Pump speed must be carefully balanced as excessive pump speed could compromise right ventricular function.[34] The device is connected to a power source or a pair of batteries via an externalised drive line.

Complications of left ventricular assist device therapy

Various complications can be attributed to the abnormal interaction between the LVAD and the biological circulation, so-called haemocompatibility-related adverse events (HRAEs). Device-related haemolysis, pump thrombosis and systemic embolism, stroke, intracranial bleeding and gastrointestinal (GI) bleeding (GIB) are major HRAEs that compromise long-term outcomes of LVAD therapy. These HRAEs occur in both axial and centrifugal flow devices, but the HM3 LVAD has been associated with a lower burden of HRAEs compared to HeartMate II.[35]

The LVAD supports the LV but often at the expense of the right. Right heart failure (RHF) is a major cause of morbidity and mortality. Studies have identified several risk factors for RHF post-LVAD implant, including pre-implant measures of right ventricular function and severity of HF and organ dysfunction; however, the ability to predict post-LVAD RHF remains challenging.[36] Severe RHF is associated with higher mortality. Timely deployment of a temporary right ventricular assist device (RVAD) may mitigate this risk.[37] Late RHF is increasingly recognised and may limit long-term QoL.

The continuous emptying of the LV and delivery of blood into the aorta pressurises the aorta and reduces left ventricular stroke volume in patients with LVADs. The aortic valve may not open if the LV fails to generate sufficient pressure to overcome the aortic pressure, with consequent loss of arterial pulsatility. Over time, the reduction in aortic valve opening may lead to degenerative changes of the valve and aortic regurgitation (AR). A competent aortic valve is a prerequisite of LVAD function. Severe AR results in the recurrence of HF symptoms and adversely affects long-term survival in patients with LVADs.[38]

As with any implantable devices, LVADs are susceptible to infection. Infection in patients with LVADs may not be attributable to the device. Infections related to the device may be localised, related to the driveline (most common) or more severe bloodstream infection related to the pump or endocarditis. The latter may be associated with neurological complications and increased mortality.[39]

Current service provision and patient pathway

In the UK, LVADs are currently commissioned in the six HT centres for the purpose of BTC and BTT. Referrals to these centres follow existing pathways in the HT service. As a BTC and BTT service, LVADs are only offered to patients who are eligible for heart transplantation. Despite the intention to bridge patients to heart transplantation, the heart allocation policy does not prioritise candidates with LVADs for transplantation.

In the most recent iteration of the heart allocation policy in the UK, patients with LVADs without complications are offered listing on the 'non-urgent' waiting list, the lowest priority of the three tiers (the other two tiers are 'urgent' and 'super urgent'). Patients with LVAD-related complications may be upgraded to the 'urgent' list following approval by an adjudication panel, consisting of representatives from each of the HT centres. Paradoxically, prioritisation and transplantation only when patients develop LVAD-related complications is associated with poorer outcomes, which is inconsistent with the original concept of BTT – to optimise the outcome of heart transplantation. In effect, most patients without LVAD-related complications would continue on long-term LVAD support, simultaneously BTT (by intent) and DT (in practice).

In the most recent iteration of the ESC Guidelines, a LVAD has been recommended in patients with INTERMACS 3 or 4 AHF with contraindications for heart transplantation (*Figure 2*). Available solely as a bridging therapy, the rate of LVAD implantation in the UK is low compared to other European countries, especially in countries where DT is established. According to a recent study, the UK has one of the

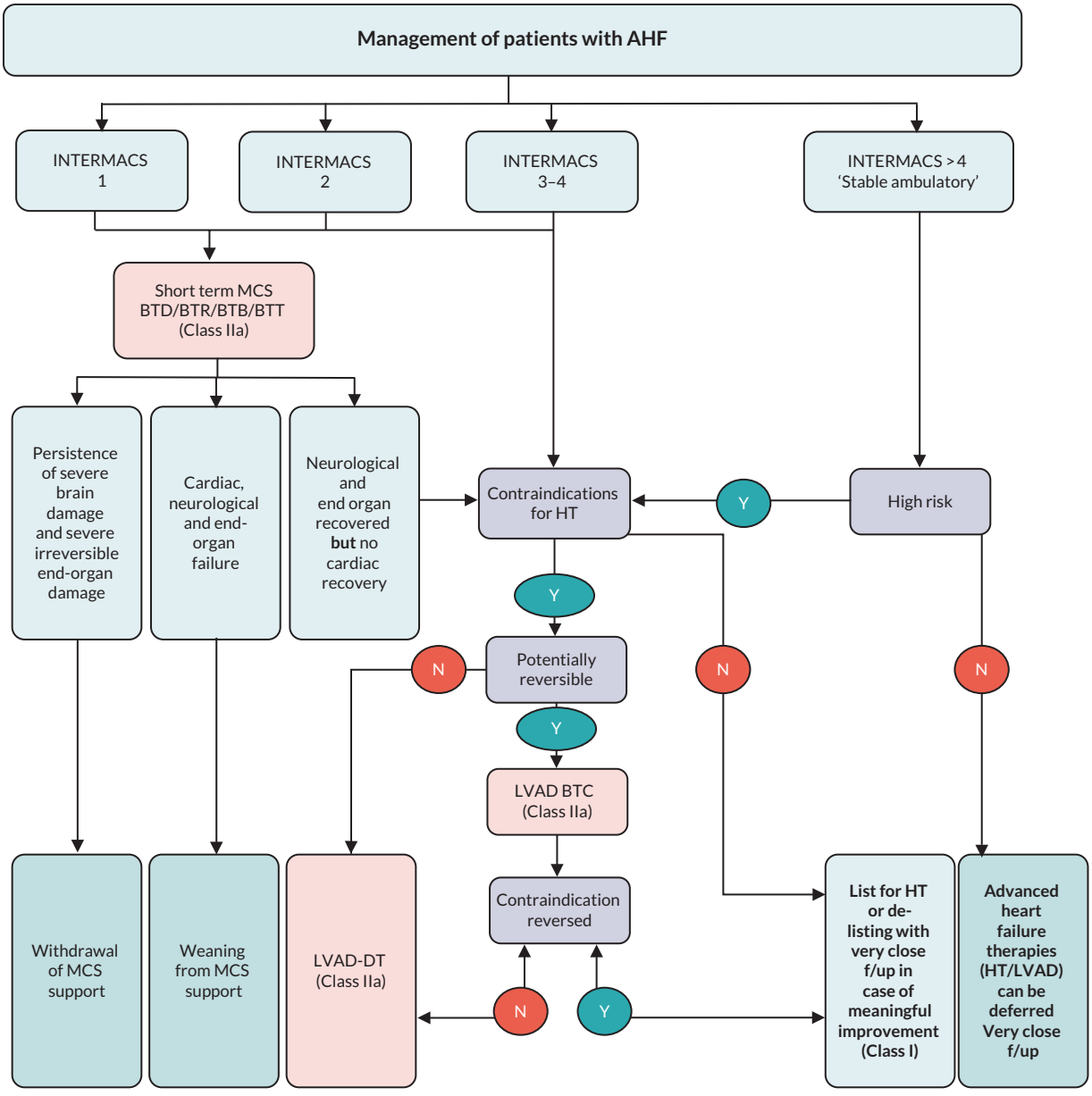
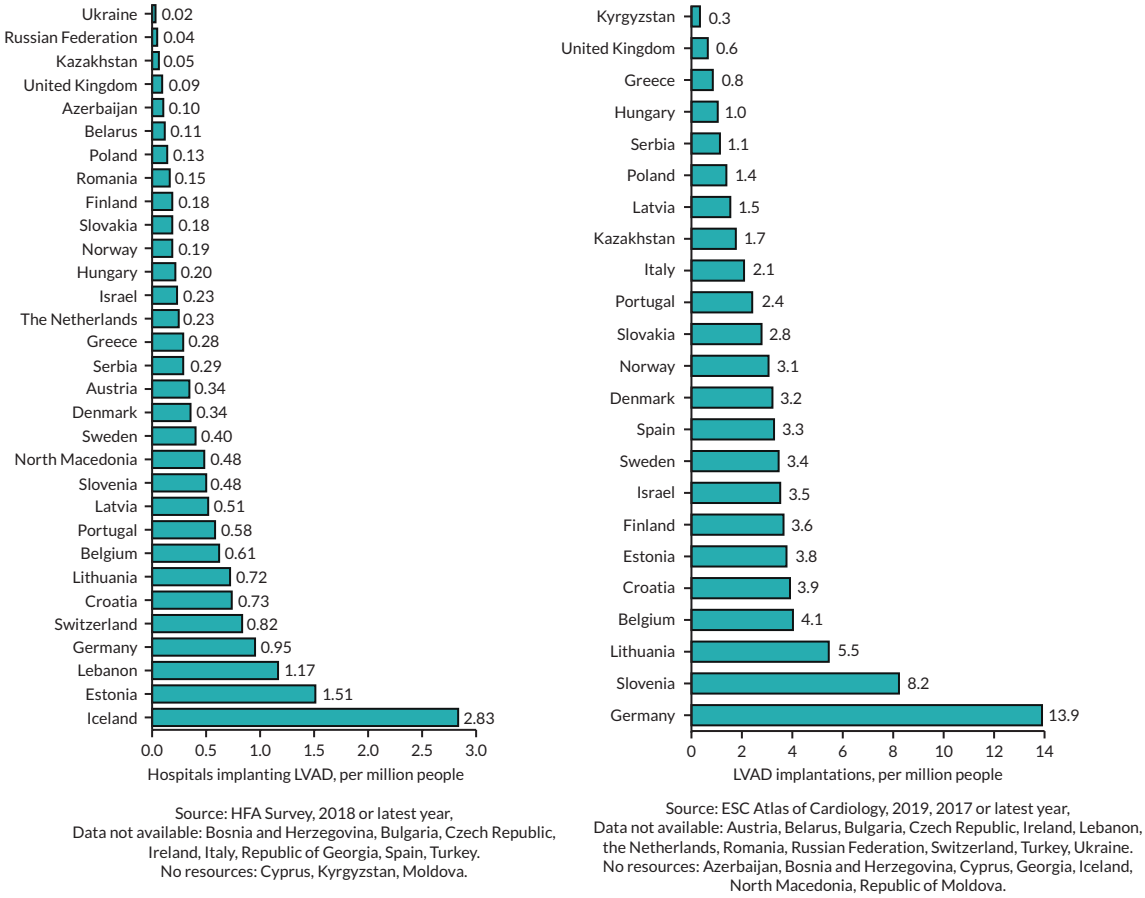


FIGURE 2 European Society of Cardiology guidelines for the management of patients with AHF. BTB, bridge to bridge; BTD, bridge to decision; BTR, bridge to recovery.

lowest LVAD implant per million population at 0.6, compared to a number of European countries (e.g. Hungary 1.0, Portugal 2.4, Spain 3.3, Belgium 4.1 and Germany 13.9) (*Figure 3*).[23]

In summary

Heart failure is an increasingly common problem with significant impact on individual patient's QoL and longevity as well as population health economics. Advanced heart failure that fails to respond to medical management (MM) may be treated by LVAD implantation and/or heart transplantation. In the UK, LVAD implantation has been commissioned as a bridging therapy to transplantation. In other countries with different healthcare delivery systems, the majority of LVADs are implanted as DT in patients ineligible for heart transplantation. In the UK, a LVAD for such patients is not currently commissioned. The lack of economic evidence is a key reason that NHS England has not recommended a LVAD for DT.



*Since Iceland has a population of approximately 350,000, data also expressed per 100,000: LVAD implanting hospitals 0.2.

FIGURE 3 Hospitals implanting LVAD per million people (left) and number of LVAD implantations per million people (right). Reproduced from Serefovic *et al.*[23] with permission from John Wiley & Sons.

Chapter 2 Aims

To make an informed decision on the use of LVADs for patients with AHF that fail to respond adequately to MM and who are ineligible for a HT, robust evidence on clinical and cost-effectiveness is required.

The aim of the research documented in this report was to address the question: What is the clinical and cost-effectiveness of a LVAD compared to MM for AHF patients ineligible for heart transplantation (DT)?

The specific objectives to address this aim were to undertake:

- a systematic review of available evidence on the clinical effectiveness of a LVAD as DT, including a network meta-analysis (NMA) to provide an indirect estimate of the relative effectiveness of currently available LVADs compared to MM (see *Chapter 3*);
- a systematic review of available economic evidence on the use of a LVAD as DT (see *Chapter 4*); and
- the development of an economic model to estimate the cost-effectiveness of a LVAD compared to MM from the UK NHS/personal social services (PSS) perspective (see *Chapter 5*).

Sources of information used in undertaking this research include trials, observational studies, economic evaluations, reports from registries, guidance from LVAD recipients and their families, clinical experts, those commissioning healthcare services and companies supplying LVADs.

An exploration of the ability of accessible data sets to provide further data relevant to LVADs as DT was also undertaken (see *Appendix 1*).

When this research was commissioned and begun, there were two predominantly available LVADs in the UK used for AHF patients. As outlined in 'Evolution of left ventricular assist devices', the HeartWare device was withdrawn in 2021. Therefore, this report, while still considering evidence from research on all LVADs for DT in part and where relevant, focuses on the remaining device, HM3. The HM3 is the only device used for AHF patients in the UK at this time.

Chapter 3 Clinical effectiveness of left ventricular assist devices compared to medical management as destination therapy in advanced heart failure patients

Introduction

Left ventricular assist device DT strategy is not currently common practice in the UK. This chapter aimed to systematically review all of the available evidence on the clinical effectiveness of LVADs as DT; including a NMA to provide an indirect estimate of the relative effectiveness of currently available LVADs compared to MM. This was also used to inform the development of the economic model in *Chapter 5*.

Methods

This systematic review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[40] The review is registered on PROSPERO (CRD42020158987).[41]

Eligibility criteria

Population
Patients (age > 16 years) with AHF who received a LVAD as DT and were ineligible for a HT or potential candidacy at the time of the LVAD implantation. Studies with mixed LVAD populations were also included where DT data were reported separately or could be easily acquired. Eligibility for heart transplantation is defined by individual centres based on international guidelines, but there may be variations in practice.

Intervention
There were no restrictions placed on the type of LVAD, either by flow design or by generational evolution (e.g. first-generation pulsatile pump, second-generation continuous axial flow or third-generation continuous centrifugal flow). All devices were included, regardless of current availability, for completeness of information and for use in the NMA. Studies of participants with biventricular assist devices, or RVADs were not eligible for inclusion.

On 3 June 2021, midway through conducting this project, one of the current third-generation continuous flow centrifugal LVADs, the HeartWare HVAD (used extensively throughout North America, UK and Europe) was withdrawn from the market. While studies on HVAD were included, the analysis focuses on the currently available device (HM3), which reflects the availability to patients as it is the only device currently available in the UK.

Comparator
Medical management or different generation or type of devices or no comparator.

Outcomes
All relevant key outcomes were considered. Outcomes were categorised in accordance with categories established for parameters in the economic model. These were survival, hospitalisations, major events (e.g. stroke, RHF), complications [e.g. GIB, driveline infection (DI), arrhythmias], any report of

QoL and functional status (e.g. six-minute walk test). The outcomes are further defined in the data extraction details.

Types of study

Any clinical trial whether randomised, non-randomised or single-arm was included, as well as all observational studies including cohort, case-controls and case series designs. This also included any reports from patient registries of MCSDs (such as INTERMACS, etc.). Studies were eligible only where they included ≥ 50 or more DT patients. A threshold was required, given the large volume of small studies with likely limited value overall to the review. The threshold was based on calculations to determine the likely volume of missed evidence when excluding studies based on various sample size cut-offs. This was carried out by taking a sample of 200 relevant full-text articles and calculating what proportion of patients we would miss by excluding studies based on different sample size cut-offs. Excluding studies with a sample size of < 50 DT patients resulted in an estimated 4.8% of patients excluded across the evidence base. As a result, it was decided to only include studies with at least 50 participants. Systematic reviews were included to identify any additional potentially relevant primary studies.

Searches

The following databases were searched initially from inception until 20 May 2020: Cochrane Library (CENTRAL), MEDLINE and EMBASE via Ovid. For any relevant systematic reviews Epistemonikos, the Cochrane Library of Systematic Reviews and MEDLINE and EMBASE were searched. Searches incorporated free text and index terms related to population and intervention, with no restriction by study design. All database search strategies are available (see *Appendix 2*). The search term combinations in the example search strategy applied to the bibliographic databases were formulated in the standard way for a review and then augmented to ensure the strategy was sensitive to capturing studies known to the reviewers while keeping the yield to manageable numbers of records.

There was no restriction by date or language of publication on searches. Reference lists of relevant systematic reviews and included primary studies were checked for additional primary studies. Grey literature (e.g. institutional reports) was sought from key organisations. Conference abstracts were included if published within the previous 3 years of the search date. Ongoing and recently completed trials were searched using the World Health Organization (WHO) clinical trials portal.

Data and reports published from relevant registries were also identified from our searches. Further targeted searching was performed to identify publications that were not found during the searches.

Search updates were carried out from April 2020 until 11 January 2022. Searches for registry reports via relevant website lists (e.g. www.uab.edu/medicine/intermacs/research/publications) were undertaken at the same time as the database searches.

Study selection

All records received from the literature searches were initially entered into EndNote X9 (Clarivate Analytics) to facilitate removal of duplicates.[42] Records were entered into Covidence for screening and selection.[43] Title and abstracts were screened for potential relevance using the study eligibility criteria.

Where it was not clear if DT patients were included in the study or if any DT data were reported from the abstract alone, the full text of the study was sought. Full texts were retrieved for any potentially relevant records and checked for eligibility.

All stages of the study selection were undertaken by two reviewers independently and disagreements were resolved by third reviewer or consensus. Reasons for exclusions were recorded via Covidence and within an Excel spreadsheet.

Search results for both the cost and clinical effectiveness reviews were combined within the same EndNote and Covidence databases. During screening and selection, appropriate tags were assigned to potentially relevant records to identify them as either relevant for the clinical or cost-effectiveness review, or both.

Data extraction

Intervention studies

Data extraction of intervention studies was carried out using a predefined data extraction form, which was piloted on two included trials. Extraction was carried out by one reviewer and checked by a second with any discrepancies discussed to reach consensus.

The following data were extracted:

- Study characteristics: including study design, setting, start and end dates, follow-up length, inclusion/exclusion criteria, number of participants who accepted, were randomised (where applicable) and completed the study, drop out and reasons.
- Participant characteristics: including summary statistics for age, sex, ethnicity, INTERMACS score, NYHA class, comorbidities, cause of HF, current RVAD and any medications and BMI.
- Intervention and comparator characteristics: including device type and name, number with each device, implantation details, MM dose and frequency.
- Statistical analysis information such as methods of analysis.
- Outcome data: survival, hospitalisation (initial length of stay, number of re-admissions), QoL (any assessment tool), major clinical events [stroke, transient ischaemic attack (TIA), RHF, RHF managed with a RVAD, myocardial infarction, pump exchange (PE)], complications (bleeding, infections, device-related infections, arrhythmias, pump thrombosis, device malfunction, hepatic dysfunction, haemolysis, hypertensions, sepsis), and functional status (any assessment tool). Outcome data were extracted at all time points reported in all measures.

Registries

Key data on all LVAD outcomes were extracted from registry reports to use alongside the trial data as trial populations were not included in the INTERMACS registry database. The following data were extracted:

- Basic cohort characteristics: including population, age, INTERMACS scores (where reported), any subgroups analysed and device data (understanding that this information was often limited in registry reports).
- Outcome data: survival, hospitalisation (initial length of stay, number of re-admissions), QoL (any assessment tool), major clinical events (stroke, TIA, RHF, RHF managed with a RVAD, myocardial infarction, PE), complications (bleeding, infections, device-related infections, arrhythmias, pump thrombosis, device malfunction, hepatic dysfunction, haemolysis, hypertensions, sepsis) and functional status (any assessment tool). Outcome data were extracted at all time points reported for all measures.

Single/multicentre observational studies

Data were extracted (as above) from all single/multicentre observational studies recruiting participants not included in any registries to supplement the data from trials and registries. Some of these studies were important in providing data from outside the USA. Single/multicentre observational studies that also contributed patient data to the INTERMACS database [and therefore International Registry for Mechanically Assisted Circulation (IMACs)] were only used if they reported key data missing from the previous evidence (such as survival, QoL and major events).

Risk-of-bias assessment

Risk-of-bias assessment was carried out by one reviewer and checked by a second. Tools appropriate for study design were used to assess risk of bias. For RCTs and non-RCTs, version 2 of the Cochrane risk-of-bias tool was used.[44] The randomisation domain was not applicable for non-randomised trials, and it was acknowledged that blinding is not possible in most surgery trials. Risk-of-bias assessment was carried out for the key outcomes of survival and QoL. These were considered as key outcomes as they were consistently reported across trials of this type and were important outcomes for the economic evaluation. Results of the risk of bias were presented in tabular format.

Data synthesis

Consideration, data extraction and reporting of the evidence were based on a hierarchical approach. RCTs and controlled non-randomised trials were considered in the first instance. Registry reports and uncontrolled observational studies were used to supplement findings where gaps were evident. Inclusion of studies with overlapping patient data was avoided where possible. However, all studies, regardless of design, were included and reported in the review.

Clinical trial participants are not eligible to be included in LVAD registries (such as INTERMACS and IMACS). To assess whether patients in trials differed from those in registries, exploratory analyses were undertaken comparing key population differences between the two. This was carried out where the data were available for key outcomes including survival and QoL. Additionally, changes over time in each population were assessed.

Overlap of participants between single, multicentre observational studies and registries was also considered. Many of these centres in the USA also contribute data to registries, including INTERMACS and by default, IMACS. To avoid overlap of participant data reported, data were only considered from studies that clearly did not contribute to the INTERMACS registry (as defined by the list of participating centres on the INTERMACS website www.uab.edu/medicine/intermacs/pedimacs/participating-centers-pedimacs).

Data were tabulated and analysed in a narrative approach in the first instance, firstly with comparative data stratified by device (e.g. HM3) and INTERMACS scores (where available), and then by outcome within this. Following this, non-comparative data were presented stratified by device type and INTERMACS scores (where available), and by outcome within this.

Due to large clinical and methodological heterogeneity expected in the data, no meta-analyses were performed.

Forest plots without pooled estimates were created for all data stratified by device type for each outcome category (survival, QoL, hospitalisations, major events and complications).

While all recent devices (e.g. HeartMate XVE™, HeartMate II, HeartWare HVAD, HM3) were included and analysed, priority was given to the HM3 device given the availability of devices in the UK and the recent withdrawal of the HeartWare HVAD device in June 2021.

Statistical analysis

Outcomes of mortality, hospitalisation, major events and complications

Potentially relevant data for these outcomes were reported in a variety of different forms. These included:

- rate per participant, rate per participant-year, rate per 100 participant-years;
- total number of events, mean number of events per participant, number of participants who had at least one event, proportion of participants who had at least one event, proportion of participants who were event free; and
- total follow-up time in person-years, average study follow-up time, overall study follow-up time.

Where possible, these data were used to estimate (1) the proportion of participants who had an event, and (2) the event rate per 100 person-years. For each of these statistics a hierarchical approach was used to calculate the sufficient statistics for each study with preference given to those approaches that made the fewest assumptions:

1. Proportion of participants who have had the event at least once by the follow-up time. Where possible, these proportions and their 95% CIs were estimated using exact binomial distribution and the results are presented in forest plots. Estimation of the number of participants with the event was as follows:

1. The number of participants with an event is reported by the study report and this number is extracted.
2. The number of participants in the study group together with the proportion of participants with the event are reported. Multiplication of these two quantities rounded to the nearest integer is used.

2. Event rate per 100 participant-years Where calculable, event rates per 100 participant-years follow-up were reported together with 95% confidence intervals (CIs) and these are displayed on forest plots. To estimate the standard errors and CIs it was assumed that patient events over the whole participant group followed a Poisson process and that the sampling distribution on the log-rate scale was normal.

Estimation of total study follow-up time in each group:

1. The total follow-up time was reported for each group and these numbers were extracted.
2. If the total number of events and the rate of events per patient-year (or 100 patient-years, etc.) were reported, these were multiplied together (after a suitable linear transformation if required).
3. If the follow-up time for the study and the number of participants in the study were reported, then these were multiplied together.

Estimating event rate per 100 patient-years follow-up:

1. The number of events per patient-year (or 100 patient-years etc.) was reported, then an appropriate linear transformation was used if required.
2. The total number of admissions divided by the total person-years follow for the patient group if these were both either reported or calculable as described above.

Estimating the number of events occurring in each study.

1. The total number of events for the patient group is reported by the study.
2. If the number of events per participant-year and the total follow-up time were reported or could be estimated as described above, then these were multiplied.
3. If the mean number of events per participant and the total number of participants was reported for each group these were multiplied together and rounded to the nearest integer.

Network meta-analysis

Indirect comparisons between all nodes in the network together with standard errors were calculated using the Butcher method (chained over indirect comparisons as required) on natural log relative risk (RR) scale.[45] As there was no closed loop evidence, no checks for evidence consistency were possible. As there was only one trial for each comparison a fixed effects model was used, and no estimates of heterogeneity were calculable.

Subgroup analysis

Key subgroups were considered following input from the steering group. This included reporting of data from participants with different INTERMACS profiles (indicating severity of HF) as well as different age categories. Subgroup analysis was considered where relevant data were available. While meta-analysis of subgroups was not possible due to a lack of data or differences in definitions, subgroup data were presented in forest plots without summary points.

Results

Selection

Searches for both clinical and cost-effectiveness studies identified 12,153 articles. Following removal of duplicates, 9006 articles remained. There were 982 articles found to be potentially relevant following title and abstract screening, and full texts were sought and checked against the eligibility criteria. Following this, 240 articles from 134 studies met the criteria for the clinical effectiveness review and were included.

There were 6 trials (1 non-randomised, 5 RCTs), 86 observational studies, reports from 5 registries, 5 ongoing studies and 32 systematic reviews (included for citation checking). It should be noted that some of these studies were from the same centres and reports from the same registries were considered as one single study. There were 24 relevant articles included following citation checking, 21 of which were relevant to the clinical effectiveness review. Seven full-text articles could not be retrieved. A summary of the selection process is given in *Figure 4*. A list of full-text articles excluded with reasons is available in *Appendix 3*.

Types of included studies

Studies included in the review were categorised as comparative trials, registry reports or single and multicentre observational studies.

Devices

Several LVADs have been used in the care of end-stage HF patients and these are detailed in *Table 6*. The pulsatile HeartMate XVE is no longer in clinical use and was replaced by the HeartMate II device. The HeartWare HVAD was withdrawn from the market in June 2021 due to concerns over increased stroke risk and pump thrombosis compared to alternative devices.[32] The HM3 device is currently the most implanted device in the USA, having been approved for clinical use by the Food and Drug Administration (FDA) for DT in 2019.[46]

Table 6 also details the EVAHEART 2 (Evaheart Inc., Houston, TX, USA) LVAD, described as a centrifugal hydraulically levitated 'open vane' impeller that supports blood circulation and high peak flows for retained native pulsatility. The device is currently being trialled in a large RCT in the USA under a FDA-approved investigational device exemption and being compared to the HM3 device with completion estimated for 2024.[47] At the time of the report's writing, no results or data have been published pertaining to the EVAHEART 2.

HeartMate 3 data

The HM3 is currently the only option for LVAD-eligible patients in the UK following the withdrawal of the HeartWare HVAD. This section will describe the available data pertaining to the HM3 device.

Trial data

There was one RCT (MOMENTUM 3) undertaken in the USA that compared the HM3 device to the older HeartMate II device. There were 1028 participants included in the study: 515 randomised to the HM3 (317 of these DT) and 505 randomised to the HeartMate II (307 DT). The mean age for all included

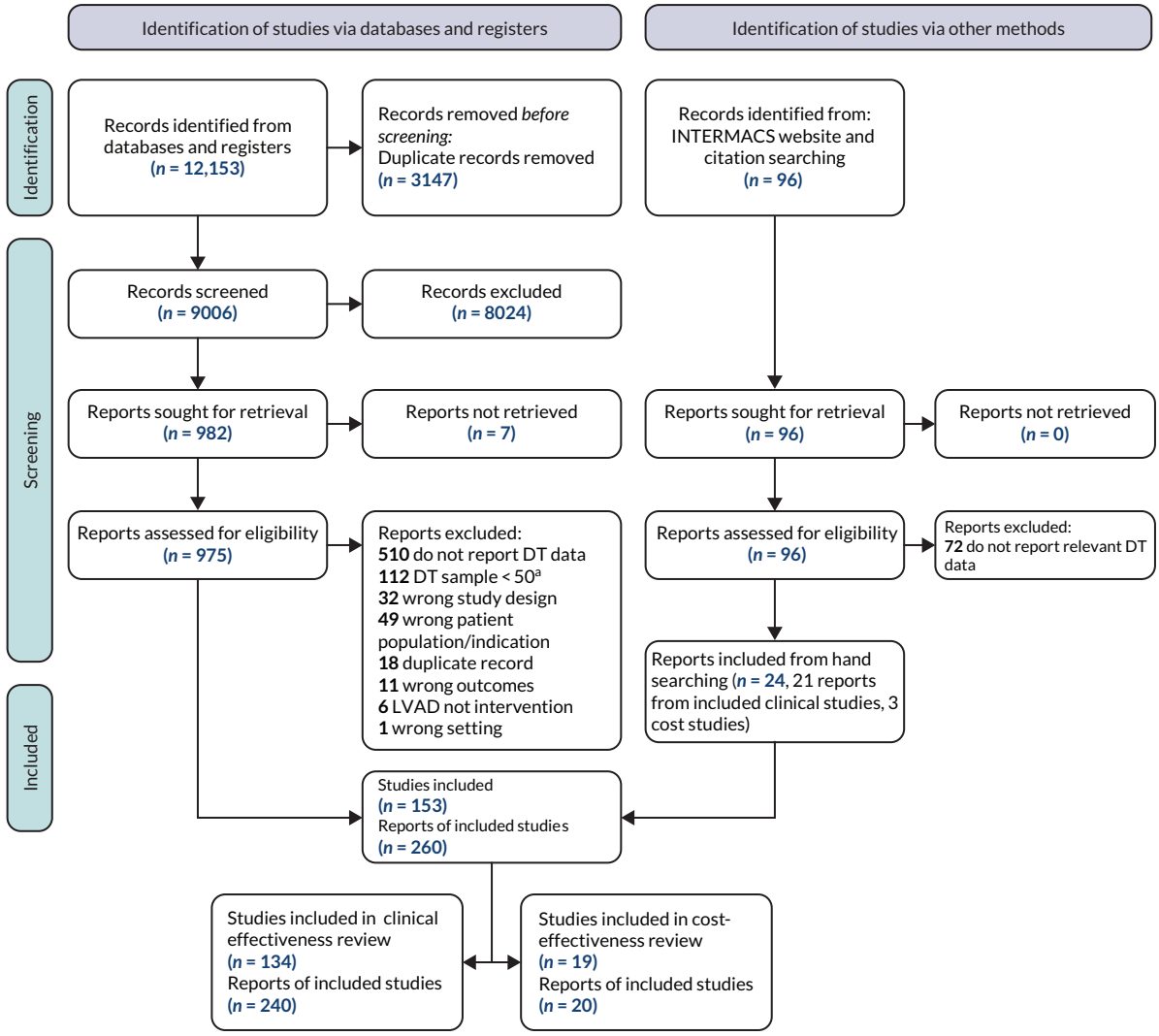


FIGURE 4 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing selection of studies. a, Only studies considered for the clinical effectivenessreview were excluded based on sample size.

DT patients was 63 (SD 12) and the majority of included participants were INTERMACS level 3 (*Table 1*). The following section reports data by outcome from this RCT.

Survival

Survival in DT patients implanted with the HM3 device was 84% at 12 months and 77% at 24 months of follow-up (*Figure 5*). This is higher than any previously reported survival data in earlier generation devices at 24 months (see *Appendix 5*). Survival in HM3 DT patients was higher than the HeartMate II patients in the MOMENTUM study at 24 months (77% vs. 59%, respectively) with a hazard ratio (HR) of 0.87 (95% CI 0.63 to 1.2), though this was not considered a statistically significant difference. However, survival free of disabling stroke or reoperation to replace or remove a malfunctioning device at 24 months was significantly higher in patients in the HM3 group compared to the HeartMate II group (73% vs. 57%), with a HR of 0.61 (95% CI 0.46 to 0.81).

Quality of life

While clear improvements in QoL were reported in DT patients with the HM3 device in both the KCCQ and the EQ-5D at 12 and 24 months compared to baseline, similar QoL improvements were also seen in the HeartMate II group. The mean visual analogue scale (VAS) summary score for the KCCQ improved from 40 at baseline to 69 at both 12 and 24 months in the HM3 group (*Figure 6*), compared to 39 at

TABLE 6 Left ventricular assist device characteristics

Device	Type	Weight	Size	Circulatory support (RPM, flow l/min)	Manufacturer
HeartMate XVE	Vented electric device, pulsatile flow	1255 g	Diameter: 11.2 cm Nominal height (excluding ports) 5.8 cm (The size of the device requires patients to have a body surface area of more than 1.5 m^2)	4–10 l/minute	Thoratec Inc., Ann Arbor, MI, USA
HeartMate II	Axial-flow pump (continuous flow)	350 g	Diameter: 4 cm Length: 7 cm	10 l/minute at RPM ranging from 8000 to 15,000	Thoratec Inc., Ann Arbor, MI, USA
HeartMate 3	Fully magnetically levitated centrifugal-flow pump (continuous flow)	200 g	Diameter: 50.3 mm Height: 55.8 mm (includes inflow cannula), 33.8 mm (excludes inflow cannula)	10 l/minute RPM ranging from 3000 to 9000	Abbott Laboratories, Chicago, IL, USA
HeartWare HVAD	Centrifugal-flow pump (non-magnetic) (continuous flow)	145 g	Diameter: 4 cm Length: < 2 cm	10 l/minute at RPM ranging from 1800 to 3000	Medtronic Inc., Minneapolis, MN, USA (formerly HeartWare Inc., Framingham, MA, USA)
EVAHEART 2 (EVA2)	Centrifugal-flow pump, hydraulically levitated impeller for retained pulsatility	NR	NR	7–8 l/minute up to 2200 RPM	Evaheart Inc., Houston, TX, USA

NR, not reported (the information could not be found).

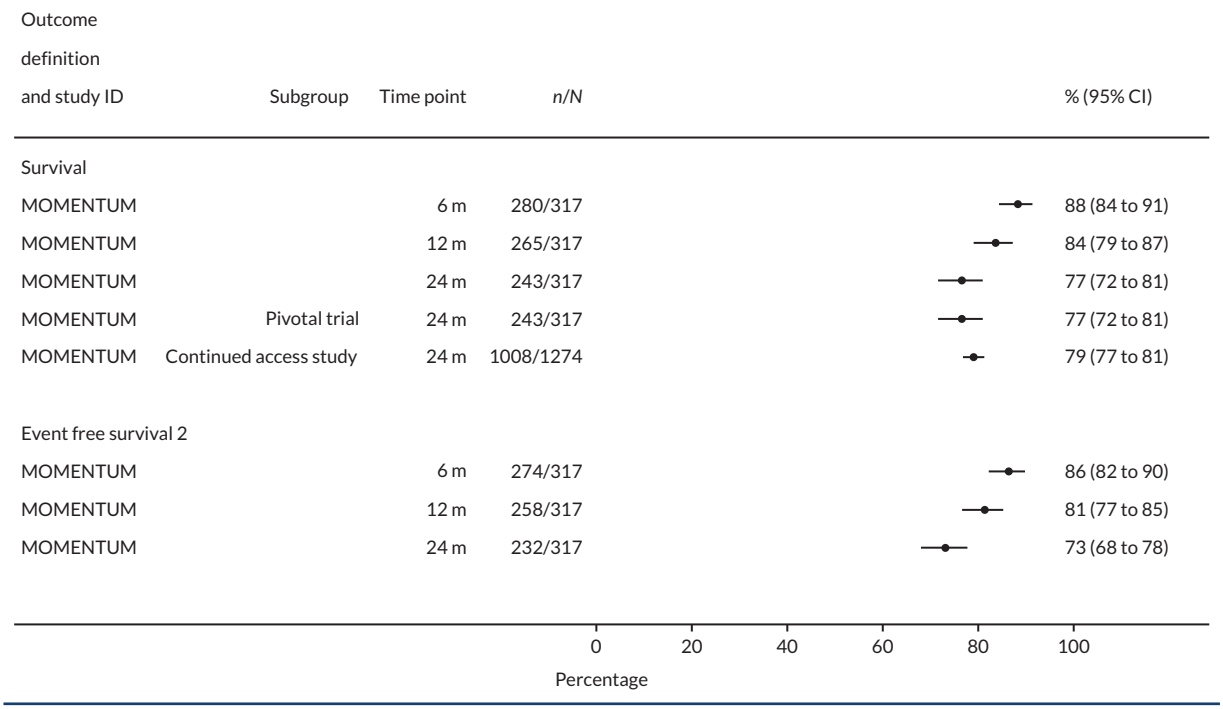


FIGURE 5 Survival data in the HeartMate 3 at all reported follow-up time points.

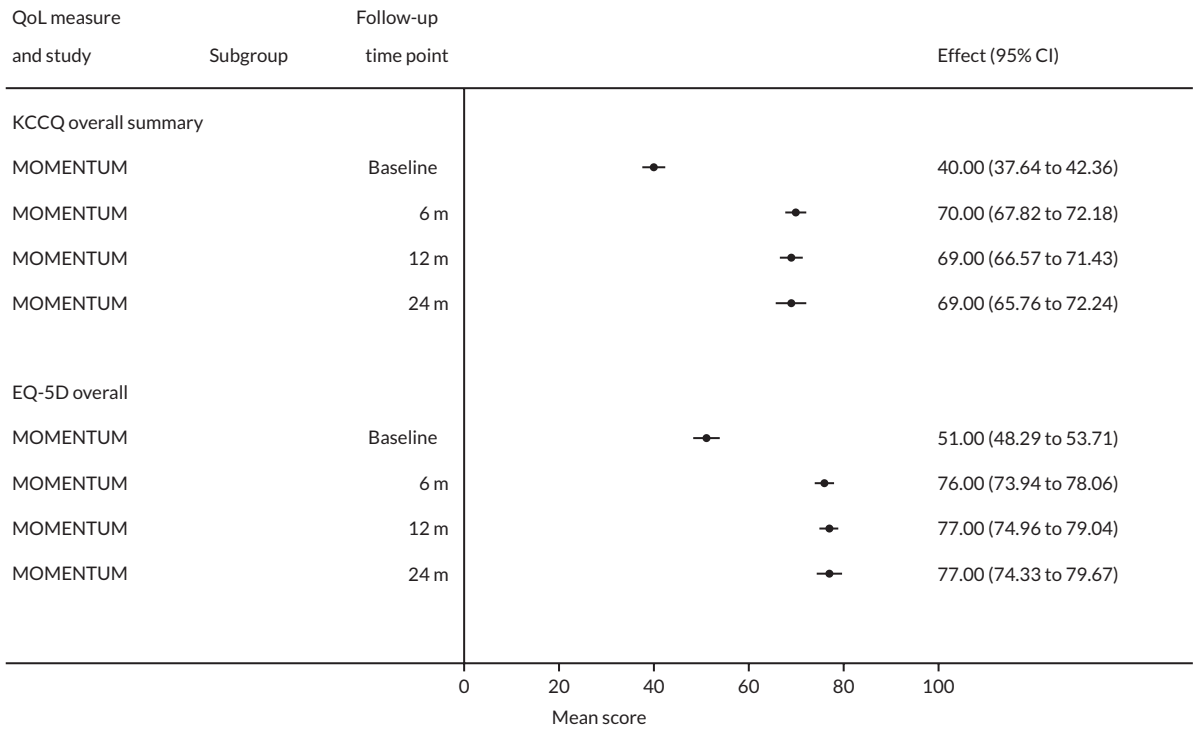


FIGURE 6 Mean QoL scores in the HeartMate 3 at all reported follow-up time points.

baseline increasing to 70 at 12 months and 68 at 24 months in the HeartMate II group. Furthermore, the EQ-5D VAS score improved from 48 at baseline in the HeartMate II group to 74 at both 12 and 24 months (compared to an increase from 51 at baseline to 77 at 24 months in HM3). Improvements in QoL appeared to peak at 12 months and remain stable at 24 months. Scores remained similar to those at 24 months at the end of study follow-up.

Hospitalisations

Rehospitalisation days were reported to be fewer in HM3 patients compared to those with the HeartMate II device (median duration 15 vs. 22 days) over 24 months. The event rate of rehospitalisation per 100 patient-years was found to be significantly lower in the HM3 group versus the HeartMate II group (212 vs. 243, HR 0.88 95% CI 0.81 to 0.96, *Figure 7* Hospitalisation rate per person-year in the HeartMate 3 at 24 months follow-up).

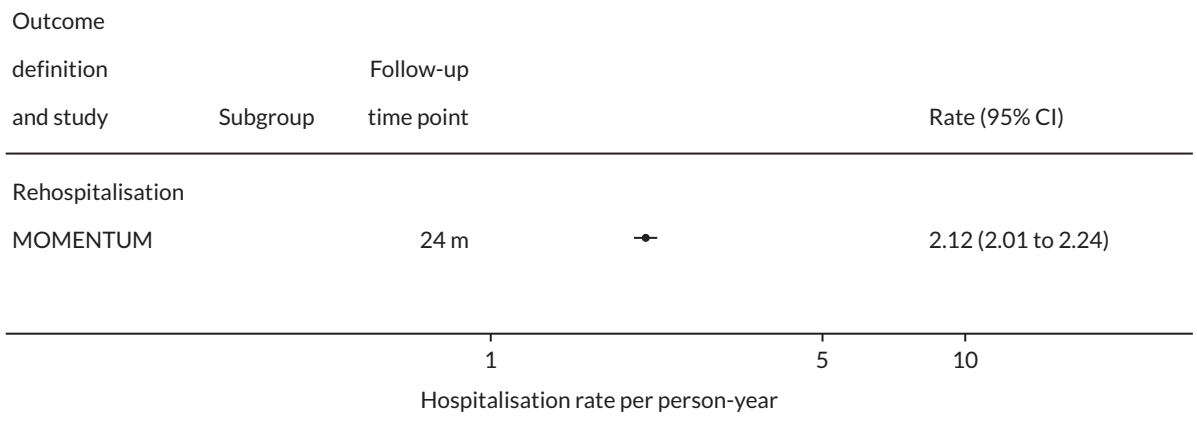


FIGURE 7 Hospitalisation rate per person-year in the HeartMate 3 at 24 months follow-up.

Major events

Stroke rates were reported to be lower than seen in the literature previously in the HM3 and lower than the HeartMate II group over 24 months. Regarding any stroke, there were 8 events per 100 patient-years in the HM3 group (*Figure 8*) (11% had a stroke at 24 months, *Figure 9*) compared to 19 events in the HeartMate II group (RR 0.42 95% CI 0.29 to 0.62). This was similar for disabling stroke: 4 events per 100 patient-years for HM3 versus 7 events per 100 patient-years for HeartMate II with a RR of 0.59 (95% CI 0.34 to 1.03). There were no significant differences in rates of RHF or RHF requiring RVAD between the device groups.

Complications

Rates of pump thrombosis were found to be significantly lower in the HM3 group compared to the HeartMate II group with 1 event versus 12 events per 100 patient-years, respectively, and a RR of 0.1 (95% CI 0.04 to 0.24). On the other hand, DIs were common and not found to be different between the two arms.

While bleeding events were still an issue in MOMENTUM 3, they occurred less frequently in patients implanted with the HM3 compared to the HeartMate II (70 events vs. 103 events per 100 patient-years) with a RR of 0.68 (95% CI 0.59 to 0.78). More specifically, bleeding requiring surgery and GIB rates

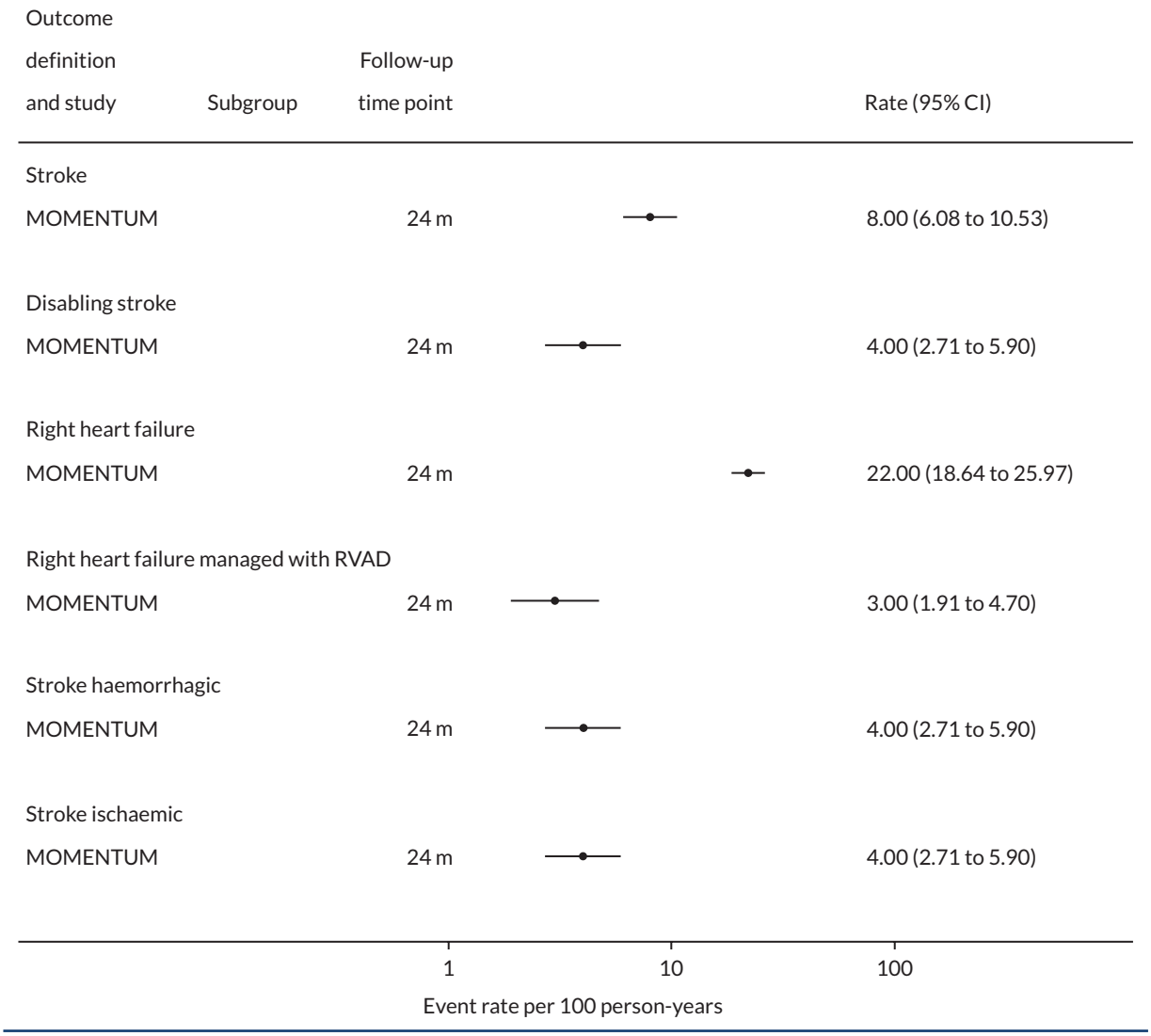


FIGURE 8 Event rate per 100 person-years in the HeartMate 3 at 24 months follow-up.

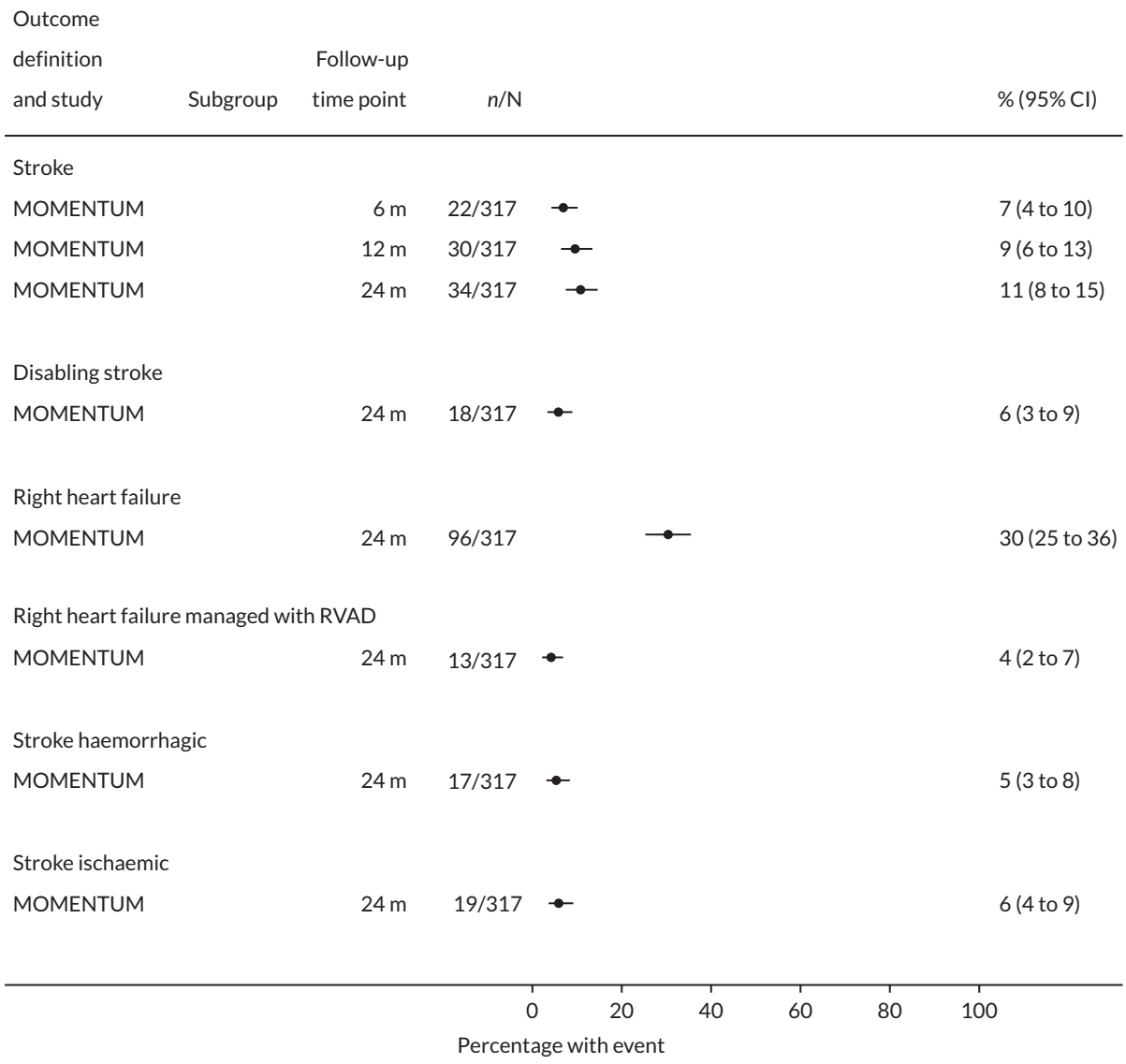


FIGURE 9 Proportion of patients with major events in the HeartMate 3 at all reported follow-up time points.

were both significantly lower in the HM3 group. The proportion of patients with complications and the complication rate are shown in *Figures 10* and *11*.

Functional status

The mean six-minute walking distance increased in HM3 patients in MOMENTUM from 137 m at baseline to 320 m at 24 months. However, the proportion of patients with NYHA Class I or II remained similar at baseline (78%) and 24 months (78%).

Ongoing trials

Currently, there are no completed trials comparing the HM3 to any other current LVADs. In addition to the ongoing North American trial of the HM3 versus the EVAHEART device, there is an ongoing Swedish RCT comparing the HM3 to MM, and this trial is expected to be completed in 2023.[47,48] Information on this study and other ongoing trials can be found in *Table 7*. The Jarvik 2000® is an older-generation device of which data have not been included in this report as it is considered out of date. However, a long-standing trial record established in 2012, which did not appear to have progressed for a long period of time, was updated during the later stages of this report to indicate that the trial of the Jarvik 2000

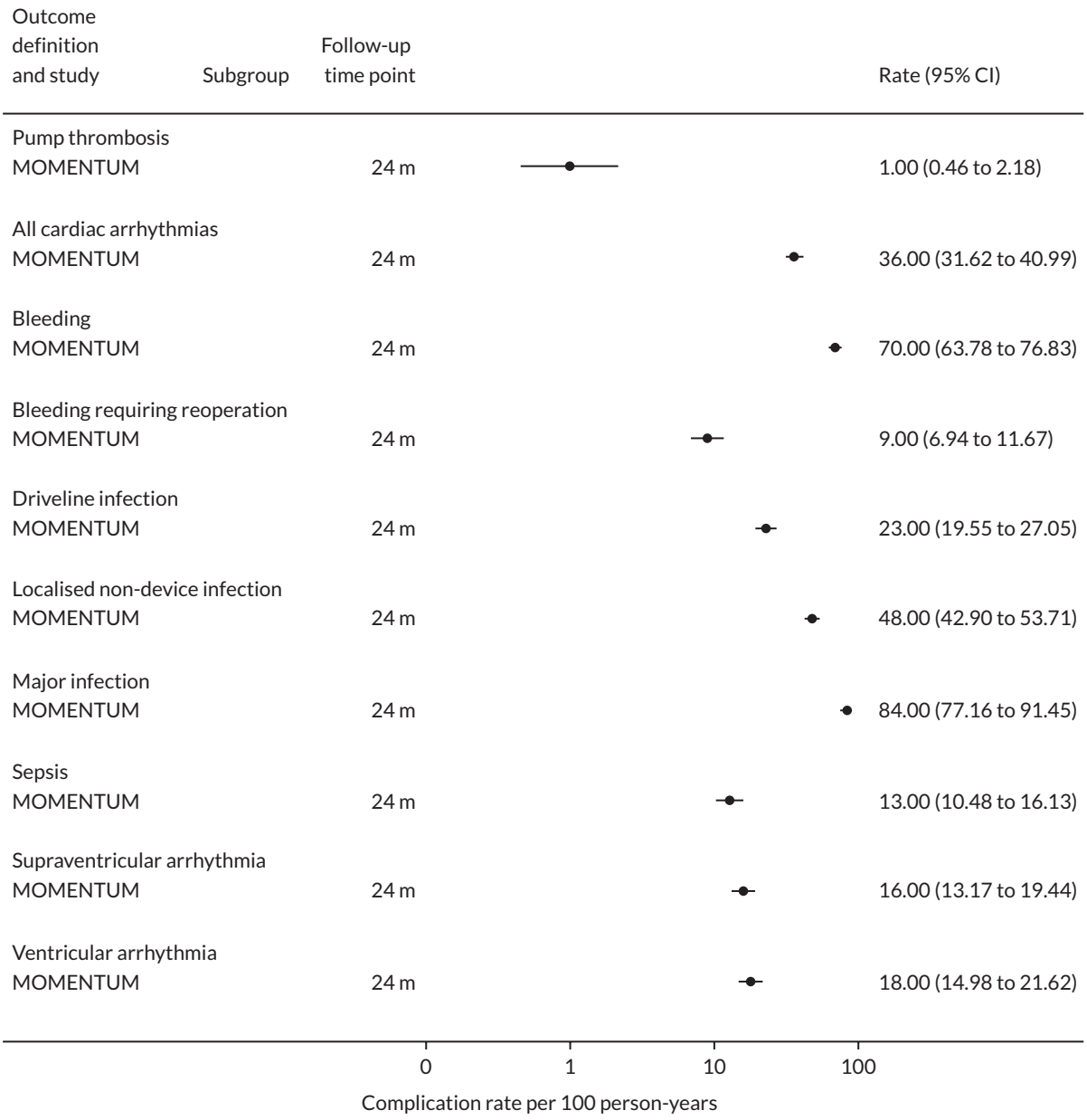


FIGURE 10 Complication rate per 100 person-years in the HeartMate 3 at all reported follow-up time points.

versus HeartMate II was ongoing, with completion due in December 2023. Therefore, this should be considered in the future.

Additional registry data

Available registries and data

Data from INTERMACS and other registry reports (including IMACS and ITAMACS) were analysed and compared to trial data. Participants enrolled in trials were not eligible for registry inclusion in North America, which means that the populations of these two categories may differ.

Of the 37 registry reports that were included in the review, 29 were from the INTERMACS registry, 2 from IMACS, 2 from ITAMACS, 2 from ELEVATE and 2 from the Thoratec® (Ann Arbor, MI, USA) DT registry (now redundant). DT-specific patient data were limited and were mostly not reported by device type, meaning most of the data were reported across multiple LVADs or sometimes by continuous

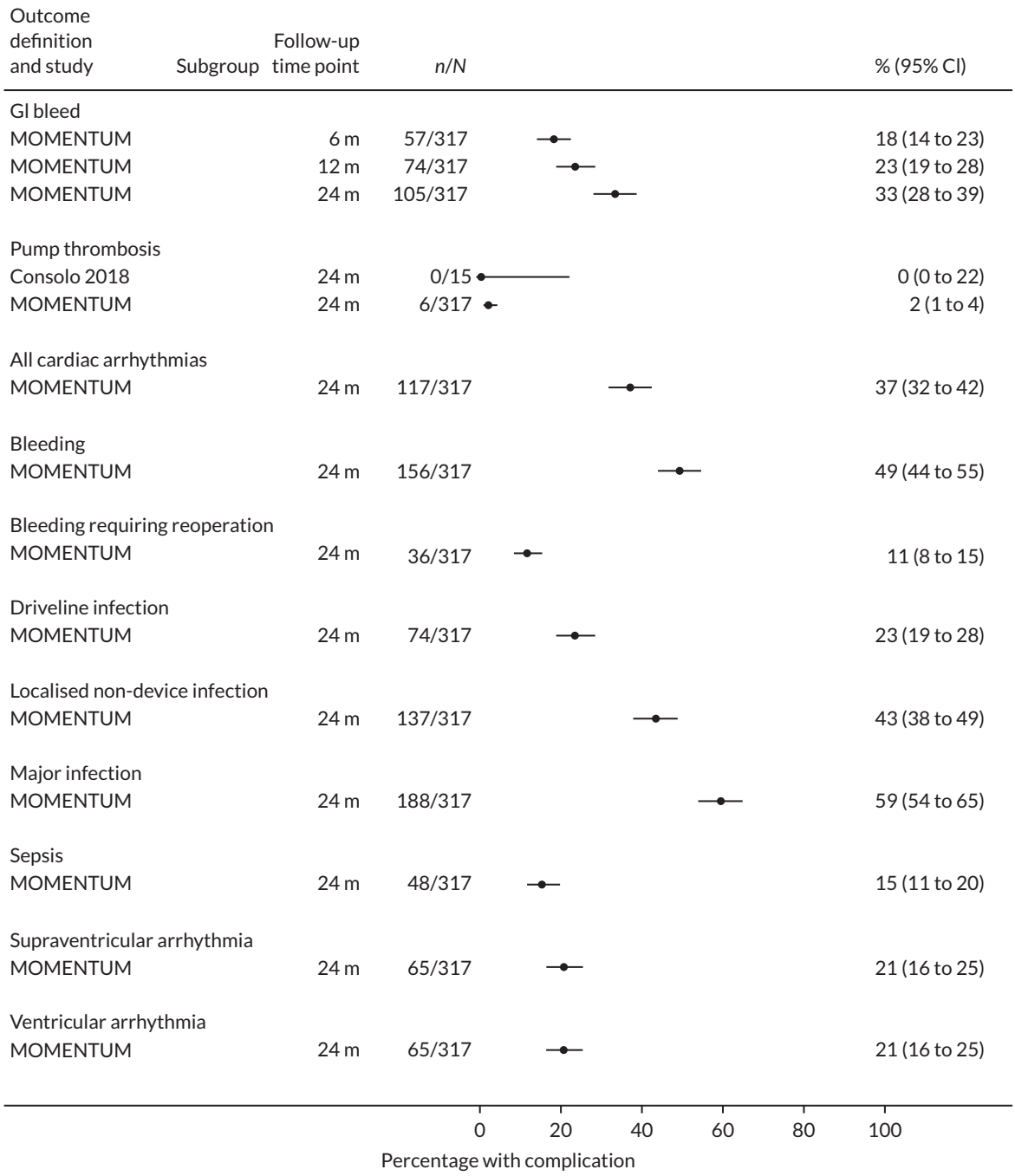


FIGURE 11 Proportion of patients with complications in the HeartMate 3 at all reported follow-up time points.

flow only or pulsatile flow types only. However, INTERMACS and IMACS reports also held the longest follow-up data, reporting up to 60 months for outcomes such as survival, major events and complications in DT patients.

INTERMACS reports contain data from sites in the USA that have agreed to supply anonymous data on registered LVAD patients at their centre. Data are entered at implant where possible, and are then entered over time for events, complications and QoL scores until death or removal/transplant. Only devices that are FDA approved are eligible for INTERMACS inclusion.

IMACS is an international registry that includes all countries and hospitals willing to participate. Currently, this also includes data from INTERMACS, European Registry for Patients with Mechanical

TABLE 7 Ongoing clinical trials of left ventricular assist devices for destination therapy

Study	Study design	Population	No. participants (no. DT)	Intervention	Comparator	Primary outcome	Length of follow-up (months)	Estimated completion date	Notes
Swedish evaluation of LVAD as permanent treatment in end-stage HF (SweVAD)[49]	RCT	End-stage HF population ineligible for cardiac transplantation	Estimated enrolment 80 participants	HeartMate 3	Optimal medical management	Survival at 2 years	24 months minimum (up to 5 years)	December 2023	Sweden NCT02592499
Sustaining QoL of the aged: heart transplant or mechanical support?[50]	Prospective observational	Older (60–80 years) AHF patients undergoing heart transplant or LVAD as permanent therapy	Estimated enrolment: 800 participants	Mechanical circulatory support	Heart transplant	Non-inferior change in patient HRQoL at 2 years	24 months	March 2022	USA NCT02568930
Prospective multicentre randomised study for evaluating the EVAHEART®2 left ventricular assist system (COMPETENCE)[47]	RCT	Adult (> 18 years old), AHF NYHA Class IV patients who are refractory to AHF management and meet study inclusion/exclusion criteria will be enrolled	Estimated enrolment: 399 participants, no. DT unclear	EVA2	HeartMate 3	Survival to cardiac transplant or device explant for recovery free from disabling stroke (Modified Rankin score > 3) or predefined severe RHF at 6 months after implantation of the originally implanted device	24 months	March 2024	USA NCT01187368
LVAD vs. GDMT in ambulatory AHF patients (AMBU-VAD)[51]	RCT	Ambulatory AHF patients ≥ 18 years	Estimated enrolment: 92 participants, no. DT unclear	HeartMate 3	Guideline directed medical therapy	All-cause mortality rate	24 months	February 2025	France, NCT04768322
Evaluation of the Jarvik 2000 left ventricular assist system with post-auricular connector--DT Study[52]	RCT	End-stage HF patients who are ineligible for transplant	Estimated enrolment: 350 participants, all DT	Jarvik 2000 VAS	HeartMate II	Non-inferiority to control group	24 months	December 2023	USA, NCT01627821

HRQoL, health-related quality of life; VAD, ventricular assist device.

Circulatory Support (EUROMACS), J-MACS and the UK registry. Not all of the contributing countries have a DT programme, therefore contributing DT data are limited to countries such as the USA, France and Kazakhstan.

ITAMACS is an Italian registry reporting the vast majority of LVADs and mechanical assist devices implanted in Italy.

ELEVATE is a registry that studies and reports the long-term outcomes of patients on the HM3 device following CE-mark approval in Europe and the Middle East. To date, few DT-specific data have been reported from this registry, though this may be important in the future.

HeartMate 3 data

No usable data specifically for the HM3 device from any registries were available. Patients who are involved in clinical trials are not able to register for INTERMACS, meaning that patients with the HM3 were not likely to enter the registry until after the trial had finished. While some of the later registry reports may include data from HM3 patients, these were not reported separately from other device data. Data were often reported by device type (e.g. centrifugal flow, axial flow), meaning that different devices could not be further distinguished.

Non-INTERMACS observational studies

To supplement findings from trials and registry reports, single and multicentre observational studies that were judged unlikely to overlap with any registry data (i.e. centres did not contribute data to a registry that was known) were analysed. These studies are detailed in *Table 8*.

Of the 86 included observational studies, 21 were judged unlikely to overlap with registry data. Of these, 2 were carried out in the USA, 13 in Europe, 1 in Kazakhstan and 4 were unclear.

HeartMate 3 data

As with data from registry reports, there were few studies that included patients implanted with HM3 and only one of these reported device-specific data for DT patients. One trial[53] reported zero pump thrombosis events in the 15 HM3 patients included in their centre over 24 months of follow-up. No further observational studies reported HM3 data specifically. Often these studies had limited numbers of HM3 patients, likely because the majority of these patients would have been in the MOMENTUM trial when the device was first approved for DT.

HeartMate 3 versus medical management

The key aim of this review is to determine the effectiveness of LVADs compared to MM in DT patients (though the HM3 is currently the only available device on the UK market). However, there are no published studies, randomised or observational in nature, comparing HM3 to MM. However, one ongoing RCT will be important in addressing this question in more detail in the future. This section of the report will detail the available HM3 versus MM data and the methods explored to indirectly compare these interventions in the absence of direct comparisons.

SweVAD study

The SweVAD study ('Swedish evaluation of left ventricular assist device as permanent treatment in end-stage HF') is an ongoing RCT comparing the HM3 to 'optimal medical management' in those ineligible for a HT.[48] The study aims to recruit 80 participants and follow them up for up to 5 years. The estimated completion date is December 2023 and it will report outcomes for survival, functional capacity, QoL and adverse events. The study is being carried out in seven University Hospitals with implantations being performed at five sites. Given that data are not expected from this study in the immediate future, methods to indirectly compare the HM3 to MM were considered.

TABLE 8 Characteristics of single/multicentre arm studies that do not contribute to INTERMACS or if it is unclear if they contribute

Study ID	Centre	Implant years	Total no. patients (no. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Ahmed 2018	University of Florida	1 January 2008–31 December 2015	111 (61)	1–2 (52, 46.8); 3–7 (59, 53.2)	57.6 (range 19–80)	92 (82.8)	NR	Low/high socioeconomic status	1-year survival, re-admission within 30 days, length of stay, aggregate VAD complications	Implant strategy was not found to significantly impact the primary outcomes
Aissaoui 2013	Clinic for Thoracic and Cardiovascular Surgery of Bad Oeynhausen (Germany)	2001–April 2011	488 (LVAD with temporary RVAD 45, DT 10; LVAD alone 443, DT 115)	NR	LVAD with temporary RVAD 53 (82) LVAD alone 56 (13)	LVAD with temporary RVAD 37 (82) LVAD alone 289 (65)	LVAD with temporary RVAD: 9 HeartMate XVE, 9 HeartMate II, 13 HeartWare, 5 VentrAssist, 5 DuraHeart, 4 Novacor. LVAD alone: 50 HeartMate XVE, 111 HeartMate II, 75 HeartWare, 47 VentrAssist, 74 DuraHeart, 53 Novacor, 18 CorAide, 9 LionHeart, 4 Incor, 2 DeBakey VADs	LVAD with temporary RVAD/LVAD alone	Complications: renal failure, sepsis, adverse cerebral events, reoperation for bleeding, pump malfunction, and arrhythmia Cerebral complications included cerebral haemorrhage, transient ischemia, and cerebral vascular accident	DT was univariate risk factor for death: odds ratio 7.39 (95% CI 4.09 to 13.4)
Akay 2019	Unclear	May 2012–July 2016	222 (144)	1–2 (124, 56) 3–4 (98, 44)	54 (12)	178 (80)	HeartMate II 164 (74), HeartWare HVAD 52 (23), HeartMate 3 6 (3)	Patients who developed DI/ patients with no DI	Associations with DI	No. DT patients who had DI 25

TABLE 8 Characteristics of single/multicentre arm studies that do not contribute to INTERMACS or if it's unclear if they contribute (*continued*)

Study ID	Centre	Implant years	Total no. patients (no. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Aldbrecht 2015	Medical University of Vienna	1997–2012	118 (All DT)	Conservative treatment median 3 (IQR 3–3) Pulsatile flow VAD median 3 (IQR 2–3) Continuous flow VAD 3 (IQR 2–4) *Patients with INTERMACS 1 were excluded*	Conservative treatment 57 (9) Pulsatile flow VAD 57 (10) Continuous flow VAD 57 (10)	Conservative treatment 46 (92) Pulsatile flow VAD 22 (88) Continuous flow VAD 38 (88)	Pulsatile flow VAD 25 (21) Continuous flow VAD 43 (36)	Conservative treatment (medial therapy) Pulsatile flow VAD Continuous flow VAD	Survival, cause of death, hospitalisations, heart transplants	All outcomes
Baudry 2021	19 French Centres	February 2006–December 2016	652 (303 of which are INTERMACS 4–7 and focus of analysis, 132 DT)	All patients were INTERMACS 4–7	61 (9.9)	263 (86.8)	HeartMate II 224 (73.9), HeartWare HVAD 52 (17.2), Jarvik 2000 27 (8.9)	N/A	Operative and postoperative outcomes, survival, risk factors for mortality	DT as a risk factor for mortality
Bugetti 2016 (CA)	Italy	June 2008–December 2015	178 (All DT)	At implant average level was 3 (1.2)	NR	NR	Jarvik 2000 Flowmaker	N/A	Survival, QoL	12 m survival 82%, 24 m 60%, 36 m 54%
Chen 2021	19 French centres	2006–16	652 (247 DT, 38)	NR	LVAD implanted < 30 days after cardiomyopathy median 55.2 (IQR 46.9–61.4) LVAD implanted > 30 days after cardiomyopathy median 60.7 (IQR 53.3–66.9)	561 (86)	HMII 475 (73) HVAD 127 (19) Jarvik 2000 50 (8)	LVAD implanted < 30 days after cardiomyopathy vs. > 30 days after cardiomyopathy	All-cause mortality, cardiovascular/non-cardiac cause of death, heart transplant, complications (thrombosis, stroke, bleeding, LVAD malfunction)	No. alive at 30 days post implant, DT as a predictor of mortality

continued

TABLE 8 Characteristics of single/multicentre arm studies that do not contribute to INTERMACS or if it's unclear if they contribute (*continued*)

Study ID	Centre	Implant years	Total no. patients (no. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Consolo 2018	San Raffaele Scientific Institute in Milan, Italy	March 2015–June 2017	68 (All DT)	1 (20, 30) 2 (17, 25) 3 (15, 22) 4 (15, 22)	64.7 (7.8)	64 (94)	HeartMate II 15 (22), HeartWare HVAD 38 (56), HeartMate 3 15 (22)	N/A	Association between platelet activation and the development of thromboembolic events	Incidence of thromboembolic events (patients with events: stroke 4, pump thrombosis 2)
Cruz Rodriguez 2020	NR	January 2008–February 2017	204 (77)	Inotrope use < 14 days: 1 (32, 37.2) 2 (44, 51.2) 3 (9, 10.5) 4 (1, 1.2) Inotrope use ≥ 14 days: 1 (49, 41.9) 2 (56, 47.9) 3 (10, 8.5) 4 (2, 1.7)	Inotrope use < 14 days 51.8 (25th–75th percentile, 38.9–63) Inotrope use ≥ 14 days 56.4 (25th–75th percentile, 48.4–62.7)	Inotrope use < 14 days 70 (81.4) Inotrope use ≥ 14 days 90 (76.9)	Only HeartMate II and HeartWare HVAD, numbers not reported	Those on inotropes for < 14 days after implant and those on inotropes for ≥ 14 days after implant	Mortality of LVAD patient on pro-longed inotropes, risk factors for early inotrope use, association of prolonged inotrope use and clinical events	Survival for DT compared to BTT HR 1.23 (95% CI 0.72 to 2.11) in a multivariate model
Drakos 2010	NR	1993–2008	175 (74)	NR	RVF 58.2 (12.9) No RVF 56.5 (14.4)	RVF 61 (79) No RVF 85 (87)	HeartMate XVE 82 (47), HeartMate VE 42 (24), HeartMate 1000 IP 17 (10), HeartMate II 25 (14), Novacor 9 (5)	RVF vs. no RVF	Survival (not by DT), predictors of RVF	DT as a predictor of RVF in a multivariate model: odds ratio 3.31 (p = 0.005)
Galand 2016 (CA)	Multicentre, France	2008–16	223 (160 ICM, 59 DT; 63 DCM, 24 DT)	NR	ICM 60.8 (9.3) DCM 61 (13.3)	ICM 145 (90.5) DCM 55 (86.9)	ICM: HeartMate II 107 (66.9), HeartWare HVAD 40 (25), Jarvik 2000 12 (7.5), Ventrassist 1 (0.6) DCM: HerrtMate II	ICM or idiopathic DCM	Survival, adverse events	24 m DT survival: ICM 52% DCM 50% No difference between ICM/DCM or by indication

TABLE 8 Characteristics of single/multicentre arm studies that do not contribute to INTERMACS or if it's unclear if they contribute (*continued*)

Study ID	Centre	Implant years	Total no. patients (no. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Galand 2020 (Same sample of patients as Chen 2021)	19 French centres	2006–16	652 (247 DT, 38)	NR	Patients aged ≥ 70 years median 71.7 (IQR 70.7–72.8) Patients aged < 70 years median 58.2 (IQR 50.0–64.7)	561 (86)	HMII 475 (73) HVAD 127 (19) Jarvik 2000 50 (8)	Patients aged ≥ 70 and patients aged < 70 years	All-cause mortality, cardiovascular/ non-cardiac cause of death, heart transplant, complications (thrombosis, stroke, bleeding, LVAD malfunction)	Survival in DT patients ≥ 70 and < 70 presented in survival curve
Jaganathan 2019 (CA)	Multicentre USA	NR	186 (53)	NR	NR	NR	NR	NR	QoL in a new LVAD QoL tool as well as already established tools	DT vs. BTT: there was no statistical difference in emotional domain(p = 0.11) Social function-ing was higher in DT vs. BTT (p = 0.04) No significant difference in PHQ-9 scores between DT and BTT (p = 0.43)
Janssen 2021 (CA)	Single centre, the Netherlands	2010–20	63	NR	Median 63 (range 29–72)	50 (79)	All HeartWare HVAD	Time in therapeutic range INR < and ≥ 60%	Death, and thromboembolic, neurologic and haemorrhagic events	13 thrombo-embolic, 19 haemorrhagic, 19 neurologic events and 34 deaths occurred

continued

TABLE 8 Characteristics of single/multicentre arm studies that do not contribute to INTERMACS or if it's unclear if they contribute (*continued*)

Study ID	Centre	Implant years	Total no. patients (no. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Kalampokas 2021 (CA)	German centre	January 2010–May 2020	227 (27 Age ≥ 70, 200 < 70)	Age ≥ 70 11 (40.7) INTERMACS 4 Age < 70 45 (22.5) INTERMCAS 4	Age ≥ 70 73.1 (2.55) Age < 70 55.3 (10.59)	Age ≥ 70 22 (81.5) Age < 70 174 (87)	NR	Age ≥ 70 and age < 70	Peri-procedural complications, mortality	All outcomes, 30 day mortality Age ≥ 70 14.8%, Age < 70 12%. Mid-term mortality (mean 2.5 years) Age ≥ 70 55.6%, Age < 70 32.5%
Kapuria 2016 (CA)	NR	2010–4	79 (DT NR)	NR	NR	58 (73)	NR	N/A	Incidence of GIB, predictors of GIB	DT recipients 6 times more likely to bleed as compared to BTT recipients (OR 6.32, $p = 0.032$)
Loforte 2018	S. Orsola University Hospital in Bologna and S. Camillo Hospital in Rome	January 2006–December 2017	Isolated LVADs 170 (30 in derivation cohort, 9 in validation cohort) Unplanned BVAD 88 (32 in derivation cohort, 7 in validation cohort)	Isolated LVAD: Derivation cohort: 1 (4, 2.9) 2–3 (102, 75.5) 4 (29, 21.4) Validation cohort: 1 (2, 5.7) 2–3 (25, 71.4) 4 (8, 22.8) Unplanned BVAD: derivation cohort: 2–3 (58, 81.6) 4 (13, 18.3) Validation cohort: 2–3 (11, 64.7) 4 (4, 23.5)	Isolated LVAD: Derivation cohort 54.1 (1.6) Validation cohort 53.1 (1.7) Unplanned BVAD: Derivation cohort 57.3 (2.6) Validation cohort 56.1 (1.4)	Isolated LVAD: Derivation cohort 120 (88.9) Validation cohort 26 (74.2) Unplanned BVAD: Derivation cohort 51 (69.9) Validation cohort 11 (64.8)	Isolated LVAD HeartMate II 56 (32.9), HeartWare HVAD 51 (30), CentriMag 35 (20.6), HeartMate 3 19 (11.2), Jarvik 2000 6 (3.5), Heart Assist 5 1 (0.59), Berlin heart Incor 1 (0.59) Unplanned BVAD CentriMag 44 (50); HeartMate II 27 (30.6) HeartWare HVAD 15 (17) HeartMate 3 2 (2.3)	Include both isolated LVADs and unplanned BVADs	Severe RVF within 30 days of LVAD implantation, all-cause mortality	DT as a predictor of BVAD requirement in multivariate model: HR 2.0 (95% CI 1.7 to 3.9)

TABLE 8 Characteristics of single/multicentre arm studies that do not contribute to INTERMACS or if it's unclear if they contribute (*continued*)

Study ID	Centre	Implant years	Total no. patients (no. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Loforte 2018 (× 2 CAs reporting results of the same study)	Italy	2006–16	215 LVAD 143, BVAD 72 (DT NR)	NR	NR	NR	NR	NR	Predictors of BVAD need	DT was a major predictor for the need for BVAD (HR 2.0, 95% CI 1.7 to 3.9)
Medressova 2019 (CA)	Khazakstan	2011–8	207 (all listed as DT though unclear as they include BTT on long-term support)	NR	49 (13)	188 (88)	HeartMate II, HeartWare HVAD or HeartMate 3	NR	Survival, survival by distance from hospital	Kaplan-Meier survival 12 m 87.3%, 24 m 68.8%, 36 m 60.6%, 48 m 47.2%
Papathanasiou 2017	West German Heart and Vascular Center	December 2010–June 2016	112 (77)	1 (31, 27.7) 2 (18, 16.1) 3 (25, 22.3) 4 (35, 31.3) 5 (3, 2.7)	58.4 (10.9)	91 (81.3)	All HeartWare HVAD	Those who underwent resternotomy and those who did not have resternotomy	Prognostic significance of resternotomy, hospitalisations, infection rates, survival	DT as predictor of mortality compared to BTT HR 2.83 (95% CI 1.207 to 6.649)

BVAD, biventricular device; CA, conference abstract; DCM, idiopathic cardiomyopathies; HR, hazard ratio; ICM, ischaemic cardiomyopathies; INR, international normalised ratio; IQR, interquartile range; NR, not reported; VAD, ventricular assist device.

Note
Data are reported for the entire cohort in each study unless otherwise stated.

Indirect comparison of HeartMate 3 versus medical management through randomised controlled trials

As described in the methods, NMA was considered, where possible, to allow for the indirect comparison of HM3 and MM. This involved sequential indirect comparisons of data through previous RCTs (HM3 vs. HeartMate II, HeartMate II vs. HeartMate XVE and finally HeartMate XVE vs. MM) to ultimately compare the HM3 and MM. To achieve this, data from all previous LVAD trials were extracted and analysed as required. These data are summarised below, in the first instance, to allow for background understanding of the trials and what they assessed and found.

Other trial data

There were five RCTs included in the review (including the HM3 MOMENTUM trial) as well as one non-randomised intervention study (ROADMAP). Generally, the studies compared to either MM (REMATCH and ROADMAP) or an alternative device. *Table 2* details the characteristics of the included trials. The most recent and relevant device, the HM3, was compared only to the HeartMate II device. No trials have been completed that compare the HM3 to MM, though ongoing studies are currently exploring this as previously described.

INTERMACS profiles were reported at baseline in all but two of the trials. Most patients were INTERMACS level 3 in ENDURANCE studies across both study groups. Conversely, the ROADMAP study included only patients who were INTERMACS level 4–7.

The mean age did not appear to differ greatly amongst the trials and the intervention groups within each trial, ranging from 62 (HeartMate II DT) to 68 (REMATCH). However, it should be noted that age was reported for different groups of participants in each study. For example, MOMENTUM 3 reported the mean age for all DT patients included, regardless of assigned intervention, whereas most other trials reported the mean age for each arm. The ROADMAP study only reported median age, though this was similar to the other studies, even with the inclusion of participants with INTERMACS profiles 4–7 only.

It is important to note that all of these trials took place in the USA, and that currently no trial data are available in the UK or Europe, though SweVAD may be useful once completed.

HeartWare ventricular assist device

Two RCTs assessed the HeartWare HVAD device. The HVAD was compared to the HeartMate II device in both trials: ENDURANCE DT and ENDURANCE DT Supplemental Trial (an extended study of the HVAD looking at stroke outcomes). The HVAD has now been withdrawn from the market and reporting of results from this device will be of limited value.

Outcomes

Event-free survival (free of death, disabling stroke and device malfunction and/or failure requiring exchange, explantation or urgent transplantation) was higher in the HVAD compared to the HeartMate II arm, reaching 76% at 12 months in the ENDURANCE Supplemental Trial (compared to 67% in the HeartMate II arm). In the original ENDURANCE trial, the same outcome was 55% at 24 months in the HVAD group and 57% in the HeartMate II group. However, stroke rates were higher in the HVAD device arm, often occurring in the first 6 months. Rates of other events and complications were similar between the HVAD and HeartMate II arms, including major bleeding, cardiac arrhythmias and DIs. In both trials, QoL improved significantly in the HVAD group and was maintained at 12 and 24 months; however, this was also evident in the HeartMate II group.

HeartMate II

The HeartMate II device has been studied in four trials in total. Firstly, as the intervention in the HeartMate II DT RCT (vs. the HeartMate XVE) and the ROADMAP study (a non-randomised comparative trial vs. MM). It was also compared to newer devices in MOMENTUM 3 and ENDURANCE DT. The HeartMate II is currently the most widely studied LVAD.

Outcomes

In the HeartMate II DT trial survival was reported to be 68% at 12 months and 55% at 24 months in the HeartMate II group. This was superior to the HeartMate XVE (survival 58% and 24% at 12 and 24 months, respectively). The HeartMate II event-free survival was 82% at 12 months in the more recent ROADMAP study and 70% at 24 months. Events such as haemorrhagic stroke, bleeding and DIs were significantly reduced in the HeartMate II patients compared to the HeartMate XVE patients in the HeartMate II DT trial. Strokes occurred at a rate of 12 events per 100 patient-years, pump replacements 6 events per 100 patient-years and RHF requiring RVAD 2 events per 100 patient-years over 24 months. Strokes in the HeartMate II group at 24 months in the ROADMAP trial were reported at a rate of 9 events per 100 patient-years. Improvements in HeartMate II device outcomes were seen over time in different trials. QoL improved from baseline at 12 and 24 months after the HeartMate II implant in both the ROADMAP and HeartMate II DT trials using the KCCQ and EQ-5D. However, similar improvements were also seen in the control groups in these trials (MM and HeartMate XVE, respectively).

HeartMate XVE

The pulsatile-flow HeartMate XVE was the first LVAD developed in the series of HeartMate devices. It was phased out of clinical use in 2010 in favour of the continuous flow HeartMate II. Outcome data for the HeartMate XVE device can be seen in *Appendix 5*.

Indirect comparison of HeartMate 3 and medical management – survival

This section discusses the results of the NMA carried out to indirectly compare HM3 and MM for survival. Direct comparison data were taken from several of the RCTs described above (MOMENTUM, HeartMate II DT and REMATCH). The network diagram *Figure 12* illustrates the comparisons available to enable the NMA.

Assessment of the transitivity assumption

Baseline patient characteristics in the three RCTs included in the NMA are shown in *Table 9*. While most patient and treatment characteristics appeared similar, it shows that IV inotropic drugs (and INTERMACs 1–3) were required by 68% in REMATCH, compared to 87% in MOMENTUM with HeartMate II in the middle at 79%. If the baseline INTERMACS level is an effect modifier for any of the comparisons made in the network, then this would break the transitivity assumption and introduce bias.

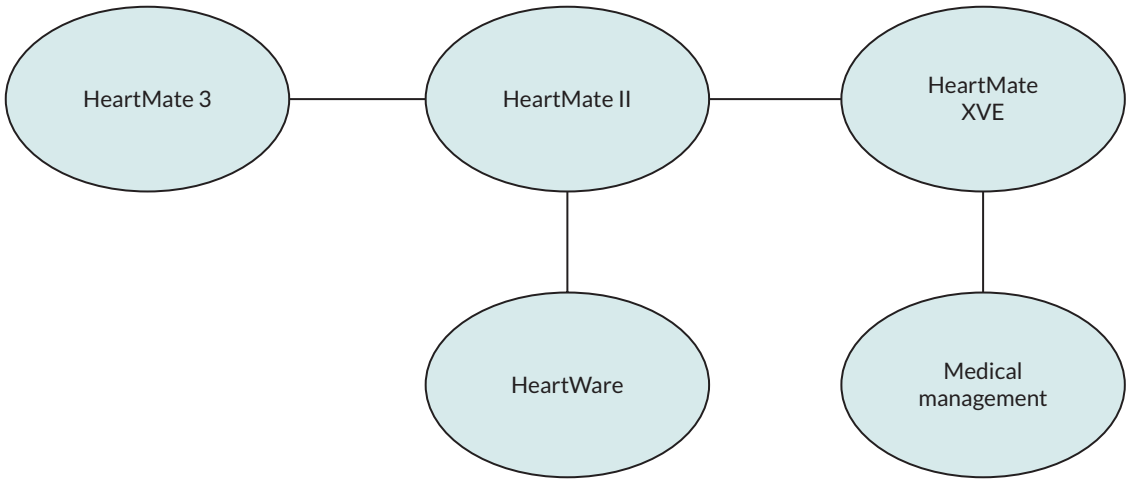


FIGURE 12 Network diagram.

TABLE 9 Table of characteristics of included intervention studies

Study ID (no. publications)	Study design	No. participants (no. DT)	Intervention	Comparator	Mean age (SD)	Sex (*n*, % male)	INTERMACS Profile (*n*, %)	Length of follow-up (months)	Notes
REMATCH 2001[54] (10)	RCT	129 (All DT)	HeartMate XVE LVAD (*n* = 68)	Medical management (*n* = 61)	HeartMate 3 66 ± 9.1 Medical management 68 ± 8.2	HeartMate 53 (78) Medical management 50 (82)	NR	24 months (1 patient in LVAD group still alive at 30 months)	
HMII DT 2009[55] (10)	RCT	200 (All DT)	HMII LVAD (*n* = 134)	HeartMate XVE LVAD (*n* = 66)	HMII 62 ± 12 HeartMate XVE 63 ± 12	HMII 108 (81) HeartMate XVE 61 (92)	NR	24 months	Seven papers are retrospective analyses of both the HMII DT and BTT trials and include HMII single arm only
ENDURANCE DT 2017[56] (22, all ENDURANCE papers)	RCT	445 (All DT)	HeartWare HVAD (*n* = 297)	HMII LVAD (*n* = 148)	HeartWare 63.9 ± 11.6 HMII 66.2 ± 10.2	HeartWare 227 (76.4) HMII 122 (82.4)	HeartWare 1: 10 (3.4); 2: 86 (29.0); 3: 120 (40.4); 4: 59 (19.9); 5–7: 22 (7.4). HMII 1: 5 (3.4); 2: 46 (31.1); 3: 60 (40.5); 4: 27 (18.2); 5–7: 10 (6.8)	24 months	
ENDURANCE DT 2 2018[57] (22, all ENDURANCE papers)	RCT	465 (All DT)	HeartWare HVAD (*n* = 308)	HMII LVAD (*n* = 157)	HeartWare 63.3 ± 11.4 HMII 64.2 ± 11.1	HeartWare 252 (82) HMII 125 (80)	HeartWare 1: 12 (3.9); 2: 101 (32.8); 3: 133 (43.4); 4–7: 62 (20) HMII 1: 4 (2.5); 2: 51 (32.5); 3: 68 (43.3); 4–7: 34 (21.7)	12 months	
MOMENTUM 3 2019[58] (17)	RCT	1028 (624 DT)	HM3 LVAD (*n* = 317 DT)	HMII LVAD (*n* = 307 DT)	Reported for all DT patients only: 63 ± 12	Reported for all DT patients only: 513 (82.2)	Reported for all DT patients only: 1: 12 (1.9); 2: 187 (30.0); 3: 325 (52.1); 4: 89 (14.3); 5–7: 7 (1.1); not provided: 4 (0.6)	24 months	
ROADMAP 2015 (8)	Multicentre, prospective observational	200 (All DT)	HMII LVAD (*n* = 97)	MM (*n* = 103)	HMII median 64 (range: 55–70) MM median 66 (range 54–74)	HMII 75 (77) MM 71 (69)	HMII: 4: 63 (65); 5: 21 (22); 6: 10 (10); 7: 0 (0). MM: 4: 35 (34); 5: 29 (28); 6: 35 (34); 7: 2 (2)	24 months	

HMII, HeartMate II; NR, not reported.

Network meta-analysis results

Analysis of survival The results of the NMA are shown in *Table 10*.

The direct evidence results reported by the three included trials were used to derive the indirect estimates using the methods described in *Network meta-analysis*. These data were used to produce a RR of death of 0.25 (95% CI 0.13 to 0.47) in the HM3 compared to MM at 24 months. This translates to a 75% reduction in the risk of death in patients with a HM3 compared to those on MM within 24 months. However, the results should be treated with caution due to the wide uncertainty levels placed around the RR and questions relating to the transitivity assumption as described above.

Other outcomes and observational data Data to carry out the NMA were only available for the survival outcome. There were insufficient data to allow for indirect comparisons of any other outcomes (QoL, major events, complications, etc.).

Concerning other comparative data, this was also considered when carrying out the NMA. The ROADMAP study was considered a non-randomised comparative intervention study. However, there were not sufficient relevant data to use in a NMA. No comparative observational studies compare MM to HVAD.

There were no other easily accessible data for direct comparative estimates from studies, even when considering observational studies.

Other registry data by outcome This section reports the remaining non-HM3 specific data that are available from registry reports. It includes data from registries such as INTERMACS, IMACS and ITAMACS. The majority of registry data are reported for a group of LVADs (e.g. continuous flow devices) or do not differentiate by device type at all. There were 47 registry report articles; 37 from INTERMACS, 4 from IMACS, 2 from ITAMACS and the remaining reports were from ELEVATE and the older Thoratec DT registry. However, seven of the INTERMACS reports were only included for completeness, but their data were not included in the analysis due to the age of the data and the duplicate reporting of outcomes from similar reports over the same implant periods.

Survival

Survival was reported in 15 INTERMACS reports at various time points, as well as for other registries including IMACS (n = 3) and ITAMACS (n = 2).[31,38,46,59–74] Survival appeared to increase over the calendar time of the data set, as expected with the introduction of newer, more effective devices (*Figure 13*). This is also in line with data reported in the trials. Recent data from INTERMACS[74] suggested survival was 80% in DT patients at 12 months in a cohort of patients implanted between 2014 and 2017, using either

TABLE 10 Results table from the NMA for the outcome of all-cause mortality at 24 months

Comparator 1	Comparator 2	Evidence type	RR	95% CI
HM3	HeartMate II	Direct[58]	0.88	0.64 to 1.22
HM3	HeartMate XVE	Indirect	0.48	0.27 to 0.84
HM3	**MM**	**Indirect**	**0.25**	**0.13 to 0.47**
HeartMate II	HeartMate XVE	Direct[56]	0.54	0.34 to 0.86
HeartMate II	MM	Indirect	0.28	0.16 to 0.49
HeartMate XVE	MM	Direct[54]	0.52	0.43 to 0.78

Note
The contrast of interest is HM3 vs. MM (highlighted in bold).

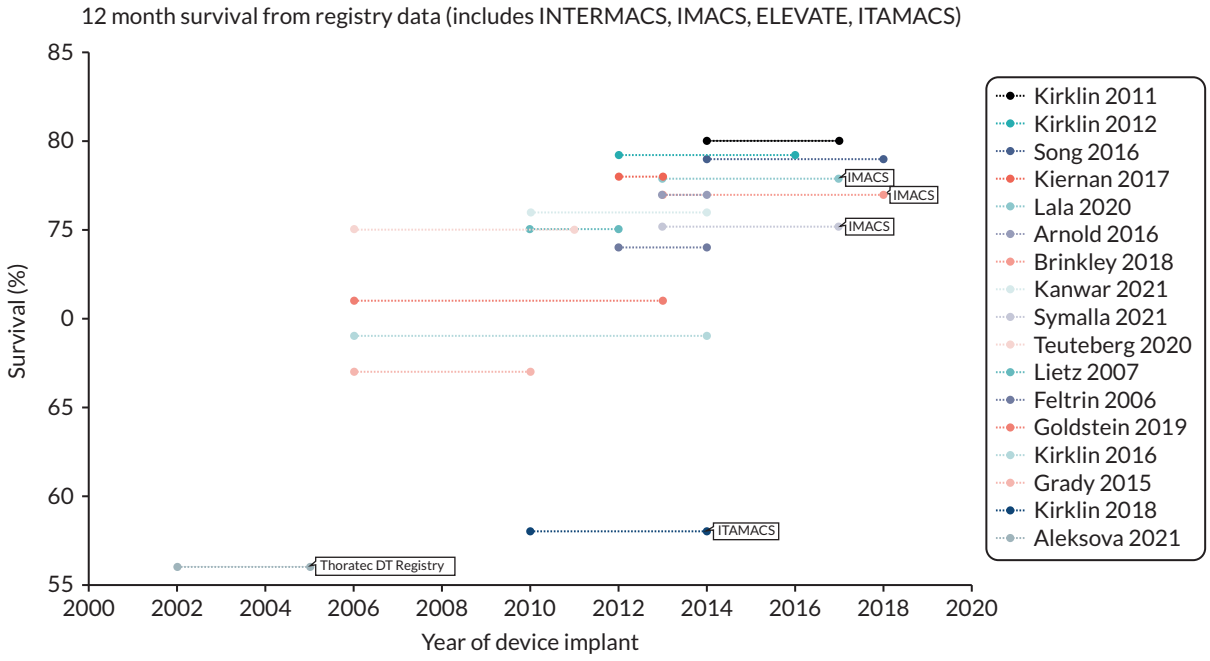


FIGURE 13 Survival data of destination therapy patients from registry reports over time on any device at 12 months.

the HVAD or HeartMate II device. The longest participant follow-up time reported was at 60 months from the INTERMACS registry in a cohort of patients implanted between 2014 and 2018 (this included 14.8% HM3 patients). Survival here was reported to be 43% in DT patients.[46] Follow-up data beyond 24 months is not reported in any of the trials; therefore registry data and observational studies are currently the only sources for this longer-term data.

Quality of life

Quality of life was reported in a small number of registry reports. Kirklin 2012 (INTERMACS) reported QoL with the EQ-5D VAS at various points in a cohort of patients implanted with continuous flow devices between 2006 and 2011.[69] Scores improved from 44 at baseline to 72.2 at 12 months of follow-up. This is similar to scores reported in other trials. A more recent report from INTERMACS continuous flow patients (implanted 2008–13) reported improvements in the KCCQ overall score from 33.6 at baseline to 67.1 at 24 months.[75] No further QoL data have been reported.

Hospitalisations

Hospitalisations were not reported widely across registry reports. An INTERMACS analysis of US patients reported that rehospitalisation's occurred in 75% of patients in transplant centres and 77% of patients in non-transplant centres at 12 months of follow-up (cohort implanted 2012–4).[62] Differential late re-admissions to hospital between shock (190 per 100 patient-years) and non-shock (181 per 100 patient-years) have been reported from the INERMACS registry in a more recent study.[74]

Major events

Nine papers reported major events from registry reports (eight from INTERMACS, one from IMACS).[37,59,60,62,68,69,74,76,77] Acharya reported that strokes occurred in 12% of DT patients (implanted 2012–5) in 35 months of follow-up.[59] In the Brinkley report, 12% of transplant centre patients suffered a stroke (censored for death, transplant or explant) at 12 months, and 8.2% in non-transplant centre patients.[62] In both groups, 19% of patients had RHF at 12 months. In the earlier Kirklin analysis, there were 20.8 events of RHF per 100 patient-years in 24 months of follow-up.[69] Pump exchange was reported in 6% of patients at 12 months in Aleksova.[60]

Complications

Seven articles reported complications including bleeding events, infections and device complications.[60,62,69,74,78–80] The Kirklin analysis reported 143 bleeding events per 100 patient-years at 24 months of follow-up.[69] There were also 13.8 device malfunction events and 97.1 infections per 100 patient-years. On the other hand, the more recent Michelis analysis reported 5.6 device malfunction events per 100 patient-years at 12 months as well as 8.7 DI events and 2.2 pump thrombosis events per 100 patient-years.[80] In the Brinkley report, 45% of transplant centre patients had bleeding events at 12 months, and 43% in the non-transplant centres.[62] It also reported device infections at 14% and 10% and device malfunctions at 16% and 14% in transplant and non-transplant centre patients, respectively, at 12 months.

Non-INTERMACS observational studies

Data from 21 observational studies thought to not overlap with patients in the INTERMACS registry are presented in this section.

Survival

Survival was reported in four of these studies but was not reported by individual device type. Adlbrecht (Germany) reported survival of 72% at 24 months follow-up in patients with continuous flow devices implanted between 1997 and 2012.[81] Medressova reported survival of 68.8% at 24 months (Kazakhstan) in patients implanted between 2011 and 2018 across multiple devices.[82] A French study (Galand) reported survival only by age in patients implanted between 2006 and 2016.[83] It reported that survival was higher in patients ≥ 70 (51%) compared to those < 70 (46%) at 24 months across multiple devices. A German study of patients implanted between 2010 and 2020 (Kalampokas), which also stratified by age, reported mortality of 55.6% and 32.5% at a mean 2.5-year follow-up in ages ≥ 70 and < 70, respectively.[76]

Quality of life

No non-INTERMACS studies reported QoL as an outcome.

Hospitalisations

Only one study reported mean months out-of-hospital as 21.6 over a 24-month follow-up period.[81] This was only reported for all continuous flow devices.

Major events

Kalampokas reported the need for an intraoperative RVAD, with 11.1% of patients ≥ 70 and 26.5% patients < 70 years of age.[76] Results were not stratified by device. The study also reported the rate of periprocedural stroke incidence (though periprocedural is not defined) as 14.8% versus 10.5% in patients aged ≥ 70 and < 70, respectively. Two studies reported major events in the HVAD device. Consolo reported 10.5% patients suffered a stroke in 24 months and Janssen reported 19 haemorrhagic events in 156 patients.[53,84]

Complications

Three non-INTERMACS observational studies reported various complications. [53,63,85] Akay reported that 17.4% patients had DIs in continuous flow devices. One study (Consolo) reported that 2.6% HVAD patients had a pump thrombosis, whereas HM3 patients (n = 15) had none in the 24-month follow-up period.

Interagency registry for mechanically assisted circulatory support observational studies

The final category of studies included were observational studies from centres that also contributed data to INTERMACS or other registries. There were 65 studies. These studies were not included in the full analysis to avoid double counting of patient data where possible *Table 30* (see *Appendix 6*) summarises the characteristics of the studies. Data from this category were only considered if key data were

unavailable from the previous study types. However, sufficient data were found in the trials, registries and observational studies not overlapping with registries.

Subgroup analysis

Some subgroups were considered important to explore to determine if any differences arose in outcomes in a particular group of patients, such as certain age groups or INTERMACS classes. However, there were no data specific to HM3 available for any relevant subgroups. Data from the HeartMate II device stratified by INTERMACS class were reported in the ROADMAP study (INTERMACS 4 vs. INTERMACS 5–7) but in no RCTs. Seven reports[59,60,69,72,74,76,86] from registries reported some outcomes by age group including survival, major events and QoL and three reported by INTERMACS class.[63,69,74] One observational study reported survival by age group (see *Appendix 6*).[83]

Subgroup comparisons within device type

Appendix 5 shows results from observational studies that show the comparative effects of different predictors on a range of outcomes such as mortality (usually) or stroke, or bleeding, etc. None of these studies reported results specific to HM3. Instead, they look at these predictors in participants who received any continuous flow device, any LVAD, or HeartMate XVE only. For the former two, study periods vary from 2006 to 2010 and 2013 to 2018, so it is likely that few participants would have received the HM3. It is unclear how well these reported results might generalise to contemporary implants of HM3.

One study reported HRs for the outcome of mortality by individual INTERMACS Class (1, 2, 3, 5, 6) versus Class 4.[69] This study included participants with any LVAD and included data from 2012 to 2014. We use these data to inform the subgroup analyses in the economic model.

Risk of bias and quality assessment

Trials

Risk of bias was varied across the trials and outcomes (*Table 11*). Three studies had low risk of bias for survival (ROADMAP, REMATCH and ENDURANCE DT). Most studies had some concerns or high risk-of-bias for QoL. A more detailed description of the risk of bias assessment is available (see *Appendix 4*).

For the randomisation process, three studies were low risk for both outcomes, though the REMATCH and HeartMate II DT trial had some concerns. While the randomisation domain was not applicable to ROADMAP, it should be acknowledged that this study was non-randomised and therefore prone to more biases.

Regarding domain two, blinding was generally an issue throughout the studies, as this could not be achieved, though it was unlikely to affect survival. Also, a per-protocol analysis was used in some studies (e.g. HeartMate II DT and ENDURANCE DT), which was not always the most appropriate method. Missing outcome data were an issue, particularly when measuring QoL (four studies had high risk of bias) and there were often many participants not completing this at follow-ups. Generally, the reporting of results did not appear to be done selectively and five studies were either low risk or had some concerns. Most trials published a protocol and extensive appendices detailing pre-planned methods and analyses.

Issues were mainly with the QoL outcomes across studies, which due to its mostly self-report nature, resulted in some concerns or high risk of bias for the missing outcome data domain and deviations from the intended outcome domain. These issues lead to the overall risk of bias being high in ROADMAP, REMATCH, HeartMate II DT and both ENDURANCE studies for the QoL outcome. The overall risk of bias remained low for survival in ROADMAP, REMATCH and ENDURANCE DT, with the other studies still having some concerns. The randomisation domain was not applicable for ROADMAP.

TABLE 11 Risk of bias of included comparative intervention trials

Study name	Outcome	Domain 1 (randomisation process)	Domain 2 (deviations from intended interventions)	Domain 3 (missing outcome data)	Domain 4 (measurement of the outcome)	Domain 5 (selection of reported result)	Overall risk of bias
ROADMAP (2015)	Survival	N/A	Low	Low	Low	Low	Low
	QoL	N/A	Low	High	Some concerns	Low	High
REMATCH (2001)	Survival	Some concerns	Low	Low	Low	Low	Low
	QoL	Some concerns	Low	High	Low	Some concerns	High
MOMENTUM 3 (2019)	Survival	Low	Some concerns	Low	Low	Low	Some concerns
	QoL	Low	Some concerns	Low	Some concerns	Low	Some concerns
HeartMate II DT (2009)	Survival	Some concerns	High	Low	Low	Some concerns	High
	QoL	Some concerns	High	High	Some concerns	Some concerns	High
ENDURANCE DT (2017)	Survival	Low	Low	Low	Low	Low	Low
	QoL	Low	Some concerns	High	Some concerns	Low	High
ENDURANCE DT 2 (2018)	Survival[a]	Low	High	Low	Low	Some concerns	High
	QoL	Low	Low	Low	Some concerns	High	High

N/A, Not applicable (study was a non-randomised intervention study).
a Survival only reported as part of composite outcome of survival free from death, disabling stroke, or need for device replacement or urgent transplantation.

Registries

Reports from the INTERMACS registry and other registries were not quality assessed in the same way the clinical trials were assessed. The validity and quality of the data were considered in relation to the methods of data collection, auditing and missing data. While data from registries could be considered as more reflective of real-world data, there are limitations.

Contributions to the INTERMACS registry are voluntary at US centres, though the majority of centres choose to input their data and the registry is now considered the gold standard for clinical outcomes registries. Only patients with FDA-approved devices are able to enrol in the registry. Centres who wish to participate must have at least one member of staff trained on all aspects of INTERMACS to allow for certification and training is offered for all staff who will be involved in entering data. Processes are in place to monitor and ensure the quality of the data including regular checks for compliance, completeness and accuracy by the data and clinical coordinating centre (University of Alabama, Birmingham). For example, improbable or impossible data combinations are flagged as errors to sites and any questionable data must be verified with the site. Further auditing to ensure the highest possible quality data is carried out via telephone calls or site visits where monitors review the accuracy of web-based data submissions and documents. An independent monitoring board also review the database and meet annually.[87,88]

Regarding outcome data, outcomes and adverse events are defined by INTERMACS and generally used consistently across reports of INTERMACS data. However, different registry reports do report different outcomes (e.g. survival, survival as part of a composite outcome, etc.) and also exclude certain populations (e.g. those with missing QoL scores, those with early deaths), which could introduce selection bias.

Furthermore, there are potential issues with the loss to follow-up of patients. For approximately 9.6% of patients in the INTERMACS registry as a whole, follow-up data are not available due to a lack of informed consent from patients. This may affect outcome data, particularly survival.[89]

One limitation of INTERMACS and other registries when compared to trials is the lack of randomisation to devices. Centres will often only use one type of LVAD, which could introduce bias (though current available device options are limited following the HeartWare HVAD withdrawal). Registries other than INTERMACS are mostly prone to the same biases and issues. IMACS is an amalgamation of various device registries (including INTERMACS, EUROMACS and ITAMACS), and therefore the validity of the data is largely based on the individual databases themselves. There is limited information available on registries such as ITAMACS and EUROMACS, so it is more difficult to ascertain the processes they have in place to maintain quality.

Discussion

Summary of findings

There is a large volume of evidence analysing and summarising the use of LVADs for DT in patients with end-stage HF, extending from RCT data to single-centre observational data. However, much of this evidence is now redundant due to devices no longer being used or having been withdrawn from the market, as well as very few comparative studies being carried out.

Findings from the NMA in this review demonstrate that LVADs are effective alternatives to transplant and may offer survival rates of nearly 77% at 24 months with the HM3 device, which is the only currently available device in the UK (based on evidence from MOMENTUM, HeartMate II DT and REMATCH). However, comparative study evidence for the HM3 is limited to one RCT, with no direct comparisons made to MM. Indirect comparisons to MM demonstrated a clear, significant benefit for HM3 when considering risk of mortality, though with a wider ranging CI and some concerns about

transitivity. The SweVAD trial results and further device-specific data at longer follow-up times would increase the certainty of the findings.[48] Complications and events such as stroke and pump thrombosis may still remain an issue.

Strengths and weakness of the review

There were several strengths to this review, which include the large body of evidence included, with this review being the most comprehensive of its kind to date. This review has considered effectiveness for important subgroups including INTERMACS level and age. The review also considered the difficulties of overlapping patient populations (e.g. within registries and observational studies) and tried to address this by including data in a hierarchical approach. The trials were assessed for risk of bias and the limitations of registry data were considered in the context of the results. Furthermore, decisions on review methods were discussed extensively with clinical experts, as well as a wider steering group of independent clinicians, specialists and LVAD patients.

While every effort was taken to minimise risk of bias during the review process, some issues remain. Due to the large volume of evidence, a pragmatic approach was required to manage the review. This involved a hierarchical approach to analysis of the evidence, meaning that some studies were only considered in the analysis if they did not overlap with other patient populations. However, this also ensured there was no duplication of patient data. To further manage the large volume of evidence, studies with < 50 DT patients were excluded, which may have resulted in missed data. However, the impact of excluding these studies was assessed and found to be minimal (approximately 4.8% of patients) and should not cause bias. Finally, to limit the search hits to a manageable volume, terms for LVAD indication were included as requirements in the strategy (e.g. DT, BTT). This could potentially have resulted in missed studies, but it is likely that any important articles were found via citation checking of key publications and searches of INTERMACS publications via the Society of Thoracic Surgeons' INTERMACS website.

Strengths and weaknesses of the evidence

One of the most significant limitations of the included evidence is the lack of direct comparisons between the HM3 and MM. No studies have been completed that compare the HM3 and MM, either randomised trials or observational studies. This means that any comparisons made between these two interventions had to be made indirectly, which requires assumptions (though the SweVAD study will address this in the near future). Much of the evidence identified is no longer relevant as devices have been withdrawn or have been superseded by newer versions.

Furthermore, there are currently no studies in DT patients in the UK due to the current guidelines for LVADs being for BTT only. Therefore, findings from studies carried out elsewhere may not be representative of the UK population.

However, there are also several strengths of the evidence that is included. The evidence is wide ranging in terms of study design, meaning that there is both clinical trial data and real-world data from comprehensive registries. This allows for consideration of the differences in these data. The registry data are extensive and INTERMACS is considered the gold standard for patient data registries in health care. However, reporting of HM3 specific data in DT patients is still limited outside of MOMENTUM.

Evidence in context

This review summarises the existing evidence on LVADs for DT. Several evidence reviews have previously explored the effectiveness of LVADs for DT from various countries. A Belgian health technology assessment (HTA) report reviewed evidence up to 2015 and included the REMATCH and ENDURANCE trials, as well as several INTERMACS reports.[90] They found that survival and QoL improved in LVAD patients, though complications (e.g. bleeding and stroke) were an issue. Another HTA report from Canada drew similar conclusions but reiterated the high costs of the devices and

surgery.[91] However, these reports were not as inclusive as this review and were carried out before approval of the HM3 so do not reflect the current device availability.

There was another NMA which previously assessed LVADs for DT.[92] This NMA included HM3, HeartWare HVAD, HeartMate II, HeartMate XVE, and MM. It included four RCTs and four observational studies. The primary analysis included the trials only. There are a number of limitations identified in this NMA. It is unclear where the incidence rate ratios (IRRs) come from, for example for the outcome of death for MOMENTUM the IRR per 100 person-years was 0.61 in the paper, whereas the HR in MOMENTUM for death was 0.87. Furthermore, the NMA appeared to only include one year of follow-up from each study.

Implications for stakeholders/future research

This systematic review has demonstrated that the HM3 LVAD is an effective alternative for patients who are not eligible for HT. The current evidence indicates a clear survival benefit in LVADs compared to MM based on early trials and this is maintained with the HM3 when indirectly compared to MM via NMA. The HM3 also shows reduced stroke and other complications and events when compared to other devices. This information may be important for stakeholders in the UK who may consider recommending LVADs and, more specifically, the HM3 for DT in the future.

However, there are still missing data that may be key in determining the true effectiveness of LVADs when compared to MM. The lack of comparative studies, whether randomised or observational, directly comparing the HM3 with MM reduces the certainty of the effect, but publication of the SweVAD trial results could be significant evidence for future decision-makers. Furthermore, the cost-effectiveness of this device will be an important consideration for stakeholders, and this will be explored in the coming chapters.

Finally, research and development of LVADs continues. The new centrifugal flow EVAHEART 2 device has a pump and impeller design, which allows for gentle blood circulation while retaining pulsatility and is currently being trialled in the USA. The FDA-approved RCT is currently comparing the EVAHEART 2 device with the HM3 and aims to enrol approximately 400 patients.[47] This could lead to the possibility of an alternative to the HM3 device for both BTT and DT patients in the future.

Chapter summary

Left ventricular assist devices, and specifically the HM3, are effective treatments for end-stage HF in patients who are ineligible for HT. The HM3 demonstrates survival of 77% at 2 years, an improvement over other devices as well as MM (based on indirect comparisons only), though some adverse events are still common. Direct evidence on the HM3 versus MM from the SweVAD trial should help to cement findings, though the cost of the device, surgery and long-term patient care should be considered when determining if the device should be recommended for DT in the UK.

Chapter 4 Systematic review of economic analyses of left ventricular assist devices as destination therapy

Introduction

There has been wide-ranging debate about the cost-effectiveness of LVAD therapy for patients with AHF both in the UK and globally.[93] In particular, there is a lack of robust evidence around the cost-effectiveness of LVADs compared to MM for patients with AHF ineligible for heart transplantation (i.e. LVAD intended as DT). In the UK, a recent NHS Specialised Commissioning consultation highlighted this lack of economic evidence, and this is a key reason why NHS England has not recommended a LVAD for DT.[89] The outcomes associated with a LVAD as DT for patients with AHF thus need to be carefully considered against the resources required, and any additional costs must be evaluated in terms of any additional benefits that can be attributed to them.[94] In this chapter, a review of the existing Health Economics Literature on the use of a LVAD as DT for patients with AHF is presented. The aim of the systematic review is to identify existing economic evidence concerning a LVAD for DT in patients with AHF who are ineligible for heart transplantation and to evaluate the methodological quality of such studies. In addition, if the findings of the systematic review indicated that a de novo model-based analysis was required, the results would also be used to inform the development of the model and the associated parameters.

Methods

A review was conducted according to the guidelines of the UK's Centre for Review and Dissemination (CRD) and reported following the PRISMA guidelines.[40,95] The review was registered on PROSPERO, the international prospective register of systematic reviews (CRD42020158987).[41] The search strategy was formulated using the population, intervention, comparator and outcomes (PICO) framework.[96]

Inclusion and exclusion criteria

Papers were included if they met the following criteria:

- *Participants* – AHF patients (age > 16 years) who are ineligible for HT and are receiving a LVAD intended as DT.
- *Intervention* – Any LVAD irrespective of type, mechanism or generation. Studies of participants with biventricular assist devices, or RVADs were not eligible for inclusion.
- *Comparators* – MM or different generation or type of devices or no comparator.
- *Outcomes* – QoL, cost or incremental cost-effectiveness ratios (ICERs).

To capture as many studies as possible, no restrictions were placed on study design, year of publication or language. Any formal economic evaluations or studies of effectiveness with an assessment of costs or QoL studies were included. Conference proceedings published in the last 3 years (from the date of the searches) were included. The economic evaluations could take the form of a cost-consequence analysis, cost–benefit analysis, cost-effectiveness analysis (CEA) or cost–utility analysis (CUA). Conference proceedings, editorials, reviews or studies that reported on the use of technology for interventions unrelated to AHF were excluded.

Search strategy

A comprehensive search of six electronic databases was conducted from inception until 20 May 2020 in the first instance. Search updates were carried out on 19 May 2021 and 11 January 2022. The electronic

databases included three general databases: Cochrane Library (CENTRAL), MEDLINE and EMBASE via Ovid; and three specialist economics databases: EconLit, CEA registry and the NHS Economic Evaluation Database (NHS EED).

Combinations of keywords with the Boolean logic terms 'OR' and 'AND' were used. Search terms were refined using the MESH library. Search terms for each search strategy are listed in *Appendix 2*.

The reference lists of key papers were hand-searched to identify additional papers.

Study screening and selection

Following the database search, removal of duplicates was facilitated with EndNote X9 and study selection was performed independently by two reviewers in two stages with the use of Covidence systematic review software.[42,43] Titles and abstracts were screened, and full texts obtained for studies that potentially met the inclusion criteria. The full texts were then checked against the inclusion criteria to assess their eligibility for inclusion in the review. All discrepancies were resolved by discussion between the two reviewers or by a third reviewer.

Quality assessment

Quality assessment of the economic evaluations was conducted with appropriate tools. For trial-based studies, the Consensus on Health Economic Criteria (CHEC) tool was applied; this tool is widely used for the appraisal of economic evaluations.[97] For model-based studies, the Philips Checklist was used.[98] The Philips Checklist is specifically designed for the assessment of modelling studies and is recommended by both the National Institute for Health and Care Excellence (NICE) and the Cochrane Collaboration.[99]

Data extraction

The selected studies were read carefully to identify data important to the systematic review. A data extraction template was developed based on the study objectives and subsequent planned analysis. Data extraction was performed independently by two reviewers (TA and CO) using a standardised form. Information was extracted from each paper on the study background and the condition that was studied.

Given the review's objectives, information on the types of models used, and especially the range of health states used in the models were extracted. Model inputs such as resource use and QoL measures were also sought.

A narrative synthesis was undertaken as is recommended when the methodologies of the included studies are heterogeneous (Centre for Reviews and Dissemination 2008).[95] The quality appraisal was undertaken to inform the analysis rather than to exclude studies. As part of the analysis, approaches to economic evaluation, model structures, time horizons, cycle lengths and parameter inputs were compared and contrasted. This included an assessment of assumptions and the validity of model inputs and the sources of the costs and utility values.

Results

Selection

There were 19 studies from 20 articles that were relevant and included in the cost-effectiveness review. Three of these studies were identified by hand searching. The identified studies included 5 cost analyses and 14 economic evaluations. The PRISMA diagram is provided in *Chapter 1*, *Figure 4*.

Included studies

The main characteristics of the included studies are summarised in *Table 12*. The majority of the studies were conducted in the USA (n = 9) and some in the UK (n = 4). Most of the studies aimed to

TABLE 12 Summary of the studies included in the cost-effectiveness review

#	Author and year	Setting	Intervention/ comparator	Study design	Perspective	Main data source	Time horizon	Currency, price year, discount rate	Main findings	Sensitivity analysis
1	Adang 2006[104]	NT	LVAD (not specified)/MM	CUA – model	Payer	52 patients from University Medical Centre Utrecht	3 years	€, 2006, 3%	Incremental cost per QALY: €112,000	Deterministic and PSA
2	Baras 2017[101]	USA	LVAD (not specified)/MM	CUA – model	Third party[a]	220 patients from Medicare database	Lifetime	US$, 2016, 3%	Incremental cost per QALY: $209,400 (low risk) 171,000 (high risk)	
3	CETZ 2000[105]	CAN	LVAD (not specified)/MM	CEA	Payer	Literature based; 1993 and 1995	12 years	CAN$, 1999, 5%	Incremental cost per LY: $67,883	Deterministic
4	Chew 2017[106]	USA	HeartMate II/MM	CUA – model	Payer	Literature based	Lifetime	US$, 2015, 1.5%	Incremental cost per QALY: $230,692	Deterministic and PSA
5	Chimanji 2016[107]	USA	LVAD (not specified)/MM	CA	Payer	121 patients from Ohio State University hospital	1 year	US$, 2014, N/A	Cost of LVAD pp: $314,851 Cost of MM pp: $299,000	Not conducted
6	Clegg 2007[108]	UK	HeartMate/MM	CUA	Payer	Literature based and internal data from NHS trust for costs	5 years	£, UN, costs 6%, QALYs 1.5%	Incremental cost per QALY: £170,616	Deterministic
7	Droogne 2014[100]	BG	HeartMate II/HT	CEA	Payer	6 DT patients (BENEMACS)	1 year	€, 2010, N/A	Incremental cost per LY: €156,100	Not conducted
8	Girling 2007[109]	UK	HeartMate/MM	CUA	Payer	Literature based and used cost data from Clegg 2007	2 years	£, UN, 3.5%	Incremental cost per QALY: £76,766	Deterministic
9	Health Qual. On. 2016[91]	CAN	LVAD (not specified)/MM	CA	Payer	Literature based, 47 BTT patients and expert opinion	1 year	CAN$, 2015, N/A	Cost of LVAD pp: $185,400 Cost of MM pp: $32,250	Deterministic
10	Lim 2021[110]	UK	HM3/MM	CUA – model	Payer	MOMENTUM 3, REMATCH and ROADMAP trial data	5 years	£, UN, 3.5%	Incremental cost per QALY: £47,361	Deterministic and PSA

continued

TABLE 12 Summary of the studies included in the cost-effectiveness review (*continued*)

#	Author and year	Setting	Intervention/ comparator	Study design	Perspective	Main data source	Time horizon	Currency, price year, discount rate	Main findings	Sensitivity analysis
11	Long 2014[111]	USA	All on INTERMACS registry by 2013/MM	CUA – model	Payer	Literature-based	Lifetime	US$, 2012, 3%	Incremental cost per QALY: $201,600	Deterministic
12	Mehra 2018[112]	USA	HM3/HeartMate II	CA	Payer	361 patients in MOMENTUM 3 trial	2 years	US$, 2017, 0%	Re-admission costs for HeartMate III DT: $39,773, HeartMate II DT: UN	Deterministic
13	Messori 2009[103]	IT	HeartMate/MM	CUA	Not stated	68 DT patients	Lifetime	€, 2004, 1%	Incremental cost per QALY: €66,683	Deterministic
14	Neyt 2013[102]	NT	HeartMate II/MM	CUA – model	Societal (payer + trans-portation costs)	REMATCH and HeartMate II DT, 69 BTT patients from University Medical Centre Utrecht	Lifetime	€, UN, 4% and 1.5%	Incremental cost per QALY: €107,600	Deterministic and PSA
15	Oz 2003[113]	USA	HeartMate II/MM	CA	Payer	52 DT patients from REMATCH	1 year	US$, UN, N/A	Initial cost of LVAD pp: $210,187 Re-admission costs pp: $105,326	Not conducted
16	Rogers 2012[114]	USA	HeartMate II/MM	CUA – model	Payer	83 DT patients	5 years	US$, 2009, 3%	Incremental cost per QALY: $198,184	Deterministic
17	Silvestry 2019[115]	USA	HeartWare/MM	CUA – model	Payer	Medicare – number not provided	10 years	US$, 2017, 3%	Incremental cost per QALY: $102,587	Deterministic and PSA
18	Schueler 2021[116]	UK	HeartWare/MM	CUA – model	Payer	ENDURANCE Sup. Trial and SHFM	Lifetime	£, 2019, 3.5%	Incremental cost per QALY: £46,207	Deterministic and PSA
19	Slaughter 2011[117]	USA	HeartMate II/MM	CA	Payer	83 DT patients	At implan-tation	US$, 2009, N/A	Cost of LVAD pp: $193,812	Not conducted

CA, cost analysis; N/A, not applicable; pp, per person; UN, unknown.
a Stated as societal but no costs other than third party payer were included.

compare the health and cost outcomes of LVADs with MM, except one study that used HT as the comparator.[100] The study population was patients who received LVADs intended as DT because of ineligibility for a HT.

Most economic evaluations (n = 12) used a CUA approach and only two conducted a CEA. Markov-based modelling was applied in eight studies. The perspective was stated as the service provider in most studies, just two evaluations reported adopting a societal perspective and in one study the perspective was not explicitly stated.[101–103] The cost data were generally based on studies with small sample sizes. Comparability across studies was very low due to the substantial differences in methodology. The findings and limitations of the studies are discussed below.

Health outcomes

The studies considered outcomes such as survival probability, initial hospitalisation and the probability of hospitalisation per year after the initial discharge. Economic evaluations conducting a CUA (n = 12) estimated incremental quality-adjusted life-years (QALYs) as well as survival and hospitalisations. *Table 13* provides the survival and hospitalisation rates and health utilities used in the included studies.

The economic evaluations mostly used clinical data from HeartMate II DT and REMATCH trials or the INTERMACS registry. However, the utilisation of data differed substantially. Only four studies

TABLE 13 Survival rates and health utilities used in the included studies

#	Study	1-year survival (LVAD/comparator)	Hospitalisation per patient per year (LVAD/comparator)	Health utilities (LVAD/comparator)
1	Baras 2017	0.83/0.84 (low risk) 0.83/0.73 (high risk)	2.00/0.84 2.00/1.80	0.70/0.40
2	Chimanji 2016	0.88/0.78[a]	Not estimated	N/A
3	Chew 2017	0.58/0.16	2.64/3.15	0.85/0.53 depending on NYHA classes[b]
4	Clegg 2007	0.52/0.25	Not provided	0.56/0.40
5	Droogne 2014	0.83/0.84[a]	Not provided	N/A
6	Girling 2007	0.50/0.25	Not provided	0.81/0.55
7	Health Qual. On. 2016	0.81/N/A	2.64/N/A	N/A
8	Lim 2021	0.85/0.25	N/A	0.55/0.74
9	Long 2014	0.77/0.26	Not provided	0.52 (first month) and 0.72/0.53
10	Messori 2009	0.52/0.28	Not provided	0.81/0.55
11	Neyt 2013	0.68/0.28	2.64/3.15	0.81/0.55
12	Rogers 2012	0.70/0.30	2.52/1.59	0.85/0.53 depending on NYHA classes
13	Silvestry 2019	0.76/0.67	N/A/0.3	0.80/0.64
14	Schueler 2021	0.79/0.36	N/A	0.72/0.54
15	Slaughter 2011	0.51/0.25	Not provided	N/A

N/A, not applicable.
a The comparator was HT not MM in this study.
b The proportion of NYHA classes assumed to be the same in LVAD and MM patients in the base case.

that conducted model-based CUAs explicitly stated how hospitalisations after the LVAD implantation were incorporated.

Generally, very few studies included utility values that were specific to DT patients rather than BTT patients. Only three studies applied utility values that were specific to DT patients.[110,115,116] Schueler *et al.* converted utility values derived from a US population to UK values, using the Dolan algorithm.[116] One study used the utilities reported by Moskowitz *et al.*, which were estimated amongst 29 bridged patients.[118] Long *et al.*[111] applied the values for BTT patients by Sharples *et al.*[102] for the first month.[119] The other utility sources used in the economic evaluations did not distinguish between DT and BTT patients. Patients' monthly NYHA classifications were used in three studies to estimate health utilities.[106,114]

Costs

Most studies reported direct medical costs, which included the device cost, initial hospitalisation, re-admissions and outpatient visits. Seven studies also considered the cost of a LVAD replacement in the case of a device failure.[101,106,110,111,114–116] In addition, the analysis by Neyt *et al.*[102] considered the travel and 'social work' costs, although no definition was provided for 'social work'. One study reported adopting a societal perspective but only the direct costs were incorporated into the analysis.[101]

The cost estimates were usually based on a small number of patients from a single centre, and this caused variability. Most studies used standard discounting rates based on setting. Four studies used cost data for BTT patients since the LVAD was not part of the standard care for DT patients in the Netherlands and the UK.[102,109,111,116,120]

There were significant variations in the cost estimates, depending on the setting, device and methodology of the studies (e.g. included costs, time horizon). The largest cost component was the initial cost of the LVAD implantation, and in 2019 prices it varied from £83,567 in Belgium and £91,162 in the UK to £220,176 in the USA (*Figure 14*).[100,113,116] It is important to note that the device and implantation costs might have included different components, considering the differences in healthcare delivery across countries. The follow-up cost estimates ranged from £33,873 for 2 years to £402,309 over a lifetime.[101,112] The estimated cost of MM varied from £6009 for 1 year to £264,271 over 6 years.[101]

The cost-effectiveness of a left ventricular assist device as destination therapy

The review identified 14 studies that estimated the cost-effectiveness of a LVAD as DT. The majority of the economic evaluations concluded that LVADs were not cost-effective compared to MM (n = 8) or HT (n = 1) as DT, while three recent evaluations, including two from the UK, found favourable results.[110,115,116] The overall conclusion was not clear in two evaluations.[103,105]

The main outcome was the incremental cost per QALY gained in 14 studies and the incremental cost per life-year gained in two studies. It is important to note that Neyt *et al.* and Clegg *et al.* applied different discount rates for costs (4% and 6%, respectively) and outcomes (1.5%), while all others used the same rate for costs and outcomes.[90,108]

The cost-effectiveness was estimated over a time horizon of 5 years or longer in nine studies (*Figure 15*), and the incremental cost per QALY ranged between £46,207 and £238,401 in 2019 prices.[108,116] These studies were comparable because all had a payer's perspective except one, which included transport costs.[90] Despite the differences in the cost estimates, there was a downward trend over time in the ICER per QALYs reported. Baras Shreibati *et al.* calculated the incremental cost per QALY to be £152,953 or £124,904, based on two different mortality risk estimates.[101] Only one study considered the impact of severity on the cost-effectiveness, based on the INTERMACS profiles.[110] In a subgroup analysis, it was found that the ICER per QALY was lower for the patients with an INTERMACS profile 1–3 (£45,616) and higher for those with an INTERMACS profile 4–7 (£65,018), compared to the base-case estimate (£47,361).

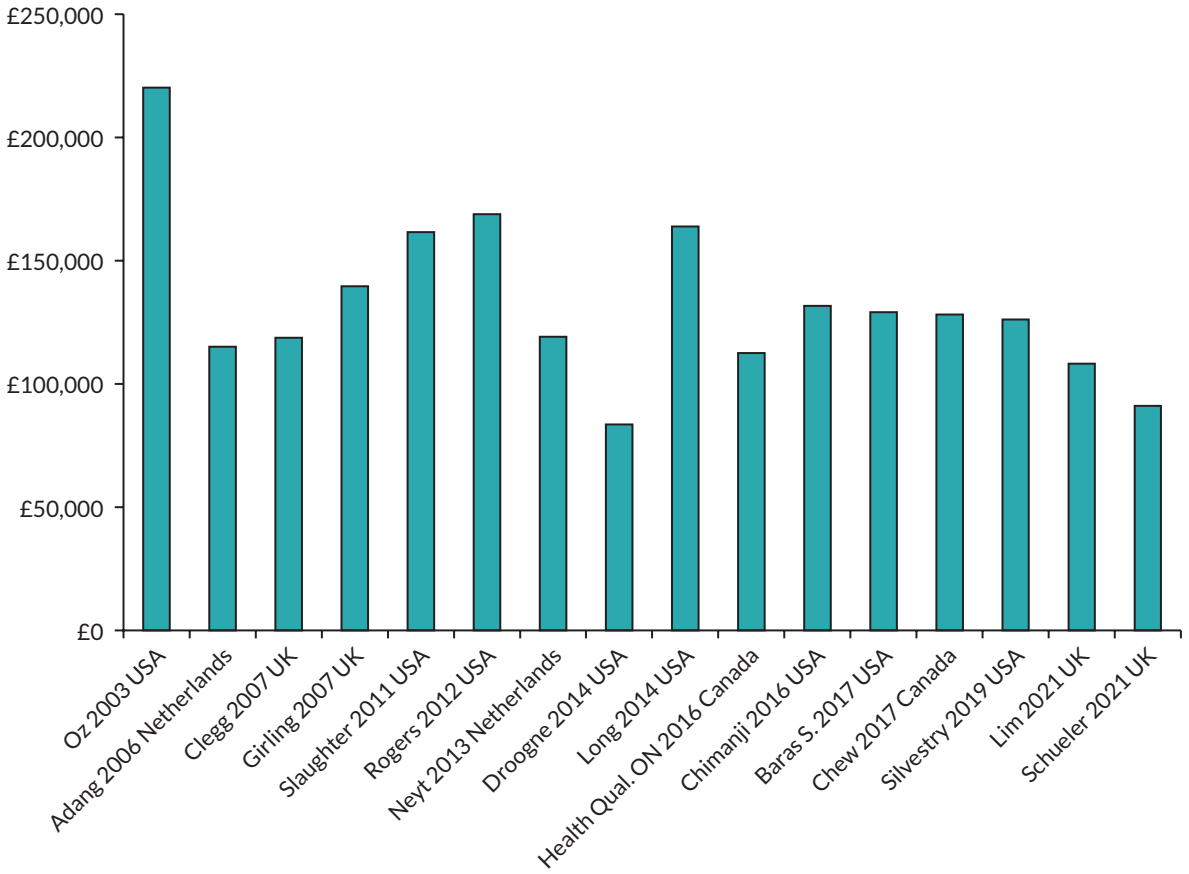


FIGURE 14 Index cost of LVAD implantation in 2019 prices.

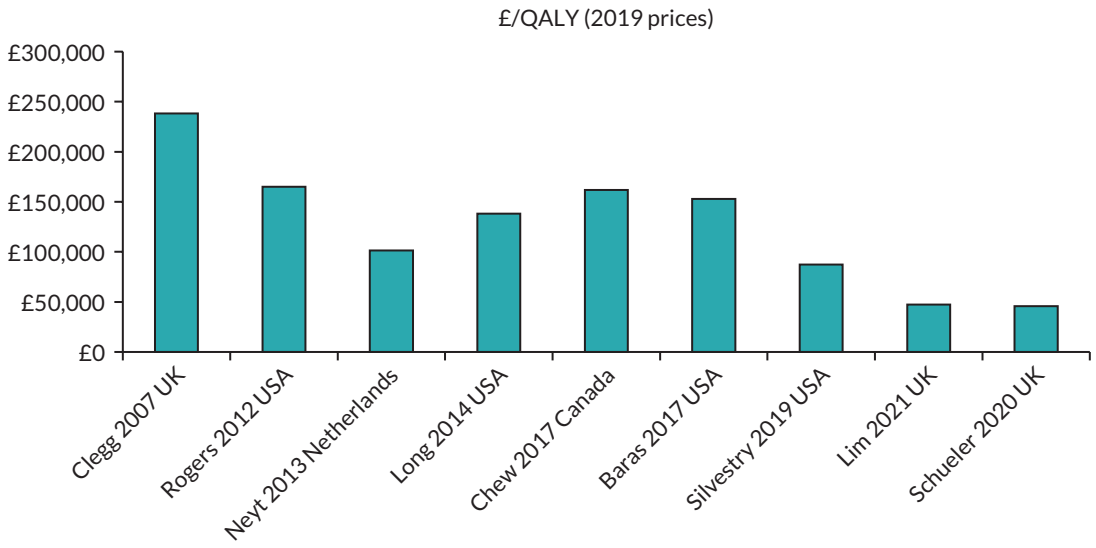


FIGURE 15 Incremental cost per QALY estimates in economic evaluations with a time horizon of 5 years or longer.

The incremental cost of a LVAD as DT per QALY was found higher than the standard thresholds in all evaluations except two studies, which estimated an ICER that was just below NICE's threshold of £50,000 per QALY for end-of-life treatments. Both were recently conducted studies from the UK health service perspective, with one based on the now withdrawn HeartWare HVAD device (£46,207), and the other on the HM3 device (£47,361).[110,116]

Economic evaluations with Markov models

Model structure and parameters

The characteristics of the economic evaluations with Markov models are summarised in *Table 12*. All the models had a time horizon of 5 years or longer, except one with a 3-year horizon.[114] All studies applied monthly cycles while Lim *et al.*[110] and Chew *et al.*[106] used three-monthly cycles.

Only two studies used health states other than being 'dead' or 'alive'.[102,111] Only Baras Shreibati *et al.*[101] considered the probability of becoming eligible for a HT after receiving a LVAD, but the probability was assumed to be the same for the LVAD and MM patients. Baras Shreibati *et al.* incorporated the increased mortality risk following a major stroke and Long *et al.*[111] modelled some of the complications as separate health states and applied specific mortality probabilities and health utilities for patients in these states.

Overall, the mortality risks for the first 2 years were obtained from the published literature, and extrapolated risks were used beyond that. One of the UK-based models used the Seattle Heart Failure Model (SHFM) to estimate the mortality risks.[116] This model estimates the survival rates at 1 and 2 years after the implantation. The second UK study extrapolated the values beyond 2 years, averaging the data available for the latest 6 months (*Table 14*).[110]

Six studies considered one or more adverse events (*Table 15*). However, the probability of stroke in the control group was considered only in two studies.[110,115] The impact of major events on mortality was incorporated only in one model for stroke, GIB and DI (Long *et al.*). All of the models assumed that after one cycle, which was 1 month in all except two that used three-monthly cycles, the impacts of the complications on morbidity and QoL were completely reversed.[106,110] However, in the model by Silvestry *et al.*,[115] BTT patients experiencing a severe stroke [modified Rankin Scale (mRS) ≥ 4] became ineligible for transplant, although the probability of experiencing a severe stroke was not provided.

Main findings of the modelling studies

All CUAs reported greater QALY gains for LVAD patients and significantly higher costs. The expected QALYs per patient on MM ranged from 0.27 over 3 years and 0.80 over 6 years and it was between 1.34 over 3 years and 4.41 over 6 years for LVAD recipients. Similarly, there was a wide variation in the expected costs per MM and LVAD recipients. The estimated incremental cost per QALY ranged from £87,370 to £165,170 in the USA, £88,595 in the Netherlands and £46,207 in the UK.[102,114,115]

Uncertainty

Uncertainty around the findings was assessed with deterministic and probabilistic sensitivity analyses (PSAs) in all modelling studies. An overview of the analyses revealed that it was difficult to identify a particular parameter as the main source of uncertainty because one-way sensitivity analyses showed that the cost-effectiveness estimates were sensitive to different parameters in each study. For example, one study found that estimates were most sensitive to re-admission rates and costs (Baras Shreibati *et al.*) and another found that estimates were most sensitive to LVAD implant cost and survival expectancy (Chew *et al.*).[101,106]

Six studies conducted PSAs.[102,104,106,110,115,116] According to the cost-effectiveness acceptability analysis, the probability of cost-effectiveness at a $100,000 threshold per QALY was 0% in one study and 33% in two analyses in the USA, while it was 50% at a €100,000 threshold per QALY in the Netherlands.[101,102,106,115] This probability was 97% at a threshold of £50,000 in one UK-based study.[110]

TABLE 14 Summary of the modelling studies

Author and year	Setting	Time horizon	Health states	Clinical inputs	Included costs	Price year, discount rate	QALY gains LVAD and MM	Cost[a] of LVAD and MM	ICER/QALY[a]
Adang 2006[104]	NT	3 years	Alive, dead	Survival, hospitalisation, QALEs	Hospitalisation, re-admission and outpatient costs	2006, 3%	1.34 (QALE) 0.27 (QALE)	£135,875 £21,200	£107,929
Baras 2017[101]	USA	6 years	Alive, dead	Survival, stroke, pump replacement, hospitalisation	Hospitalisation, re-admission and outpatient costs	2016, 3%	4.41 2.67 (low-risk MM) 1.63 (high-risk MM)	£530,442 £183,120 (low-risk MM) £264,271 (high-risk MM)	£124,904 (low risk) £152,953 (high-risk)
Chew 2017[106]	CAN	Lifetime	Alive, dead	Survival, hospitalisation, device failure, QALYs	Hospitalisation, re-admission and outpatient costs	2015, 1.5%	1.48 0.39	£172,610 £19,420	£140,068
Lim 2021[110]	UK	5 years	Alive, dead	Survival, stroke, GIB, DI, pump failure, QALYs	Hospitalisation, re-admission and outpatient costs	UN, 3.5%	2.83 0.43	£141,598 £28,047	£47,361
Long 2014[111]	USA	Lifetime	Stroke, GIB, DI, pump failure, dead	Survival, stroke, GIB, DI, pump failure, QALYs	Hospitalisation, re-admission, outpatient and end-of-life care costs	2013, 3%	2.79 0.41	£406,497 £77,187	£138,195
Neyt 2013[102]	NT	Lifetime	No event, hospitalisation, death	Survival, hospitalisation QALYs	Hospitalisation, re-admission and outpatient costs, travel costs	UN, 4% and 1.5%	Incremental QALY gain: 2.83	Incremental cost of LVAD: £281,602	£101,305
Rogers 2012[114]	USA	5 years	Alive, dead	Survival, hospitalisation QALYs	Hospitalisation, re-admission and outpatient costs	2009, 3%	1.87 0.37	£300,370 £52,385	£165,170
Silvestry 2019[115]	USA	10 years	Alive, dead	Survival, stroke, GIB, DI, pump failure, RHF, QALYs	Costs of adverse events, re-admission for MM patients, outpatient costs	2017, 3%	3.83 0.80	£344,662 £79,847	£87,370
Schueler 2020[116]	UK	Lifetime	Alive, dead	Survival, stroke, GIB, DI, PE, RHF, other adverse events, QALYs	Hospitalisation, costs of adverse events for LVAD patients, inpatient and outpatient costs for MM patients	2019, 3.5%	3.42 0.54	£204,222 £77,790	£46,207

UN, unknown.
a Costs were converted to 2019 GBP using the Bank of England end-of-year exchange rates and PSSRU inflation indices.

TABLE 15 Probability of major events in the previous models

Economic evaluation	Major events	Monthly event rate	Source
Lim *et al.* 2022[110] (3-monthly values)	Stroke	0.006 (1–3 months) 0.008 (4–6 months) 0.012 (7–9 months) 0.014 (10–12 months)	MOMENTUM 3
	PE	0.004	Same as above
	DI	0.023 (1–3 months) 0.030 (4–6 months) 0.031 (7–12 months)	Same as above
	GIB	0.138 (1–3 months) 0.041 (4–6 months) 0.031 (7–9 months) 0.025 (10–12 months)	Same as above
	RHF hospitalisation	0.046 (1–3 months) 0.027 (4–6 months) 0.034 (7–9 months) 0.009 (10–12 months)	Same as above
	RVAD	0.05 of all patients	Same as above
	Sepsis	0.107 (1–3 months) 0.008 (4–6 months) 0.007 (7–9 months)	Same as above
Schueler 2021[116]	Stroke	0.014 (ischaemic) 0.005 (haemorrhagic)	ENDURANCE Supplemental data, Medtronic internal data
	PE	0.006	Same as above
	DI	0.020	Same as above
	GIB	0.048	Same as above
	RHF	0.025	Same as above
Silvestry 2019[115]	Stroke	0.014 (ischaemic) 0.005 (haemorrhagic)	ENDURANCE Supplemental data, Medtronic internal data
	VAD thrombus	0.005	Same as above
	Device failure	0.001	Same as above
	DI	0.020	Same as above
	GIB	0.048	Same as above
	RHF	0.025	Same as above
	RVAD	7% of the RHF population	Same as above
	Other AEs	0.038	Same as above
	Stroke MM	0.002	Baras 2017
	Re-admission MM (apart from stroke)	0.300	Baras 2017

TABLE 15 Probability of major events in the previous models (*continued*)

Economic evaluation	Major events	Monthly event rate	Source
Baras 2017[101]	Stroke LVAD	0.008	ROADMAP study, SCD-HeFT trial
	LVAD pump replacement	0.004	ENDURANCE trial, INTERMACs
	HT received annual (LVAD and MM)	2.4%	ROADMAP
	Stroke MM	0.002	ROADMAP study, SCD-HeFT trial
	Death after HT	0.05 (1 month) 0.0135 (2–12 months) 0.0087 (13+ months)	Healy 2016 Lund 2015
	Death after stroke	0.4	Holloway 2005
Chew 2017[106]	Device failure	0.005	Cook 2014
Long 2014[111]	Stroke (first 12 months)	0.004	INTERMACS
	Device failure (first 12 months)	0.004	INTERMACS
	DI (first 12 months)	0.019	Aggarwal 2012
	GIB (first 12 months)	0.011	INTERMACS
	Death due to stroke	0.40	Not provided
	Death due to DI	0.23	Not provided

VAD, ventricular assist device.

Risk of bias

The quality of the economic evaluations was assessed using the CHEC and Philips criteria and overall judged as poor to moderate (see *Appendix 7*). Some important issues were identified in terms of the quality of the studies. For example, none of them justified the sources of parameters except two, which used systematic reviews to identify the mortality risk and health utilities within the first 2 years.[110,116] Additionally, some studies did not provide all the parameters used in the estimates. For instance, two studies did not provide the estimated mortality risks beyond 2 years despite using extrapolated data.[106,110] Similarly, Silvestry *et al.* did not provide the number of patients in different stroke groups generated based on the mRS.[115] Furthermore, studies did not fully explain how the complications were incorporated, although many included the hospitalisation costs.

Some studies did not consider all important cost components, for example, some omitted hospitalisation costs or the cost of device replacement in the case of a device failure. Similarly, some relevant variables, such as improvement in QoL, were not subjected to sensitivity analysis in some studies. Only Rogers *et al.* explored the alternatives to the assumptions about the estimated mortality risks beyond the available data in a sensitivity analysis.[114] The studies used data from small numbers of patients from a single centre to identify the cost inputs. Moreover, some studies used data from BTT patients in the absence of cost estimates specific to DT patients.[111]

Limitations of the existing economic evaluations

The existing economic evaluations had important limitations. Firstly, only four studies adopted a lifetime perspective.[101,106,111,116] Although the average life expectancy for LVAD DT patients is low,

some patients may live beyond the limited time horizons adopted in the existing studies. In addition, it is important to consider the impact of patients' characteristics such as gender, INTERMACS profile and age.

Another limitation was that the models generally only had only two health states (dead, alive), and only two studies included other health states.[102,111] Although two studies modelled some complications as separate health states, it was assumed that after a month, the impact of the complications would be reversed. Hence, the long-term impacts of the complications on DT patients (both LVAD and MM) have not been fully considered in existing economic evaluations.

A further consideration was that only one model considered the probability of DT patients becoming eligible for a HT.[102] However, in this study, the same probability of eligibility for HT was assumed for both LVAD and MM patients, but DT patients ineligible for a transplant would not be able to become BTT if they are receiving MM.

None of the studies considered the impact of INTERMACS profiles or age on mortality, morbidity or QoL except one (Lim *et al.*[110]), which might have an important impact on the cost-effectiveness outcomes.[101]

Discussion

Summary of findings

This review aimed to identify existing economic evidence concerning the use of LVADs in patients with AHF who are ineligible for a HT. The study identified 19 economic analyses focusing on the cost implications based on the screening criteria. Among these 19 studies, 14 were full economic evaluations, assessing both the health and cost impacts of LVADs. Most economic evaluations (n = 8) concluded that LVADs were not cost-effective compared to MM for patients with AHF who are ineligible for a HT. On the other hand, two UK-based evaluations reported favourable findings. The studies had some limitations, such as limited consideration of time horizon and the omission of some clinically significant adverse events.

Strengths and weakness of the review

The review was conducted based on a preregistered protocol (CRD42020158987) and the CRD and PRISMA guidelines were followed. The review was comprehensive as there was no restriction on the database search concerning dates or languages. Two independent reviewers conducted the study selection and quality assessment.

There are some limitations to be acknowledged. In line with the study objectives, the quality assessment focused on economic evaluations only. Thus, the quality of the cost analysis studies was not evaluated.

Strengths and weaknesses of the evidence

The cost-effectiveness outcomes were consistent in the published studies, given that the majority found that a LVAD was not a cost-effective alternative to medical therapy in patients with AHF who were not eligible for heart transplantation. The only two studies reporting favourable outcomes estimated ICER per QALYs to be just below the £50,000 threshold, defined as the end-of-life criteria in the UK.

However, the data inputs and methods used in the studies varied widely. For example, the index cost of LVAD implantation differed considerably from one study to another. It is difficult to explain this variation because studies from the same countries reported considerably different figures. In contrast, the variation in the ICER per QALY estimates was low within the same country in the studies published over the last 10 years. The studies from the European countries were more likely to report lower ICER per QALY estimates compared to the US-based studies.

The evidence on the cost-effectiveness of LVADs for patients with different INTERMACS profiles was not conclusive since only one study conducted an analysis based on the INTERMACS profiles, and the model inputs used in this study were not provided.[110]

The economic evaluations had some significant limitations regarding the data used. For example, very few studies used DT-specific health utility data and the others relied on utility estimates for BTT patients. The impact of LVADs on health utilities might be different in DT patients compared to BTT patients. Similarly, the cost data were usually based on a small number of patients and there was limited consideration of the ongoing costs such as outpatient costs. In most studies, these were not addressed, for example, by conducting a sensitivity analysis. There were also some methodological limitations in the economic evaluations included in the review. For instance, only three studies adopted a lifetime perspective, estimating long-term health and cost impacts. Additionally, there was a lack of data on outpatient costs and palliative care, especially for the MM patients.

Additionally, most economic evaluations used clinical data based on HeartWare HVAD. However, HeartWare HVAD has recently been withdrawn by the producing company due to safety concerns. Thus, the findings of these studies should be interpreted with caution.

Evidence in context

Only two UK-based studies found LVADs a cost-effective treatment compared to MM in patients with AHF who are ineligible for a HT, both reporting ICER per QALY estimates just below the £50,000 threshold.[110,116] However, the evidence was not conclusive since these evaluations had some limitations. Firstly, one of these studies focussed on HeartWare HVAD, which has recently been withdrawn.[116] Secondly, these studies did not consider the impact of adverse events on life expectancy, utilising two health states in the economic models. Additionally, the cost inputs used in these two models varied considerably. For example, the cost of LVAD implantation was £91,162 in the study by Schueler *et al.*[116] and £108,223 in the study by Lim *et al.*;[110] however, as these are two different devices, this could account for some of the cost differences. Additionally, the latter study estimated the additional cost of a LVAD compared to MM at £113,552. Thus, the key difference between the two treatment options was the device cost, estimating only a small cost for the cost of adverse events (£5329). However, the corresponding figure in the study by Scheuler *et al.* was £35,070.

Implications for stakeholders/future research

There were some limitations in the economic evaluations regarding their methodology and data inputs. Additionally, discrepancies were found between two recent UK-based models, which reported ICERs just below £50,000. Thus, the existing evidence is not sufficient to make commissioning decisions in the UK.

A new economic evaluation, which considers all the important adverse events with more recent data over a lifetime horizon, is needed. Considering the scarce data available regarding the ongoing costs of both MM and a LVAD, it would be valuable to identify the key parameters that have a significant impact on the ICER per QALY estimates and demonstrate how they influence the cost-effectiveness findings. This would guide future research.

Chapter summary

The evidence identified in this systematic review suggests that the estimates of the cost-effectiveness of a LVAD as DT has improved over time. This may be explained by the increased life expectancy associated with newer generation devices and a reduction in adverse events and device costs. However, the estimated incremental cost per QALY has tended to remain higher than the accepted thresholds in most studies.

The existing evaluations have important limitations, such as not considering a number of important complications that can occur after the LVAD implantation. In addition, none of the existing studies

considered the impact of INTERMACS profiles and age at the time of implantation. In terms of setting, there were only two UK-based economic models, but one study evaluated a device that has since been withdrawn due to safety concerns. Hence, the findings of this review suggest that a novel and more comprehensive economic evaluation of using LVADs as DT in patients who are not eligible for a transplant is needed.

Chapter 5 Economic evaluation

Introduction

The previous chapter presented a review of published cost-effectiveness studies and highlighted a range of limitations in the existing evidence base relating to the cost-effectiveness of a LVAD as a DT for patients who are ineligible for a transplant. The review concluded that, in light of these limitations, it was necessary to build a new model.

This chapter presents the methods and results of the model-based economic evaluation, which was undertaken to determine the cost-effectiveness of a LVAD as DT for this patient group, compared to MM. Benefits of treatment for patients need to be balanced against the resources required to achieve this outcome, and additional costs must be assessed in terms of any additional benefits that can be attributed to them.[94] Initially, there is an explanation of the methods employed in this analysis, in terms of the model structure, input parameters and the analyses undertaken, followed by a presentation and discussion of the results. The evaluation and reporting were informed by a range of relevant guidance.[121,122]

Methods

Model description

Economic modelling was required to estimate the long-term implications and to be able to incorporate all the key information collected in the different trials into an economic model. A Markov model was designed to evaluate the cost-effectiveness of a LVAD as DT for patients who are ineligible for a HT, compared to MM. A Markov model was appropriate for this analysis due to the chronic nature of the condition under consideration.[123]

Figure 16 presents the simplified overall model structure. In the intervention group, HT ineligible patients received a LVAD, while the comparator group received MM (representing usual care for DT patients in the UK).

The cycle length for the model was 1 month, and at the end of the first cycle, patients could be either alive without any major event, alive with major events, or dead. The health states for patients receiving LVADs and MM are demonstrated in *Figures 17* and *18*, respectively.

A major event was defined as any health condition that substantially increases long-term mortality risk, and these were modelled as separate health states. The major events identified for patients receiving LVADs were stroke, RHF and AR. For the MM group, the major event included was stroke. In addition, complications with no or limited impact on long-term mortality were incorporated in the model for LVAD patients to estimate their QoL impacts and the costs. These conditions are GIB, DI, PI, PE and arrhythmia.

In the base case, it was assumed that patients would not be eligible for HT at all. This was to reflect the central aim of the analysis, which focused on patients who were ineligible for transplant. However, given that some patients may become eligible for transplant at a later date, a sensitivity analysis was conducted to explore this impact on the results. For the sensitivity analysis, two additional health states were added to the model structure, BTT and HT. These states are shown in *Figure 17* for completeness.

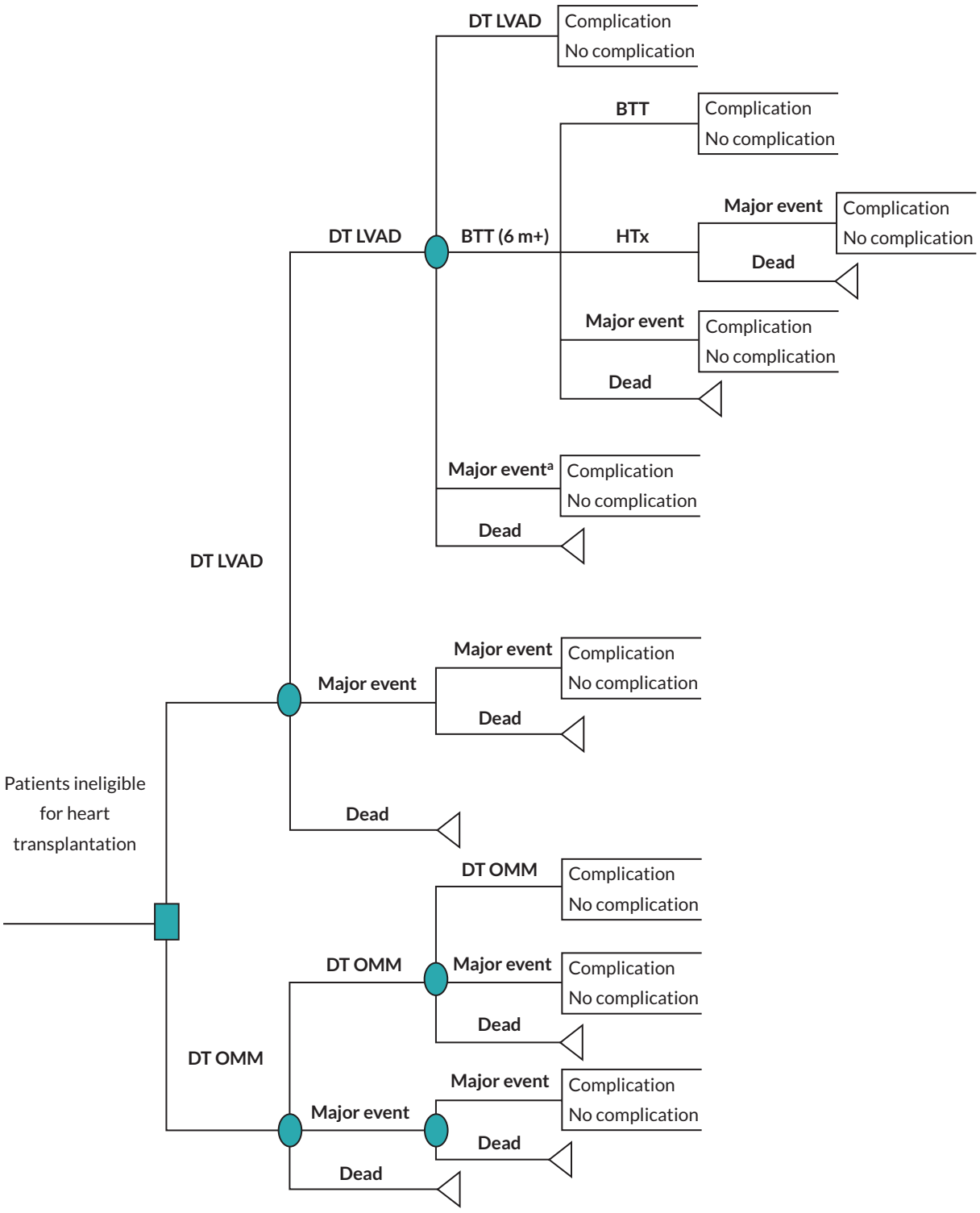


FIGURE 16 Simplified model structure. a, Major event: stroke, GIB, DI, LVAD failure as relevant.

Development of the model

A decision-analytic model was developed to synthesise the most appropriate evidence identified by the systematic reviews in *Chapters 3* and *4*. The model development was informed by expert opinion, one patient and public involvement (PPI) meeting, and three steering committee discussions, which included clinicians, commissioners and patient representatives. All of the probabilities and utility values used in the model are provided (see *Appendix 8*).

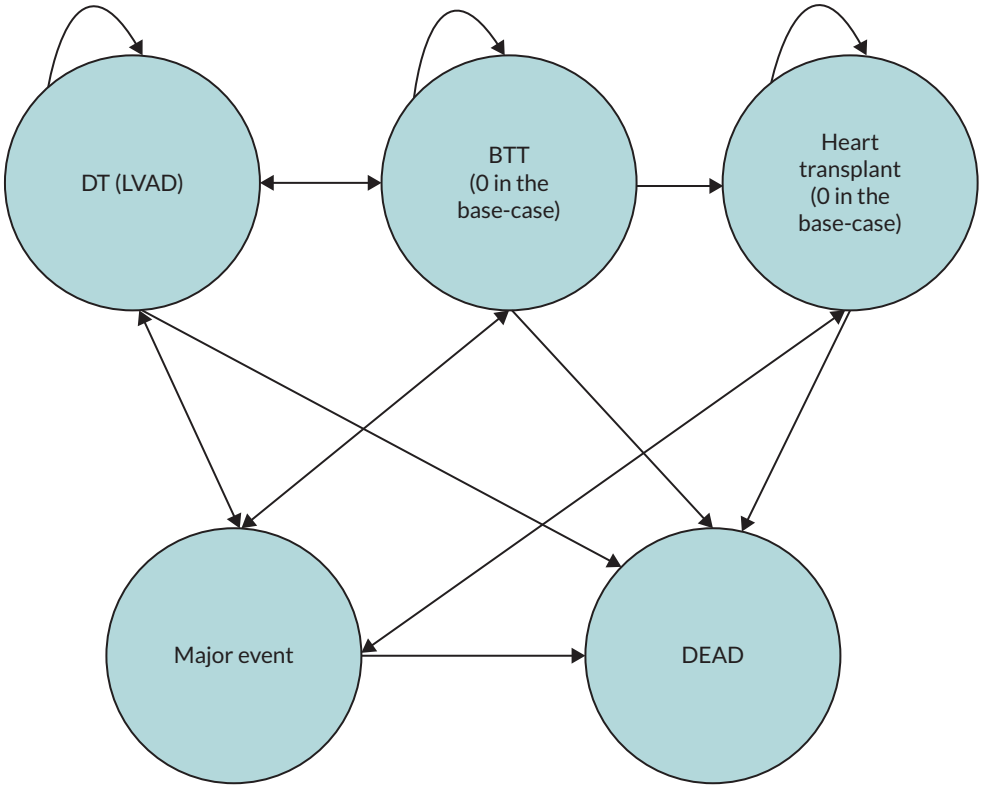


FIGURE 17 Health states for LVAD recipients.

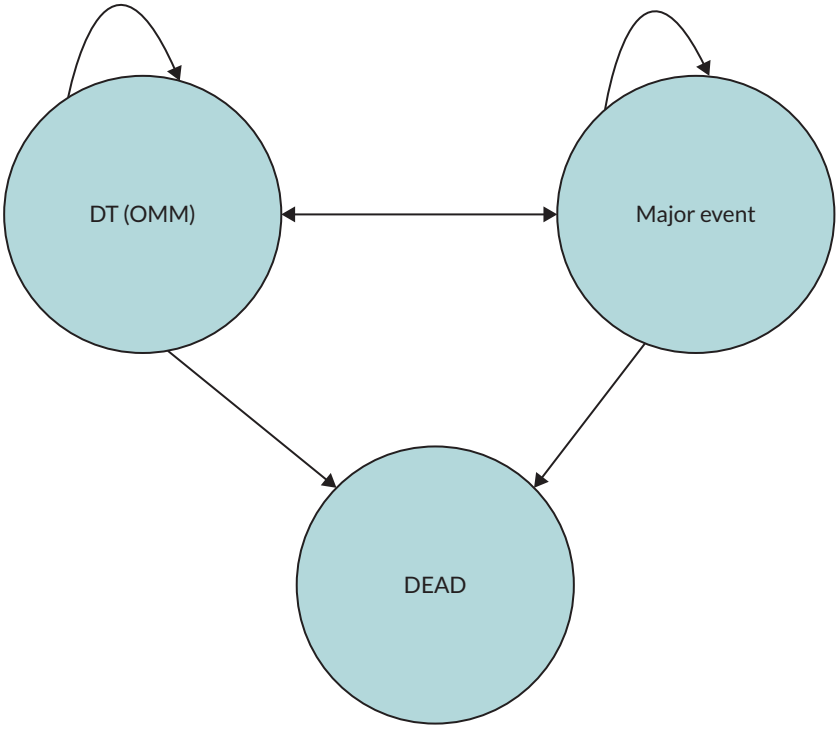


FIGURE 18 Health states for medical management patients.

Mortality risk

Mortality rates published by the Office for National Statistics were used to obtain the age-standardised mortality risks.[124] The age at the time of the implant was assumed to be 65 years in the base case. The overall mortality risks for DT and MM patients were adjusted for the probability of death due to the major events, applying the below formula where ME stands for major events.[125]

$$Mortality\ \ (no\ ME) = \frac{Overall\ Mortality - (Prevalence\ of\ ME \times Mortality\ due\ to\ ME)}{1 - Prevalence\ of\ ME} \quad (1)$$

As the systematic review of the clinical literature found no trial comparing contemporary LVADs to MM directly, estimating the mortality risks in the LVAD and MM arms required some assumptions. Four different potential methods were identified:

1. *Non-comparative, net weight estimates:* The mortality risks reported for LVAD recipients in the MOMENTUM trial and MM patients in the REMATCH trial were utilised to obtain monthly probabilities in the model.[54,126] Thus, it was assumed that the profiles of patients in the MOMENTUM trial matched perfectly to the MM patients in the REMATCH trial, and the clinical effectiveness of standard care had not changed over the last 20 years.
2. *Non-comparative, weighted estimates for MM:* The mortality risks for LVAD recipients in the MOMENTUM trial were used. The mortality risk in the MM arm was obtained based on a weighted average, using data from the REMATCH and MEDAMACS trials and the proportions of INTERMACS 2 and 3 and INTERMACS 4 and 5 patients in the MOMENTUM trial, respectively (Rose, Mehra, Ambardekar).[54,126,127] Thus, it was assumed that the mortality risks reported in the REMATCH trial included MM patients who could be considered to have a similar disease progression to INTERMACS 2 and 3, and that the MEDAMACS data included MM patients who could be considered to have a similar disease progression to INTERMACS 4 and 5 patients.
3. *Comparative estimates mapped to MM in REMATCH:* The mortality risks for MM patients in the MM arm were used. The mortality risks for the LVAD patients were obtained based on the RR estimated in the NMA reported in *Chapter 3* and the mortality risks for MM patients. Thus, it was assumed that the profiles of patients in the MOMENTUM trial matched perfectly to the MM patients in the REMATCH trial, and the other trials that were used in the NMA reported in *Chapter 3*. It was also assumed that the mortality risk estimates for the MM patients in the REMATCH trial were more reliable than the mortality risk estimates for the LVAD recipients in the MOMENTUM trial.
4. *Comparative estimates mapped to the LVAD in the MOMENTUM trial:* The mortality risks for LVAD patients in the MOMENTUM trial were utilised. The mortality risks for the MM patients were obtained based on 1/RR estimated in the NMA reported in *Chapter 3* and the mortality risks for MM patients. Thus, it was assumed that the profiles of patients in the MOMENTUM trial matched perfectly to the MM patients in the REMATCH trial and the other trials that were used in the NMA. It was also assumed that the mortality risk estimates for the LVAD recipients in the MOMENTUM trial were more reliable than the mortality risk estimates for the MM patients in the REMATCH trial.

It was deemed important to explore the impacts of incorporating the estimates from these four options into the evaluations, since all included different assumptions. The estimated mortality risks based on the four options are provided (see *Table 33* and *Appendix 8*).

In the absence of mortality data beyond 2 years, it was necessary to extrapolate the limited trial data to estimate cost-effectiveness for a longer time horizon. The model assumed that the mortality risk after the 24th month would be the same as the risk reported for the months between 13th and 24th.

Major events

The major events were modelled separately, and every major event was represented in a health state (*Figure 19*).

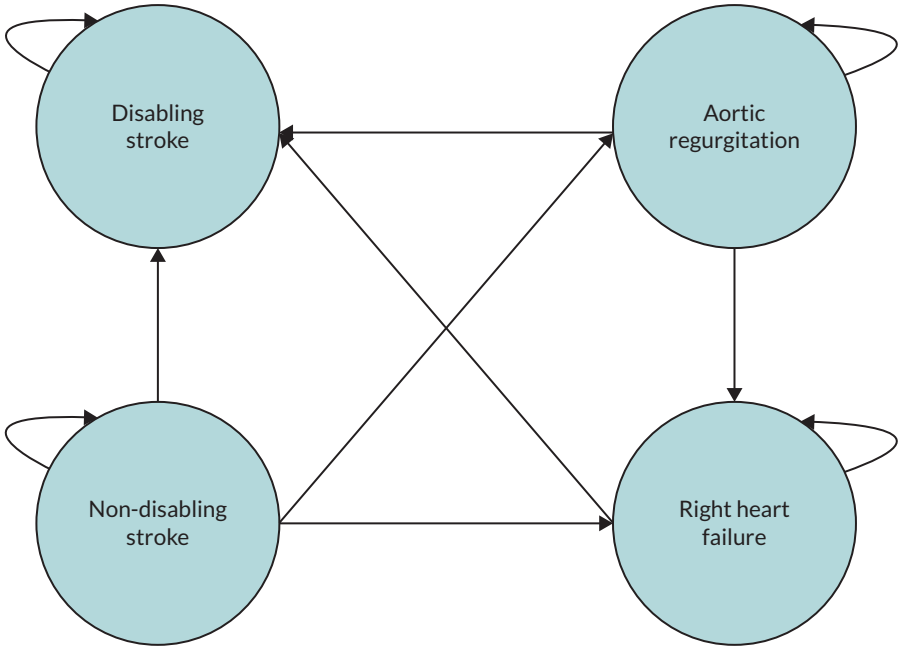


FIGURE 19 Transition between major events.

Stroke

Stroke was incorporated as two different health states to take account of symptoms and disability using the widely used mRS to define non-disabling stroke as a score < 4, and disabling stroke for patients with a mRS score ≥ 4.[128] The model used age-specific probabilities for stroke. Patients experiencing a stroke could die or move to the states for non-disabling stroke or disabling stroke. Among those experiencing a stroke, it was assumed that 0.25 of them died, and the mortality risk was assumed to be reversed within a month for non-disabling stroke, while with disabling stroke the risk increased to 0.035/month permanently.[57,129]

Right heart failure

Right heart failure is usually defined as early and late RHF because of the greater health and cost impacts of early RHF.[130] However, there is no consensus on the definition of early RHF in the literature, varying from 14 days to 300 days.[131,132] In this study, early RHF was defined as RHF occurring during the first month after LVAD implantation, because this was the most widely used definition.[133,134] Late RHF was defined as any RHF after the first month, which required hospitalisation.

Patients experiencing RHF within the first month could either die or move back to their previous states in the next cycle, because early RHF is usually a transient state. Patients experiencing late RHF could die or stay in the RHF state, due to the long-term impacts on mortality and QoL. Early RHF was assumed to cause a postoperative mortality risk (0.035), while late RHF would increase the mortality risk to the level expected for MM patients (0.021). The probability of receiving a RVAD was applied to the patients who experienced early RHF, while it was assumed that late RHF would not generate a need for a RVAD, in line with current UK guidelines.

Aortic regurgitation

Patients experiencing AR could die, have a stroke or stay in the AR state. Similar to RHF, a postoperative mortality risk (0.035) was applied for AR. For those who survived, an increased mortality risk (0.008) was assumed.[38]

Experiencing more than one major event

In the case where patients experienced more than one major event, the major event with the greatest impact on mortality and QoL was utilised. For example, patients who previously experienced a stroke could go on to experience a disabling stroke, and after that they would stay in the disabling stroke state or die. Since the impacts of RHF and AR on mortality and QoL are greater than the impacts of non-disabling stroke, patients experiencing non-disabling stroke and AR or RHF moved back to the AR or RHF states in the next cycle, unless they died due to stroke. However, patients experiencing disabling-stroke and AR or RHF stayed in the disabling-stroke state because the health impacts of disabling stroke are likely to be greater than the impacts of AR and RHF. Similarly, patients experiencing RHF and AR stayed in the RHF state.

The transitions within the model are summarised in *Table 16*.

Complications

The complications incorporated into the model could be experienced by all patients receiving LVADs.

Health utilities

To estimate QALYs, baseline health utilities were first applied to all the patients in the model. The baseline utility value reported in the MOMENTUM trial was used for the MM patients in the model (0.51). Similarly, the utility values reported in the MOMENTUM trial were utilised in the LVAD arm (0.76 and 0.77, Mehra).[126]

Utility decrements

Utility decrements were applied to those who experienced a major event or complication. It was assumed that major events would cause a permanent utility loss, while complications would result in a reduction in utility during the cycle in which the complication occurs.

Utility loss due to stroke

In a recent study, the health utilities (and utility losses) after stroke based on the mRS scores were estimated in *Table 17*.[135]

Kirklin *et al.*, based on INTERMACS, reported proportions of patients by mRS, 3 months after stroke as follows: mRS 0 & 1: 31/115 = 0.27 and mRS 2 & 3: 10/115 = 0.09.[129] Thus, the percentage within non-disabling stroke were: mRS 0 & 1: 31/41 = 0.76 and mRS 2 & 3: 10/41 = 0.24.

TABLE 16 Transitions within the LVAD model

Starting state	Jump to state	Complications
DT (LVAD)	Death Non-disabling stroke, disabling stroke, RHF, AR, DT (LVAD)	GIB, DF, DI, PE, arrhythmia
Non-disabling stroke	Death Non-disabling stroke, disabling stroke, AR, RHF	GIB, DF, DI, PE, arrhythmia
Disabling stroke	Death Disabling stroke	GIB, DF, DI, PE, arrhythmia
RHF	Death Disabling stroke, RHF	GIB, DF, DI, PE, arrhythmia
AR	Death RHF, disabling stroke, AR	GIB, DF, DI, PE, arrhythmia
MM	Death Non-disabling stroke, disabling stroke	Re-admission for any reason

TABLE 17 Modified Rankin Scale scores and health utilities

mRS score	Utilities	Utility losses
mRS 0	1	0
mRS 1	0.91	0.09
mRS 2	0.76	0.24
mRS 3	0.65	0.35
mRS 4	0.33	0.67
mRS 5 & 6	0	1

The average utility loss for non-disabling stroke was calculated as:

$$[(0 + 0.09)/2] \times 0.76 + [(0.24 + 0.35)/2] \times 0.24 = 0.11 \quad (2)$$

Utility loss due to disabling stroke

The patients who experienced a disabling stroke experienced a utility decrement of 0.67.[135]

Costs

The costs and resource use associated with the intervention and comparator were estimated using a range of sources. To identify the one-off cost inputs, for example the costs associated with stroke, NHS reference costs were used for the operation costs while the number of hospital days in the intensive care unit (ICU) and in a cardiac ward were estimated through discussions with two practicing heart surgeons, working in the NHS. The ongoing cost inputs, for example outpatient costs for LVAD recipients, were identified from the systematic review (see *Chapter 3*). All the costs are presented in 2019 prices and the future costs and benefits were discounted at 3.5% as per NICE guidelines.

For LVAD recipients experiencing early RHF, the usual practice in the UK is to make some adjustments to the existing LVAD setting (in addition to the treatment with inotropes) or insertion of a temporary RVAD rather than implanting a RVAD into the right ventricular, and thus the cost of the device is expected to be much lower.

The cost inputs used in the model are provided (see *Appendix 8* and *Table 35*).

Modelling assumptions

A range of assumptions were required for the analysis due to the limitations associated with the data available and for computational practicalities. The assumptions were as follows:

- Any patient could experience only one major event within a given month. Patients experiencing a major event were assumed not to experience any of the complications within the same month.
- Disabling stroke was assumed to comprise 4.6% of all stroke cases (mRS > 4), both in LVAD and MM recipients.[57,136]
- Patients who experienced AR or RHF could experience non-disabling stroke unlimited times. This is because those patients would transition back to the AR or RHF states in the following cycle, unless they died.
- The probability of a disabling stroke amongst patients with a prior non-disabling stroke experience was estimated based on the study by Kirklin *et al.* who reported that 17% of those who experienced non-disabling stroke had a second stroke within 3 years, which was 0.002 monthly.[137] The probability of death amongst patients experiencing a second stroke was assumed to be the same as for the first stroke (0.25). Similarly, it was assumed that of the patients who survived a second stroke, 4.6% would have a mRS > 4, as in the first stroke.

- Apart from the relationship between stroke and disabling stroke, previous experience of major events and complications was assumed not to have an impact on the probability and outcomes of a major event or a complication. This was to reflect the published evidence, for example Truby *et al.* found that experiencing AR did not have a significant impact on the risk of stroke, bleeding and arrhythmia, conditional on survival to 1 year.[38]
- For model simplicity, it was assumed that valve replacement did not have any impact on QoL or life expectancy.
- It was assumed that 57% of arrhythmia cases would be ventricular and a higher QALY loss (0.06) was applied for these patients.[112,138]

Population

The study population was a hypothetical cohort of 1000 patients with AHF deemed ineligible for heath transplant. The mean age was 65 years and 50% of the cohort was assumed to be female, based on the findings of the systematic review.

Intervention and comparator

The patients in the intervention group received LVADs, while those in the control group received usual care. Usual care was defined as MM, which consisted of treatment with inotropes to enhance cardiac contractility and ongoing monitoring.

Outcomes and analysis

The main outcomes were expressed in terms of incremental costs per life year (LY) and QALY gained. For this, the healthcare costs, LYs and QALYs per patient were calculated for the MM and LVAD arms. The incremental cost per QALY and LY was estimated as follows:

$$Incremental\ cost\ per\ \mathrm{QALY}\ (LY) = \frac{Costs\ (LVAD) - Costs\ (OMM)}{QALYs\ (LVAD) - \mathrm{QALYs}\ (OMM)} \quad (3)$$

All of the analyses were conducted from the NHS/PSS perspective over a lifetime horizon and the outcomes at shorter time periods (i.e. 2 and 5 years) were also estimated. According to NICE guidelines, health technologies with a ICER per QALY between £20,000 and £30,000 are considered cost-effective in the UK.[122] Until recently, NICE allowed using a higher threshold (£50,000 per QALY) if the treatment is indicated for patients with a short life expectancy, normally < 24 months and that there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. As the clinical evidence summarised in *Chapter 3* indicates, providing LVADs as DT for AHF patients who are ineligible for a HT meets these criteria.

The recently updated guidelines suggest a severity weighting based on a QALY shortfall estimate. The absolute QALY shortfall is defined as the difference between the expected QALYs for a specific age and sex group in the general population and the expected QALYs for the patient population if not treated. The proportional QALY is estimated by dividing the absolute QALY shortfall by the remaining QALYs for the same age and sex group in the general population. The QALY Shortfall Calculator developed by Sheffield University was used to estimate the QALY shortfalls in this study.[139] Weights were then applied following NICE recommendations on specific weights, based on the estimated QALY shortfalls (*Table 18*).

TABLE 18 Quality-adjusted life-year shortfall weightings recommended by NICE

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	< 0.85	< 12
× 1.2	0.85–0.95	12–18
× 1.7	At least 0.95	At least 18

Sensitivity analysis

A range of deterministic and probabilistic sensitivity analyses were conducted to explore the uncertainties around the model parameters. In the first sensitivity analysis, the impact of incorporating the probability of transitioning to BTT and then HT for LVAD patients on the model outcomes was estimated. Secondly, key parameters were varied and the impacts on the model outcomes were presented on tornado diagrams. Finally, PSAs were conducted to estimate the uncertainties around the model outcomes. The details of these analyses are provided below.

Transition to bridge to transplant and heart transplant

In order to explore the impact of LVAD patients becoming eligible for transplant, a sensitivity analysis was conducted to incorporate a small proportion of LVAD recipients moving to the BTT state (0.06/month), starting 6 months after the implant and until 3 years after the implant.[130] In the next cycle, some BTT patients (0.028/month) would have the probability of receiving a HT until 3 years after the implant.[137] BTT patients could experience a major event, have a HT, or die. BTT patients experiencing a major event became ineligible for a HT and moved back to the DT state or died. The model inputs used for this analysis are provided (see *Table 35* and *Appendix 8*).

One-way sensitivity analysis

There was limited or conflicting evidence on some of the model parameters in the literature, such as the monthly ongoing costs for MM and LVAD patients. Different values were used for these parameters to estimate the impact on the model outcomes and to identify the parameters with the greatest impact. The model inputs used for this analysis are provided in *Appendix 8*, *Table 37*.

Probabilistic sensitivity analyses

A PSA involves running thousands of different versions of the model where parameters are varied randomly alongside the prespecified distributions around parameter values.[140] The distributions were defined based on the nature of the parameters, with beta distributions used for binomial data and gamma distributions for costs.[94] Additionally, the difference in sampling method was applied for the parameters, which had different probabilities at different time points.[141] This method takes the relationship between the probabilities at different time points into account, by estimating the mean and variance of the logit distribution for each parameter to obtain the probabilistic values. The independent random sampling method was utilised for the remaining probabilities that did not require such adjustment and for the cost inputs.

Additionally, a cost-effectiveness acceptability curve was produced, to allow estimation of the cost-effectiveness outcomes at different willingness to pay (WTPs) thresholds.[142]

Value of Information analysis

Value of Information (VoI) analysis is an appropriate tool to determine whether a further trial is needed, and to calculate the optimal trial size.[143] The simplest measure is the expected value of perfect

information (EVPI); this represents the net benefit, expressed in monetary terms, of making the decision after all uncertainty has been resolved rather than under the current conditions of uncertainty. To express the health benefit in monetary terms requires the WTPs per QALY to be specified, for example the £20,000–30,000 per QALY specified by NICE.[144] The population level EVPI reflects the number of individuals who will benefit from the decision.

Any study costing more than the EVPI can be ruled out, but a study costing less than the EVPI may still not be worthwhile, and further types of analysis of VoI are required. Expected value of perfect parameter information (EVPPI) gives the value of certainty for a subset of the parameters in a model.

To determine whether a new primary study is worthwhile requires an assessment of the expected value of sample information (EVSI). This considers the possible outcomes from a study. The expected net benefit of sampling (ENBS) is the EVSI less than the cost of the study. The optimal sample size is the one that maximises the ENBS, except that, if no sample size can be found to give a positive ENBS, the study can be ruled out.

Exploratory subgroup analysis by Interagency Registry for Mechanically Assisted Circulatory Support profiles

An exploratory subgroup analysis was undertaken to assess the cost-effectiveness of LVADs based on the clinical characteristics of patients. The cost-effectiveness of LVADs was analysed separately for INTERMACS profiles 1, 2 & 3, 4 & 5. INTERMACS 1 was evaluated separately, but not included in the base case because DT patients in this group usually do not receive a LVAD. In the absence of trials that compared LVAD recipients to patients on MM by the INTERMACS profiles, the best available evidence and expert views were used to define the key model inputs in this analysis.

The mortality risks and health utilities used for this analysis are provided in *Table 39* (see *Appendix 8*). Based on expert view, it was assumed that all medically managed DT patients with an INTERMACS 1 profile would die within 6 months. In the absence of evidence on the QoL amongst MM patients with an INTERMACS 1 profile, it was assumed to be 0.1 within the first month and after that QoL in ICU (0.26) was applied as a proxy. Grady *et al.* reported that LVAD implantation increased QoL by 0.11 units amongst patients with an INTERMACS 1 profile, and this was used to estimate the health utilities in INTERMACS 1 DT patients who received a LVAD (0.26 + 0.11 for the first year).[145]

Results

Primary analysis

To be comprehensive, two base-case analyses were undertaken for the primary analysis, using two separate estimates of mortality risks and utilities. Based on the systematic review of the clinical literature, four different methods were defined to estimate mortality risks and health utilities. Economic evaluations were conducted for all four of these options, keeping all the remaining parameters constant, to identify the base case. Based on the face validity of the model outcomes and the assumptions associated with each option, it was decided to present two base cases: *non-comparative*, *net weight estimates* and *comparative estimates mapped to LVAD in MOMENTUM*. The justifications for not including the other two options are provided below and the model outcomes for these options are provided (see *Appendix 8*).

1. *Non-comparative*, *net weight estimates:* Taken forward as one of the two base cases and the outcomes are provided below.
2. *Non-comparative*, *weighted estimates for MM:* This option required combining data from three different trials and the modelling outcomes were similar to the non-comparative, net weight estimates. Thus, it was decided to present the outcomes as an appendix.

3. *Comparative estimates mapped to MM in REMATCH:* The model outcomes were not realistic for the LVAD recipients. It suggested that patients receiving a LVAD would have 2.86 LYs and 2.02 QALYs on average. This was deemed too low, underestimating the benefits of LVADs compared to the findings of recent trials. Thus, it was decided to present the outcomes as an appendix.
4. *Comparative estimates mapped to LVAD in MOMENTUM:* Taken forward as one of the two base cases and the outcomes are provided below.

Deterministic model outcomes

The deterministic lifetime outcomes provided in *Table 19* showed that using the non-comparative, net weight estimates and the comparative estimates (mapped to LVAD in MOMENTUM), LVAD would be expected to produce additional QALYs of 2.86 and 2.51 per patient, respectively, compared to MM. The incremental costs were £152,735 and £146,275, respectively. Therefore, although the QALY and cost estimates in the MM arm were higher using the comparative estimates mapped to LVAD in MOMENTUM (compared with the non-comparative net weight estimates), the ICERs produced were similar at £53,496 and £58,244, respectively.

Table 20 provides the model outcomes at the end of 2 years. These estimates showed that by the end of the second year, LVADs would reduce expected deaths by 66% using the non-comparative, net weight estimates and by 44% using the comparative estimates mapped to LVAD in MOMENTUM. The ICERs at 2 years were estimated to be £131,593 and £151,101, respectively.

Table 21 provides the model outcomes at the end of 5 years. These estimates showed that by the end of the first 5 years, LVADs would reduce expected deaths by 46% using the non-comparative, net weight

TABLE 19 Deterministic model outcomes in the base case

	Non-comparative, net weight estimates			Comparative estimates mapped to LVAD in MOMENTUM		
Lifetime outcomes	**MM**	**LVAD**	**Incremental**	**MM**	**LVAD**	**Incremental**
Expected LYs per patient	0.92	4.65	3.73	1.68	4.74	3.06
Expected QALYs per patient	0.46	3.32	2.86	0.85	3.36	2.51
Cost per patient	£18,886	£171,621	£152,735	£26,534	£172,809	£146,275
Incremental cost per LY			£40,911			£47,818
Incremental cost per QALY			**£53,496**			**£58,244**

TABLE 20 Deterministic model outcomes at 2-year follow-up

	Non-comparative, net weight estimates			Comparative estimates mapped to LVAD in MOMENTUM		
Two-year outcomes	**MM**	**LVAD**	**Incremental**	**MM**	**LVAD**	**Incremental**
% of deaths	91	25	−66	69	25	−44
Expected LYs per patient	0.85	1.71	0.87	1.09	1.72	0.63
Expected QALYs per patient	0.43	1.23	0.80	0.55	1.23	0.68
Cost per patient	£17,173	£121,843	£104,670	£17,576	£121,853	£104,277
Incremental cost per LY			£120,868			£164,831
Incremental cost per QALY			**£131,593**			£154,101

TABLE 21 Deterministic model outcomes at 5-year follow-up

	Non-comparative, net weight estimates			Comparative estimates mapped to LVAD in MOMENTUM		
Five-year outcomes	**MM**	**LVAD**	**Incremental**	**MM**	**LVAD**	**Incremental**
% of deaths	100	54	−46	92	52	−39
Expected LYs per patient	0.92	3.30	2.38	1.57	3.34	1.77
Expected QALYs per patient	0.46	2.36	1.90	0.79	2.38	1.59
Cost per patient	£18,855	£148,002	£129,148	£24,815	£148,522	£123,707
Incremental cost per LY			£54,314			£69,936
Incremental cost per QALY			**£67,997**			**£77,775**

estimates and by 39% using the comparative estimates mapped to LVAD in MOMENTUM. The ICERs at 5 years were estimated to be £67,997 and £77,775, respectively.

Severity weighted incremental cost-effectiveness ratio estimates

The updated NICE guidelines recommend using QALY weights based on the QALY shortfalls a certain population faces as a result of an illness.[122] The absolute QALY shortfalls for the study population were estimated as 10.38 using the non-comparative, net weight estimates and 9.95 using the comparative estimates mapped to LVAD in MOMENTUM, while the proportional QALY shortfalls were 0.96 and 0.92, respectively. The incremental QALY gains estimated by the model were weighted according to the proportional QALY shortfalls, as recommended.

The appropriate weighting was 1.7 in the non-comparative, net weight estimates, and 1.2 in the comparative estimates mapped to LVAD in MOMENTUM. The weighted ICER per QALY estimates were £31,468 and £48,537, respectively (*Table 22*). Therefore, although the QALY-weighting reduced the ICERs, they were still above the upper bound of NICE's recommended cost-effectiveness threshold (£30,000 per QALY).

Sensitivity analyses

One-way and probabilistic sensitivity analyses were conducted to address the structural and parametric uncertainties in the model estimates.

Transition to bridge to transplant and heart transplant

The impact of incorporating the probability of transition from DT to BTT states and from BTT to HT states was estimated in a sensitivity analysis. The analysis showed that the ICER was reduced slightly to £52,762 and £57,470, respectively (*Table 23*).

TABLE 22 Weighted incremental cost-effectiveness ratio per quality-adjusted life-year estimates

Base-case analyses	Mean QALYs for MM	Proportional QALY shortfall	Recommended QALY weight	ICER per QALY	Weighted ICER per QALY
Non-comparative, net weight estimates	0.46	0.96	1.7	£53,496	£31,468
Comparative estimates mapped to LVAD in MOMENTUM	0.85	0.92	1.2	£58,244	£48,537

TABLE 23 Model outcomes when the transition to bridge to transplant and heart transplant was incorporated

	Non-comparative, net weight estimates			Comparative estimates mapped to LVAD in MOMENTUM		
Lifetime outcomes	**MM**	**LVAD**	**Incremental**	**MM**	**LVAD**	**Incremental**
Expected LYs per patient	0.92	4.58	3.66	1.68	4.66	2.98
Expected QALYs per patient	0.46	3.26	2.80	0.84	3.30	2.45
Cost per patient	£18,886	£166,433	£147,547	£26,534	£167,540	£141,006
Incremental cost per LY			£40,351			£47,279
Incremental cost per QALY			**£52,762**			**£57,470**

One-way sensitivity analyses

Figures 20 and *21* show the results of the one-way sensitivity analyses, conducted by varying one parameter at a time to understand their impact on the ICER estimates. The input values were chosen from the studies identified in the systematic review reported in *Chapter 3* and from two previous UK studies.[110,116] The analysis showed that the outpatient costs for LVAD recipients had the greatest impact on the ICER estimates. This was followed by the outpatient costs for patients on MM and the mortality risk amongst LVAD patients.

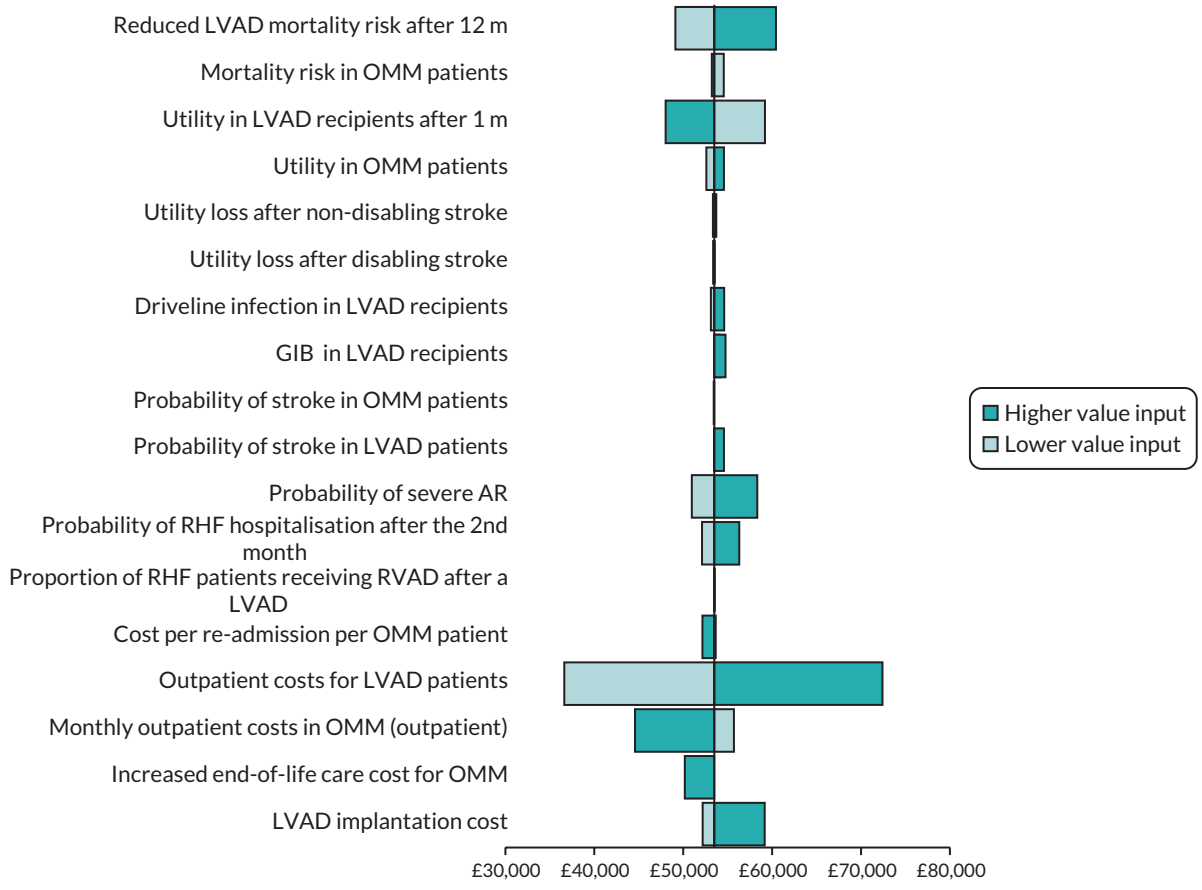


FIGURE 20 One-way sensitivity analysis for non-comparative, net weight estimates. OMM, optimal medical management.

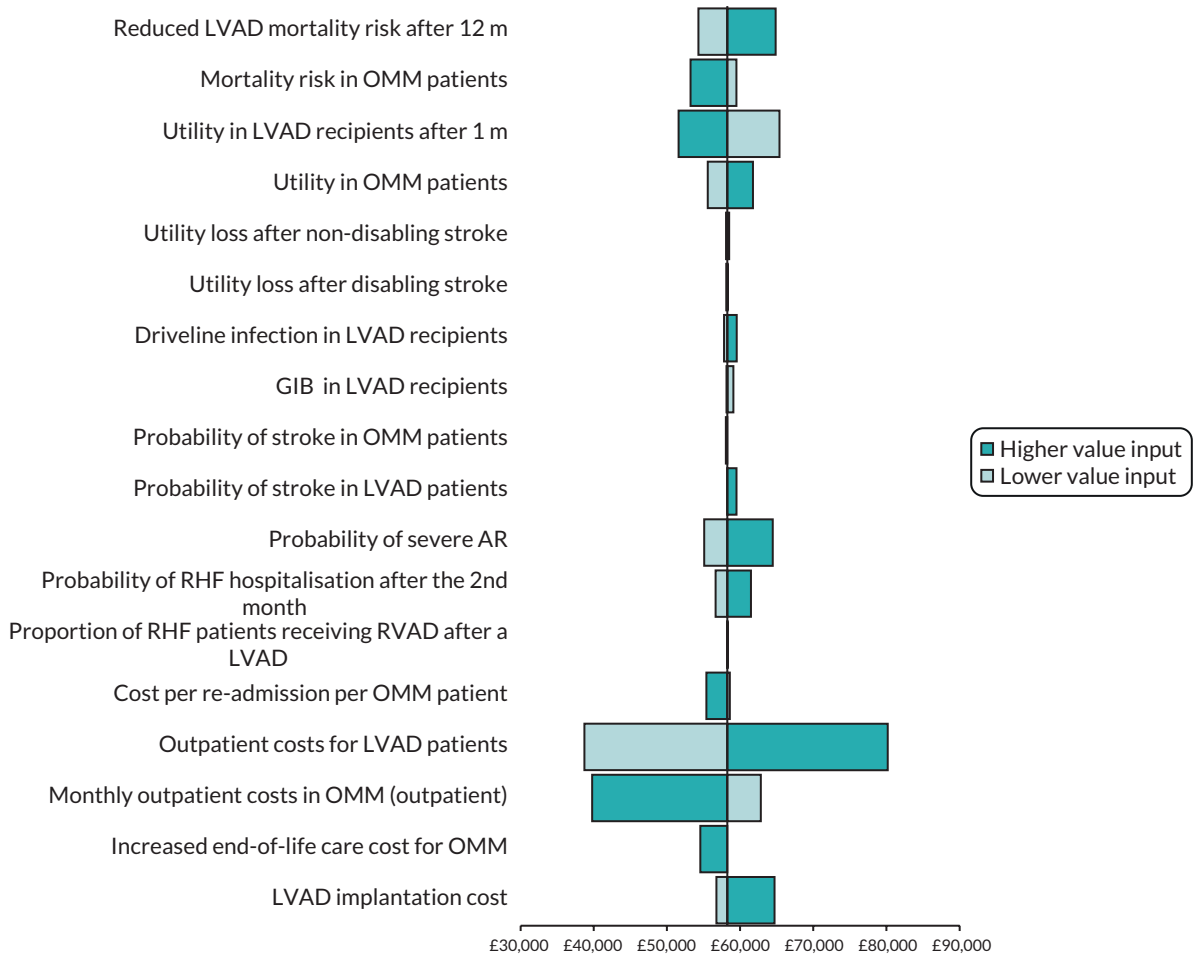


FIGURE 21 One-way sensitivity analysis for comparative estimates mapped to LVAD in MOMENTUM.

Since the deterministic sensitivity analysis showed that outpatient costs had a substantial impact on the ICER estimates, further analyses were conducted to explore how the results changed when different values reported in the literature were utilised for these specific parameters. The parameters used in these analyses and the impact on results are provided in *Tables 24* and *25*, and the details of these values are summarised in *Table 37* (see *Appendix 8*).

The findings showed that the ICER estimates ranged between £36,623 and £94,394, but remained above £50,000 except for four cases where the input values were significantly different from the others reported in the literature.

Additional analyses were also conducted to vary the mortality risk for the LVAD after 24 months to understand the impacts of incorporating the values used in the most recent economic evaluations conducted in the UK (*Table 26*). The estimated ICERs ranged between £43,380 and £58,844 using the non-comparative, net weight estimates, and between £45,807 and £59,846 in the comparative estimates mapped to LVAD in MOMENTUM.

When the mean of all the values identified for these three parameters (ongoing costs for the LVAD and MM and mortality risk in LVAD recipients after 24 months) were entered into the model simultaneously, the ICER values were £60,272 and £61,675 using the non-comparative, net weight estimates and the comparative estimates (mapped to LVAD in MOMENTUM).

TABLE 24 Impact of outpatient costs for LVAD on ICER per QALY

	ICER per QALY estimates		
Value (£)	Non-comparative, net weight estimates (£)	Comparative estimates mapped to LVAD in MOMENTUM (£)	Source
72	36,623	38,714	Lim *et al.* 2021[110]
958	53,946	58,244	Chew 2017[106]
986	54,029	58,861	Neyt 2013[102]
1943	72,253	79,956	Rogers 2021[114]
1952	74,424	80,155	Clegg 2007[108]
2139	75,986	84,277	Long 2014[111]
2172	76,614	85,004	Shreibati 2017[101]
2598	84,726	94,394	Silvestry 2019[115]
1603	65,769	72,462	Mean value

TABLE 25 Impact of outpatient costs for medical management on ICER per QALY

	ICER per QALY estimates		
Value (£)	Non-comparative, net weight estimates (£)	Comparative estimates mapped to LVAD in MOMENTUM (£)	Source
72	55,706	62,824	Lim *et al.* 2021
336	54,686	60,710	Adang 2006
644	53,496	58,244	Clegg 2007
958	52,282	55,730	Chew 2017
1187	51,397	53,897	Neyt 2013
1943	48,475	47,843	Shreibati 2017
2457	46,489	43,728	Rogers 2021
2951	44,579	39,773	Silvestry 2019
1886	48,695	48,300	Mean value

TABLE 26 Impact of varying LVAD mortality risk after 24 months on ICER values

	ICER estimates		
Value	Non-comparative, net weight estimates (£)	Comparative estimates mapped to LVAD in MOMENTUM (£)	Source
0.0020	43,380	45,807	Lim *et al.* 2021
0.0070	53,496	58,244	MOMENTUM
0.0110	58,884	65,376	Scheuler 2021
0.0067	52,721	59,846	Mean value

Probabilistic sensitivity analysis

The PSA showed some uncertainty around the model outputs based on 10,000 iterations. The mean estimates and the 95% CIs are provided in *Table 27* and the ICER estimates are shown in *Figures 22* and *23*. The uncertainty around incremental QALY gains was greater using the comparative estimates mapped to LVAD in MOMENTUM compared to the non-comparative, net weight estimates, although the uncertainty around cost differences was similar.

The analysis also found that the probability of cost-effectiveness at a WTP threshold of £30,000 was 0%.

The probability of cost-effectiveness of a LVAD as DT at different WTP thresholds were explored in a cost-effectiveness acceptability analysis (*Figures 24* and *25*). This analysis showed that the probability of cost-effectiveness was 21% and 11% at a WTP threshold of £50,000 per QALY using the non-comparative, net weight estimates and the comparative estimates mapped to MM in REMATCH, respectively. The probability of cost-effectiveness reached 100% at a WTP threshold of £75,000 and £91,000 per QALY using the non-comparative, net weight estimates and the comparative estimates mapped to LVAD in MOMENTUM, respectively.

Value of Information analysis

The EVPI at different WTP thresholds was explored (*Figures 26* and *27*), and at a WTP of £30,000 per QALY, EVPI was estimated as £0 both using the non-comparative, net weight estimates and the comparative estimates mapped to LVAD in MOMENTUM. EVPI per person was highest when the WTP per QALY was £55,000 using the non-comparative, net weight estimates and £60,000 in the comparative estimates mapped to LVAD in MOMENTUM, reaching £6957 and £8436, respectively.

In additional analyses, EVPPI and EVPPI per person were found to be £0 for all the parameters. Since the EVPI estimates were too low and indicated that conducting further trials was not advisable, analysis whose principal purpose is to estimate the optimal size for a future trial (i.e. EVSI and ENBS values) was deemed unnecessary.

Exploratory subgroup analysis by Interagency Registry for Mechanically Assisted Circulatory Support profiles

The subgroup analysis by INTERMACS profiles showed that patients in the LVAD arm who had less severe HF would gain more LYs and QALYs compared to patients with more severe conditions (*Table 28*). ICER per QALY estimates were estimated as £84,800, £65,458 and £58,815 for the INTERMACS groups 1, 2 & 3 and 4 & 5, respectively. Thus, the ICER remained above the £30,000 threshold in all cases.

Discussion

Summary of findings

This study involved an economic evaluation of LVADs as DT for AHF patients ineligible for a HT compared to MM from the NHS/PSS perspective. A decision-analytic model with a lifetime horizon and one-month cycles was developed based on the systematic reviews in *Chapters 3* and *4*.

The economic evaluation found that a LVAD would increase life expectancy by 3.73 and 3.06 years, produce an additional 2.86 and 2.56 QALYs per person and the incremental costs to the NHS would be £152,735 and £146,275 per person using the non-comparative, net weight estimates and the

TABLE 27 Probabilistic model outcomes

	MM			LVAD			Incremental		
Outcomes	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
Non-comparative, net weight estimates									
Expected LYs per patient	0.93	0.80	1.08	4.59	4.14	5.10	3.67	3.19	4.19
Expected QALYs per patient	0.48	0.41	0.55	3.26	2.94	3.61	2.7824	2.46	3.14
Cost per patient	£18,953	£17,107	£21,016	£171,281	£144,725	£200,692	£152,329	£125,665	£181,812
Incremental cost per QALY **£54,748**									
Probability of cost-effectiveness at £30,000 **0%**									
Comparative estimates mapped to LVAD in MOMENTUM									
Expected LYs per patient	1.67	0.70	2.77	4.71	4.23	5.27	3.04	2.04	3.98
Expected QALYs per patient	0.86	0.36	1.43	3.31	2.98	3.68	2.4512	1.91	2.97
Cost per patient	£26,473	£16,488	£37,929	£173,151	£146,703	£203,179	£146,677	£119,015	£177,751
Incremental cost per QALY **£59,840**									
Probability of cost-effectiveness at £30,000 **0%**									

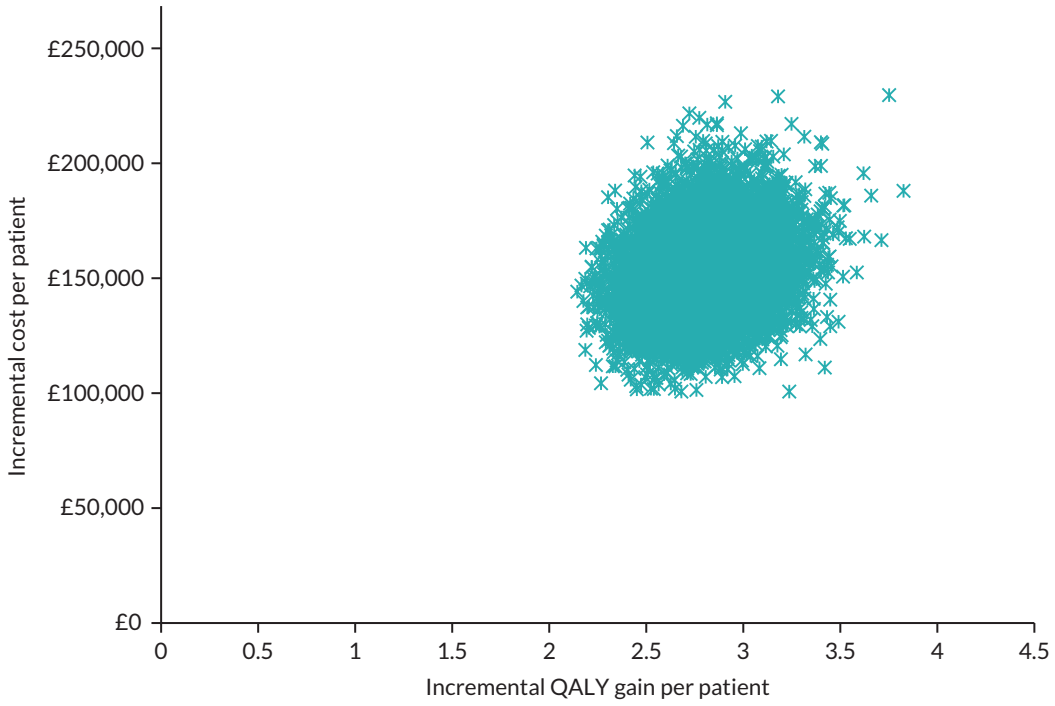


FIGURE 22 Probabilistic sensitivity analysis based on 10,000 iterations for non-comparative, net weight estimates.

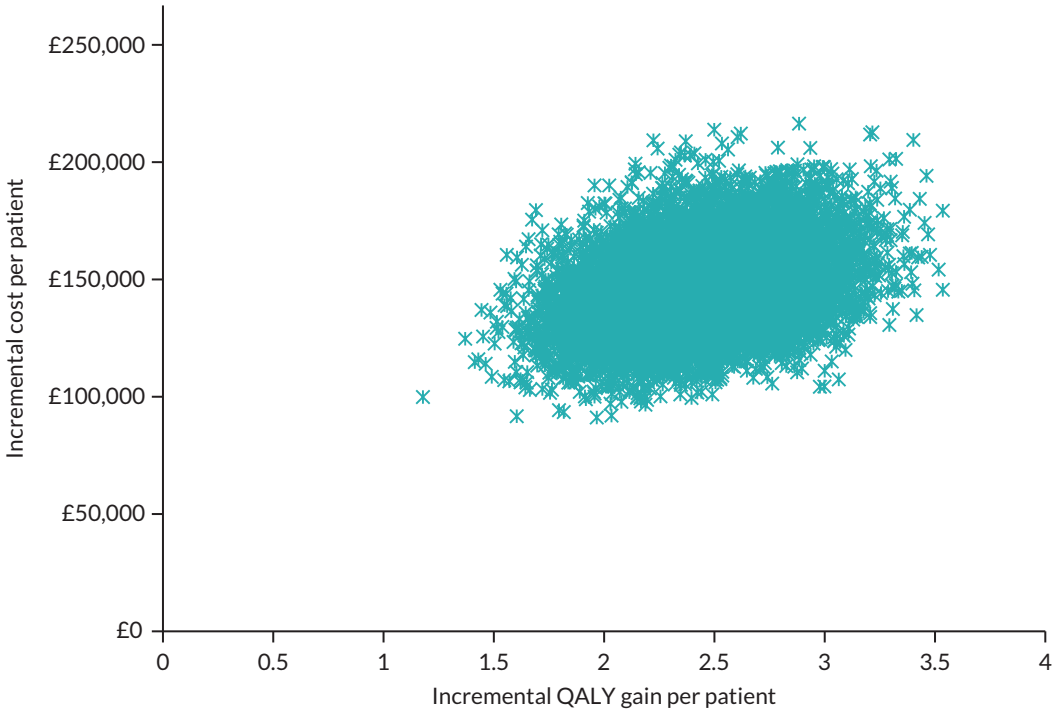


FIGURE 23 Probabilistic sensitivity analysis based on 10,000 iterations for comparative estimates mapped to LVAD in MOMENTUM.

comparative estimates mapped to LVAD in MOMENTUM, respectively. Thus, at a WTP threshold of £50,000 per QALY, LVADs were not cost-effective compared to MM for AHF patients ineligible for a HT. The deterministic sensitivity analysis showed that inclusion of the probability of becoming eligible for a HT did not change the findings, while the outpatient costs for LVAD recipients had a significant impact

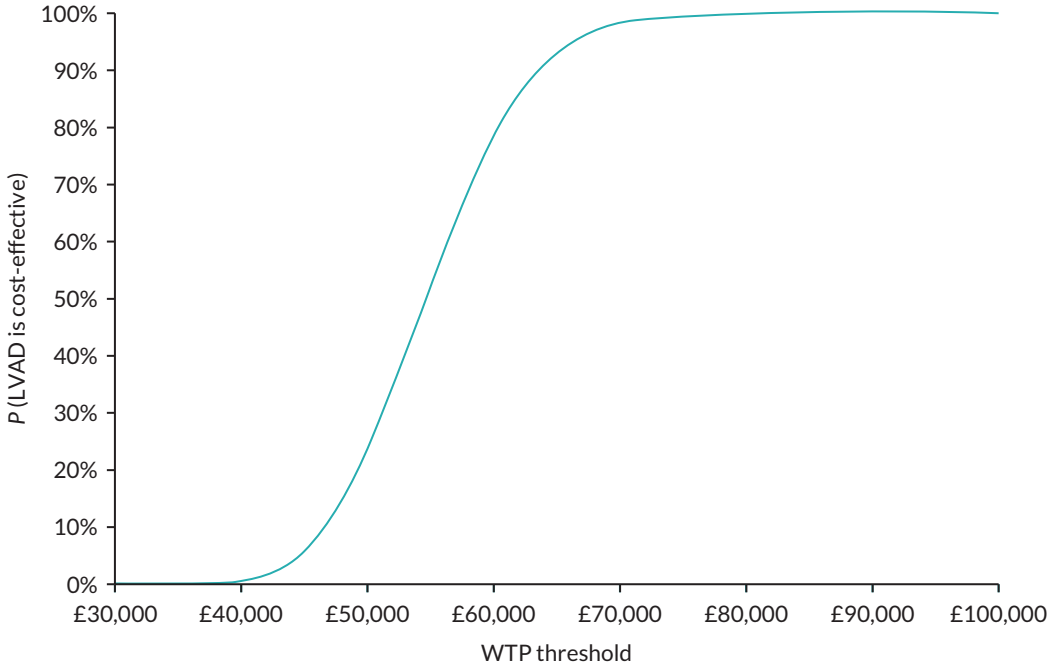


FIGURE 24 Cost-effectiveness acceptability curve for non-comparative, net weight estimates.

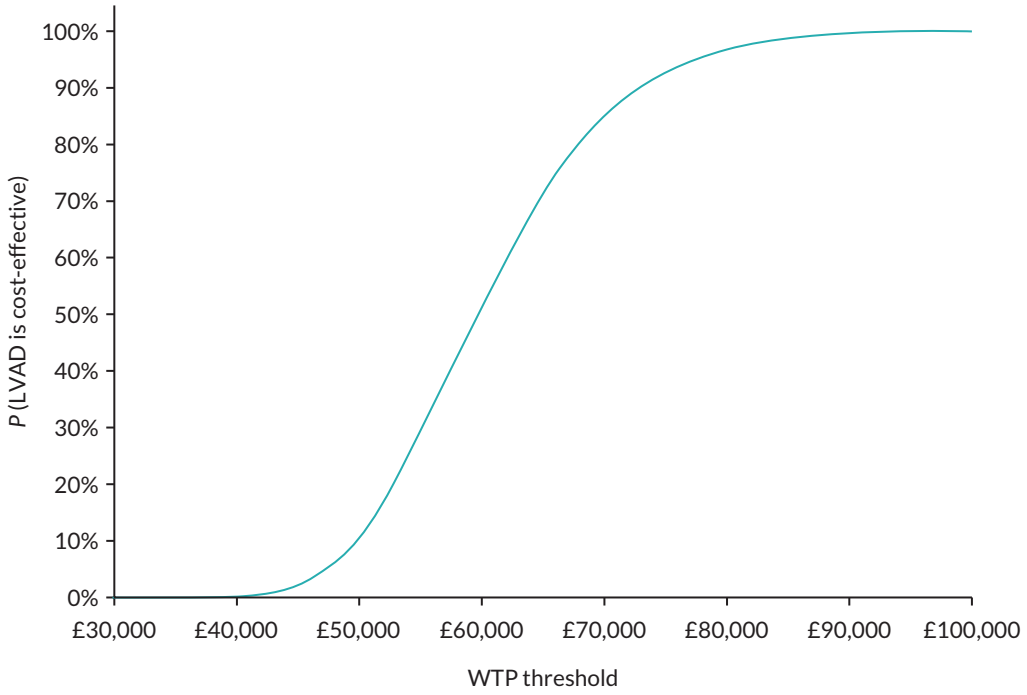


FIGURE 25 Cost-effectiveness acceptability curve for comparative estimates mapped to LVAD in MOMENTUM.

on ICER estimates. The PSA showed some uncertainty around the model outcomes, especially in terms of the incremental QALY gains. The probability of cost-effectiveness at a WTP threshold of £30,000 was 0% based on 10,000 iterations. According to the exploratory subgroup analysis, a LVAD was not cost-effective for any specific INTERMACS group evaluated (£84,800 for INTERMACS 1, £65,458 for INTERMACS 2 & 3 and £56,256 for INTERMACS 4 & 5).

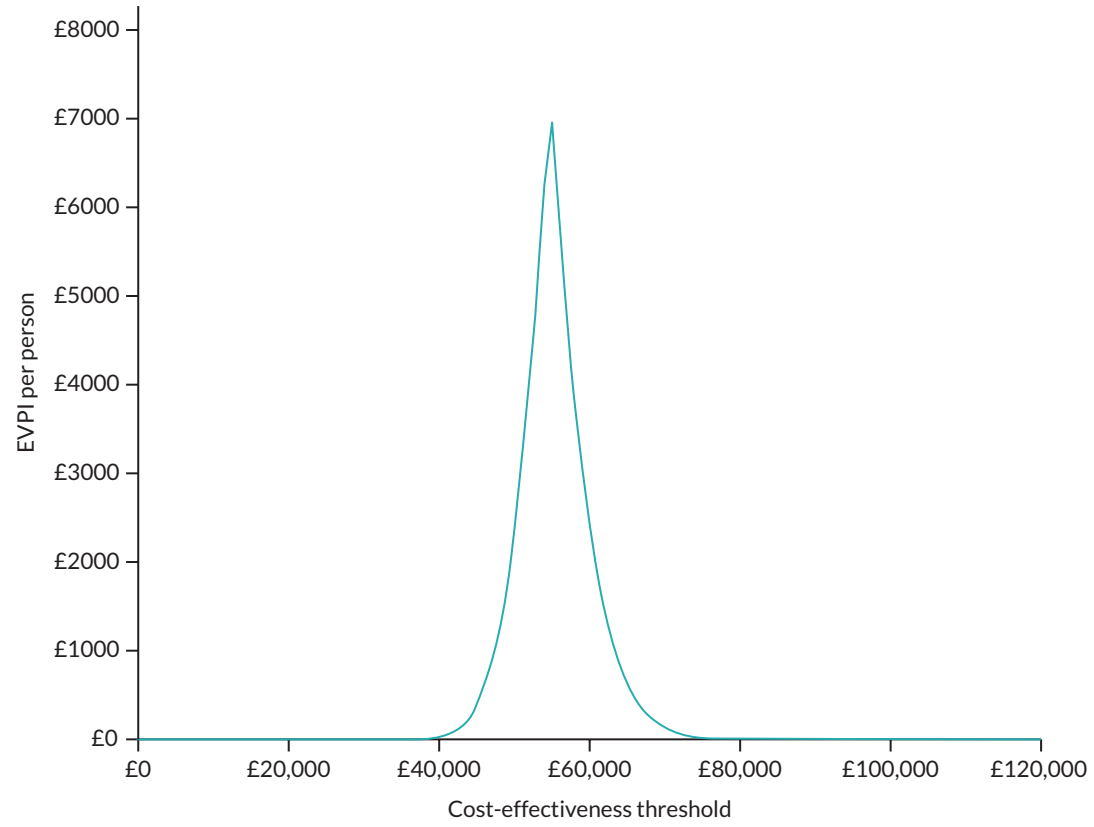


FIGURE 26 Expected value of perfect information for non-comparative, net weight estimates.

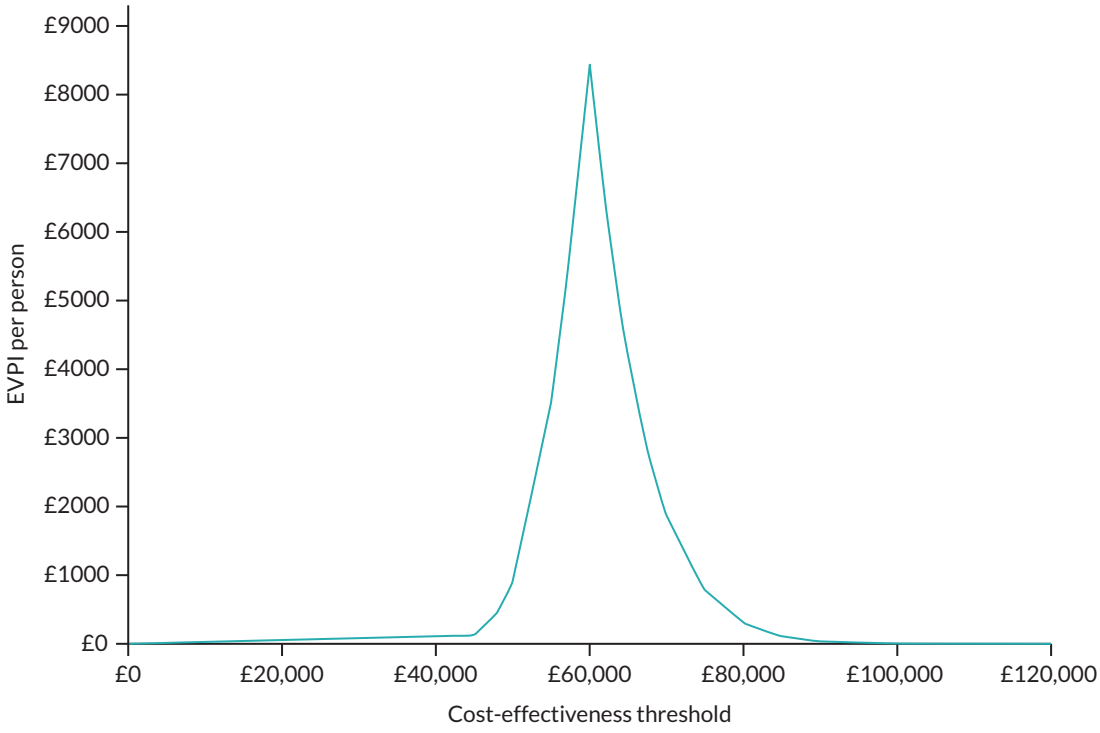


FIGURE 27 Expected value of perfect information for comparative estimates mapped to LVAD in MOMENTUM.

TABLE 28 Model outcomes by INTERMACS profiles

Lifetime outcomes (INTERMACS 1)	**MM**	**LVAD**	**Incremental**
Expected LYs per patient	0.37	3.05	2.68
Expected QALYs per patient	0.06	1.65	1.59
Cost per patient	£13,333	£148,214	£134,882
Incremental cost per LY			£50,336
Incremental cost per QALY			**£84,800**
Lifetime outcomes (INTERMACS 2 & 3)			
Expected LYs per patient	0.92	3.93	3.01
Expected QALYs per patient	0.36	2.54	2.17
Cost per patient	£18,886	£161,052	£142,166
Incremental cost per LY			£47,198
Incremental cost per QALY			**£65,458**
Lifetime outcomes (INTERMACS 4 & 5)			
Expected LYs per patient	1.00	4.14	3.14
Expected QALYs per patient	0.51	2.96	2.45
Cost per patient	£19,714	£163,958	£144,244
Incremental cost per LY			£45,967
Incremental cost per QALY			**£58,815**

Decision-making based on severity weighted bridge to transplant estimates

The updated NICE guidelines recommend using QALY weights defined based on the shortfall between the expected QALYs in the same age and sex group of general population and the expected QALYs in the study population in the absence of the novel intervention being evaluated. This study estimated the expected QALYs for MM patients as 0.46 using the non-comparative, net weight estimates and 0.85 using the comparative estimates mapped to LVAD in MOMENTUM, and the corresponding proportional QALY shortfalls were 0.96 and 0.92. The recommended QALY weights were 1.2 if the proportional QALY shortfall was between 0.85 and 0.95, and 1.7 if the shortfall was above 0.95. Thus, there was a substantial gap between the weights recommended for the two base-case analyses in this study, although the proportional QALY shortfalls were close.

Utilising different QALY weightings increased the difference between ICER estimates in the two base-case analyses from £4748 (£53,496 and £58,244) to £17,069 (£31,468 and £48,537). Applying the higher weight (1.7) to ICER estimates for the comparative estimates mapped to LVAD in MOMENTUM would reduce the ICER from £58,244 to £34,261, and the weighted ICER was £31,468 for the non-comparative, net weight estimates. On the other hand, applying the lower weight (1.2) to the non-comparative, net weight estimates would reduce the ICER from £53,496 to £44,580, and the weighted ICER was £48,537 for analysis using the comparative estimates mapped to LVAD in MOMENTUM. From a decision-maker's perspective, the subgroup analysis based on clinical characteristics suggested that severity did not make a difference to the overall results, given that the ICER remained above £30,000 in all estimates.

Strengths and limitations of modelling

The economic model was developed based on the best available evidence identified by the systematic reviews of the clinical and economic evidence. The model development was also informed by discussions with clinicians, commissioners and patient representatives.

In the absence of a direct comparison between the contemporary LVADs and MM, specific attention was paid to the parameters selected for mortality risks, and four different sets of mortality risks were defined. The impacts of these four options on modelling outcomes were explored and discussed with the clinicians in the research project team. Since each of these options were based on different assumptions, it was deemed appropriate to present two base-case estimates, namely using the non-comparative, net weight estimates and the comparative estimates mapped to LVAD in MOMENTUM.

The non-comparative, net weight estimates used life expectancy data on MM dated from 2001, thus the estimates assumed that the clinical effectiveness of standard care had not changed over the last 20 years Therefore, these estimates might be overestimating the benefits of LVADs, if the life expectancy of MM patients has improved over the last 20 years. Additionally, it was assumed that the profiles of patients in the MOMENTUM trial matched perfectly to the profiles of MM patients in the REMATCH trial. This was a reasonable assumption given that the MM patients in the REMATCH trial were on inotropes and the majority of LVAD recipients in the MOMENTUM trial were classified as INTERMACS 2 & 3. However, if this assumption is incorrect and MM patients in the REMATCH trial had worse health statuses compared to the baseline health statuses of the patients in the MOMENTUM trial, the model outcomes might be overestimating the benefits of LVADs.

In the comparative estimates mapped to LVAD in MOMENTUM, considering that trials might have chosen healthier patients to implant LVADs, estimating the mortality risks in the MM arm based on the mortality risks reported in the MOMENTUM trial and the RR estimated in *Chapter 3*. The clinical effectiveness of LVADs compared to MM as DT in AHF patients was reasonable. However, this assumed that the profiles of patients in the MOMENTUM trial matched perfectly to the MM patients in the REMATCH trial and the other trials used for the statistical analysis reported in *Chapter 3*. The model outcomes provided a higher life expectancy and QoL for the MM arm and a higher ICER estimate compared to the non-comparative, net weight estimates and the previous UK studies.[110,116] Therefore, the comparative estimates mapped to LVAD in MOMENTUM might be underestimating the benefits of LVADs.

Another consideration was the lack of mortality data beyond 2 years. This required making an assumption to extrapolate the mortality data. The model used the mortality risk reported for the months between 13 and 24 in the trial for the time points beyond 2 years. The sensitivity analyses showed that this was a conservative assumption and had a modest impact on the cost-effectiveness outcome. Therefore, the model might be underestimating the cost-effectiveness of LVADs if the impact on mortality beyond 2 years is greater than the values used in the model. On the other hand, the model might be overestimating the cost-effectiveness of LVADs if the impact on mortality beyond 2 years is lower than the values used.

Additionally, data on the ongoing cost for patients on MM were limited. There was only one UK-based estimate, but the details of this estimate were not clear and the reported value was deemed too high. Thus, estimates from other studies in countries with similar healthcare systems were utilised in the base case. Specific attention was paid to these parameters, and the impact of using different value inputs on the model outcomes was explored in the deterministic sensitivity analyses. When the mean of all the values identified in the literature were utilised, the ICER estimates were similar to the base-case estimates.

Since currently only one type of LVAD is available, the key model parameters were defined from the studies that included only this type of LVAD. However, device-specific data were not available

for some major events and complications and data that included previous versions of the LVAD were used for these parameter estimates. This means that the model might be underestimating or overestimating the benefits of the LVAD, depending on the parameters chosen. However, the deterministic sensitivity analysis showed that none of these parameters had a substantial impact on the model results.

Another consideration, there was no trial that compared a LVAD to MM for defined INTERMACS profiles. Hence, the subgroup analyses were based on discrete data from different sources, and for some parameters assumptions were made based on expert views. It is difficult to speculate on the impacts of these assumptions on study findings in the absence of data, and therefore, the subgroup analyses should be considered exploratory.

Findings in context

The systematic review in *Chapter 4* identified two recent UK-based economic evaluations.[110,116] One of these studies focused on a type of LVAD that was withdrawn from use in the course of this project.[116] The other study estimated an ICER of £47,361 per QALY gained.[110] The key difference between the two studies related to the mortality risks assumed for LVAD recipients beyond 24 months. Lim *et al.* extrapolated the values, averaging the changes in the last 6 months while in this study the risk for the 24th month was used for the remaining cycles.[110] When the extrapolated values used in that study were entered into the current model, the ICER per QALY estimates reduced from £54,295 to £49,120, as shown in the deterministic sensitivity analysis. In terms of the incremental costs, for the study by Lim *et al.* the cost difference between the LVAD and MM arm was only £113,552, which was mainly related to the cost of the device (£109,140).[110] The corresponding figure in the current analysis were £152,735 and £146,275. Thus, the study by Lim *et al.* assumed very little difference between patients on MM and LVAD in terms of adverse events and complications.[110]

The systematic review in *Chapter 4* as DT identified only one study that considered the impact of INTERMACS profiles on the cost-effectiveness estimates.[110] That study estimated a lower ICER for patients with INTERMACS 2 & 3 profiles and a higher ICER for the INTERMACS 4–7 group. This contradicts the findings of the current evaluation, which suggests that LVADs are less cost-effective in more severe patients compared to patients who are less unwell. It is not possible to explain the reasons behind this difference since the model inputs for the INTERMACS profiles-based analyses were not provided in the previous study.

Parameters with the greatest impact on incremental cost-effectiveness ratio per quality-adjusted life-year estimates

The deterministic sensitivity analyses indicated that two parameters had substantial impacts on the model results: outpatient costs for LVAD and MM patients. Thus, additional analyses were conducted to estimate the impact of using different value inputs for the parameters with the greatest impact. The value inputs for these analyses were taken from the studies identified in the systematic review reported in *Chapter 3* and their applicability to the UK setting was unclear. Thus, these analyses were only exploratory and are not intended to guide decision-making.

The outpatient costs for LVADs had a substantial impact on the ICER estimates due to the wide range of values reported in the literature, ranging from £72 to £2598. The differences between the cost estimates from the published studies can be partly explained by the differences in healthcare provision across countries, given that the highest figure was reported in a study from the USA while the lowest figure was from a UK-based study.[110,115] Another potential reason might be the costs of different procedures delivered during an outpatient appointment. Depending on the values chosen, ICER estimates in the non-comparative, net weight estimates varied between £36,623 and £84,726, while they were between £38,714 and £94,394 in the comparative estimates mapped to LVAD in MOMENTUM. Different values were also reported for the outpatient costs in MM patients, varying between £72 and £2951. The highest cost estimate (£2951/month) resulted with ICER estimates of

£44,579 in the non-comparative, net weight estimates and £39,773 using the comparative estimates mapped to LVAD in MOMENTUM.

Implications for stakeholders/future research

The economic evaluations reported in this chapter show that from the NHS/PSS perspective, LVADs as DT for AHF patients are not cost-effective compared to MM at a WTP threshold of £30,000 per QALY. This finding is unaltered by applying severity weightings to the QALY estimates as recommended by the updated NICE guidelines.

The sensitivity analyses indicate that varying the outpatient costs for patients on LVADs and MM had a significant impact on the results. Thus, future research focusing on defining these cost items might be helpful for decision-makers in the UK, although the VoI analysis suggested that the current evidence is sufficient for decision-making. The exploratory subgroup analyses conducted based on the best available evidence and expert views were consistent with the base-case analysis. However, the existing evidence was insufficient to reach a full conclusion on the cost-effectiveness of LVADs for patients with different INTERMACS profiles. Further research is needed to estimate the impacts of INTERMACS profiles on the cost-effectiveness estimates. Thus, these findings should be interpreted with caution.

Another consideration is the impact of applying severity weights as recommended by NICE on the study results. Although the severity weighted estimates did not change the cost-effectiveness findings of this evaluation, the increased differences between the outcomes of the two base-case analyses warrant attention. Health conditions that result in 0.95 QALY shortfalls would require a QALY weighting of 1.2, but the weight would jump to 1.7 for a QALY shortfall of 0.96. NICE defined the weight groups based on how the end-of-life criteria were applied in previous appraisals, and there is no evidence on whether this truly reflects societal preferences. In addition, the QALY shortfall cut-offs are higher than those used in other countries, such as the Netherlands (0.70).[146] Further research is needed to understand the appropriateness and potential implications of the severity-weightings on cost-effectiveness decisions for different health technologies and interventions.

Chapter summary

This chapter presented the findings of an economic evaluation of LVADs compared to MM as DT amongst patients with AHF ineligible for a HT from the NHS/PSS perspective. The analysis in this chapter indicates that LVADs are not cost-effective compared to MM based on current WTP thresholds recommended in UK national guidelines. The economic evaluation was developed based on the best available evidence and expert views. However, it is important to take into account the limitations arising from the available data and the modelling assumptions that needed to be adopted. In particular, the value of estimates for outpatient costs for LVAD and MM patients had a substantial impact on the cost-effectiveness estimates, and thus further research is needed to obtain more accurate information.

Chapter 6 Discussion

Research question and aims

We aimed to answer the following research question:

1. What is the clinical effectiveness and cost-effectiveness of LVADs for DT in patients with AHF when compared to MM?

Objectives

The clinical effectiveness and cost-effectiveness evidence were summarised in two systematic reviews, using the same search strategy. All study designs were included, and the analysis and reporting were focused on the HM3 device. Outcomes in the clinical effectiveness review were categorised as survival, major events, complications, hospitalisations, QoL or functional status. Appropriate, validated risk-of-bias tools were applied to assess the quality of the included evidence in both reviews. A NMA was undertaken to allow an indirect comparison of the HM3 and MM to be made for the survival outcome.

Evidence from the systematic reviews and NMA, as well as guidance from clinical experts, patients and commissioners were used to inform the development of a Markov model to compare costs and effectiveness of LVADs used for DT when compared to MM. Two base cases were presented based on differing assumptions of mortality risks for both arms. Both deterministic and probabilistic sensitivity analyses were carried out, as well as subgroup analyses to explore the potential impact of different INTERMACS profiles.

Summary of findings

Systematic review of clinical effectiveness

The systematic review summarised a large volume of evidence analysing the use of LVADs for DT in patients with end-stage HF with over 130 studies included. The withdrawal of the HeartWare HVAD during the review process meant that priority of reporting was given to data from HM3, the only available device in the UK.[32] One RCT (MOMENTUM 3) assessed the HM3 in comparison to the HeartMate II and reported survival of 76.7% at 24 months compared to 59% in the HeartMate II, the highest survival noted for a device at this follow-up point.[147] The HM3 device also demonstrated fewer bleeding and stroke events than earlier devices; issues that contributed to the withdrawal of the HeartWare HVAD. Furthermore, pump thrombosis could still be considered an issue in the HM3.

Data from the 5-year extended observational follow-up of MOMENTUM 3 were recently presented at the ESC congress.[148] While this was outside of our latest search update and therefore not included in the analysis, overall survival was reported at 54.8% in DT HM3 patients at 5 years, compared to 39.4% in those with the HeartMate II. This was higher than any survival figures reported in INTERMACS analyses of multiple device types, though these analyses did not include the HM3.[31,46,72] This reiterates the survival benefit of the HM3 over other devices and may be useful in future economic models.

While the HM3 has demonstrated clinical effectiveness, there is no direct evidence comparing the device to the standard treatment of MM. To determine this, a NMA was undertaken to establish an indirect comparison using data from previously conducted RCTs. The analysis demonstrated a significant benefit for HM3 compared to MM for risk of mortality, but there were concerns regarding transitivity, and CIs around this indirect estimate were wide.

Systematic review of cost-effectiveness

There was limited evidence pertaining to the cost-effectiveness of LVADs for DT. Most of the 19 studies included were conducted in the USA and were from the perspective of the service provider. The incremental cost per QALY estimates ranged from £46,207 to £238,401 in 2019 prices. Of the studies, 14 were full economic evaluations, which looked at the health and cost impacts of LVADs with 8 of these studies reporting that LVADs were not cost-effective when compared to MM for DT patients. However, two of the UK-based evaluations did report positive findings with the ICER per QALYs reported to be just below the £50,000 threshold, defined as the end-of-life criteria in the UK. Some studies did not include adverse events and there was often limited consideration of time horizon.

Economic evaluation

Based on the two base cases employed in the model, neither found LVADs to be cost-effective at a WTP threshold of £50,000 per QALY when compared to MM in DT patients. The non-comparative, net-weight estimates approach yielded an additional 2.86 QALYs per person with an ICER of £53,496. On the other hand, the comparative estimates mapped to LVAD in MOMENTUM approach produced an additional 2.51 QALYs per person with an ICER of £58,244.

Furthermore, subgroup analysis by INTERMACS profile did not demonstrate cost-effectiveness of LVADs for DT in any specific INTERMACS groupings. LVADs were closest to cost-effectiveness at the £50,000 threshold in patients with INTERMACS profiles 4 & 5 (ICER of £58,815), using the non-comparative, net-weight estimates approach.

Strengths and weaknesses of the reviews and economic evaluation

Systematic review of clinical effectiveness

The systematic review included a large volume of evidence sourced using a comprehensive search strategy in key databases. Articles were also sought via citation checking and targeted searching of mechanical circulatory support registry reports (e.g. INTERMACS, IMACS). Input was sought from clinical experts as well as patients when considering aspects of the review such as the search strategy, outcome definitions and when planning the synthesis. Robust methods were used throughout to ensure the potential for bias was limited.

However, some limitations were evident. Due to the high volume of evidence found, studies with a sample size of < 50 DT patients were excluded in the clinical effectiveness review. While this may have resulted in the loss of some evidence, calculations (previously described) determined that this would result in < 5% loss of patients across the evidence base.

A pragmatic approach to searching was also applied to manage the huge database of hits that were produced with a less specific search strategy. Various terms for ‘DT’ as well as ‘bridge to transplant’ were used to reduce hits from over 20,000 to around 12,000 across all databases. This could potentially have resulted in the loss of some relevant evidence. Finally, approximately four single-centre observational studies could potentially have had comparative data on different devices available that were not reported. However, the authors of these papers were not contacted due to project time constraints and the likelihood of obtaining any valuable evidence.

Weaknesses were also noted within the included evidence. For example, there was very limited device-specific data reported outside of the trials, which made it difficult to make meaningful comparisons and analyses. Furthermore, subgroup data (by INTERMACS or age) were also sparse, which meant it was difficult to determine if devices were more or less effective in patients in different subgroups. No direct comparisons were made in the evidence between the HM3 and MM, which resulted in the need to carry out a NMA. However, there were concerns regarding the transitivity assumption and CIs around this indirect estimate were wide.

Systematic review of cost-effectiveness

Many of the strengths and limitations of the clinical effectiveness review are also applicable to the cost-effectiveness review, due to the use of the same search strategy, duplicate screening, selection and implementation of appropriate and valid risk-of-bias checklists and piloted data extraction. Further studies were found via systematic review citation checking and contact with clinical experts.

All modelling studies were quality assessed in duplicate. Furthermore, limitations with the evidence itself were also present. The overall quality of the included studies was not high and various issues were evident. For example, only two studies justified the sources of parameters, and many studies did not explain how complications were incorporated. Finally, all but two of the economic evaluations included were not UK-based.

Economic evaluation

Strengths of the economic model produced were clear. The model itself was comprehensive and developed based on the best available evidence produced from the systematic reviews. It considered clinical perspectives as well as device and class of INTERMACS. Clear sources for the parameters were presented and these were based on the best available evidence as well as input from clinicians, commissioners and patients. Decisions of which base cases to use were made following in-depth discussions and processes, and these were presented alongside clear justifications together with descriptions of all of the options considered.

Limitations were, however, unavoidable and mostly pertained to the costs of MM. These costs were not clear from the UK perspective and while attempts were made to acquire data, which more accurately reflected the MM costs, these were unsuccessful. Therefore, data from various sources were used, which could now be considered potentially inaccurate. Questions were also raised over other health-related costs that are not related to a LVAD and whether these should be included in the model.

While the base cases were discussed and considered at length, various assumptions had to be made for each. The non-comparative, net weight estimates approach assumed that the INTERMACS profiles across the MOMENTUM trial and the REMATCH trial were the same. This approach also used life expectancy data for MM from 2001, meaning the estimates assume that the clinical effectiveness of standard care has not changed over the last 20 years.

Finally, no direct relative effect measures were available between the HM3 and MM as there are currently no completed trials comparing these interventions. Data from patients with particular INTERMACS profiles were also limited, meaning that subgroup analysis carried uncertainties.

Findings in context

Previous systematic reviews of clinical and cost-effectiveness

Several systematic reviews and HTAs have been carried out which assessed both the clinical and cost-effectiveness of LVADs for DT. Reports from Canada, Belgium and Sweden all found LVADs to be beneficial for survival compared to MM, though there were some concerns over thromboembolic and device complications.[90,91,149] However, these reports were published before any HM3 data were available and therefore are not reflective of the current device market in the UK. The Canadian report also reiterated the high costs of devices and implant surgery, though once again these were not reflective of the current HM3 device.

A previous NMA assessed LVADs for end-stage HF, but this did not focus solely on DT patients but included patients with all LVAD indications.[92] The NMA included the HM3, HVAD, HeartMate II, HeartMate XVE and MM and focused on four RCTs and four observational studies. Results showed a RR for death of 0.62 in the HM3 when compared to HeartMate XVE; however, this only appeared to

be for 12 months of follow-up. The paper also demonstrated further limitations as described earlier in *Chapter 3*.

Comparisons between the HeartMate 3 and medical management

Issues were highlighted in both systematic reviews due to the lack of available direct comparative evidence between the HM3 and MM. This meant using indirect data produced from the NMA (which relied upon various assumptions and resulted in uncertainty) for the economic model. While no results were published at the time of write-up of this report, an ongoing RCT is currently comparing the HM3 with MM in Sweden. The SweVAD trial aims to enrol 80 participants of DT indication who will be randomised to the HM3 or MM across seven Swedish University Hospitals.[48] The study will follow-up patients for a minimum of 2 years and is estimated to be completed in December 2023. Results of this trial will be important for updating any economic models with more robust comparative data between the HM3 device and MM.

Previous economic models

The systematic review of cost-effectiveness identified two previous UK economic models, both of which found LVADs to be cost-effective in comparison to MM in patients with AHF ineligible for transplant, in contrast with both base-case analyses presented here.[110,116] Both models reported ICER per QALY estimates at just below the NICE £50,000 threshold. However, one of these models was based on the now withdrawn HeartWare HVAD and is no longer relevant. Additionally, applying the severity weighting suggested by NICE (2022) did not change the cost-effectiveness outcomes.

The Lim *et al*. HM3 model found a ICER of £47,361 per QALY gained (compared to £54,748 and £59,840 in each of our base cases).[110] Differences were evident between the model presented here and the Lim model. Lim *et al.* extrapolated the mortality risk values, averaging the changes in the last 6 months while in this model, the risk for the 24th month was used for the remaining cycles. Differences in assumed rates of adverse events and complications were evident, with Lim *et al.* assuming very few differences between patients on MM and the HM3 compared to this model. The Lim model also used only two health states and did not consider the impact of adverse events on life expectancy.

Overall, while the model in this report did not find the HM3 to be cost-effective compared to MM when considering the current NICE thresholds, it does remain close to this cut-off and is not drastically different to the previously reported models.

Implications for practice and future research

Implications for practice

The systematic review of clinical effectiveness and NMA demonstrate a survival benefit for the HM3 compared to MM in end-stage HF patients ineligible for transplant. However, the economic model did not find the HM3 to be cost-effective when compared to MM at the £50,000 threshold. This would suggest that currently, though the clinical evidence supports the use of LVADs for DT, there may not be enough evidence to support the use in the UK setting in regard to cost-effectiveness. This remained the case when analyses were limited to particular INTERMACS groupings, suggesting that there is not enough evidence to support use in particular groups of patients either. However, data on survival and other outcomes in DT patients by INTERMACS profile were limited and therefore more data are required to produce more robust results. Future research may be key in refining the estimates of cost-effectiveness of the HM3 compared to MM in DT patients, allowing for clear recommendations to be made.

Recommendations for future research

The systematic reviews and economic evaluation have highlighted gaps and issues with the current available evidence. These issues may help to direct key areas for future research.

Ongoing trials

The lack of direct comparative data between the HM3 and MM remains an issue and future research needs to address this. The ongoing SweVAD trial, as mentioned earlier, will provide this comparison. This data will be useful in future economic models. Further ongoing trials may also be important in addressing outstanding questions and uncertainty. The AMBU-VAD is another ongoing RCT comparing the HM3 to MM in ambulatory HF patients (INTERMACS ≥ 4), with a proposed enrolment of 92 patients taking place in France.[51] The study is expected to be completed in February 2025 and may help to inform whether the HM3 could be particularly useful in the ambulatory population, which have only been explored minimally in previous studies.

Another ongoing trial is currently assessing a new LVAD, the EVAHEART 2, compared to the HM3 device.[47] This is a RCT with an estimated enrolment of 400 patients aiming to determine non-inferiority of the EVAHEART 2 compared to the HM3. This trial is ongoing under a FDA investigational device exemption, to allow the study of the safety and effectiveness of the new device with the aim of introducing it to the market. This may offer an alternative to the HM3 in the future, depending on the results of the trial, which is expected to be completed in March 2024. Any future economic evaluations may need to consider this new device when determining the cost-effectiveness of LVADs.

Cost of medical management

One important issue is the uncertain costs for patients with AHF on MM. There are few to no data available on the current costs of MM in the UK, and all recent models have relied upon cost data, which are either very old or from other countries that could be considered to have similar healthcare systems. Alternative value inputs were considered in the deterministic sensitivity analysis and when the mean of all the values identified in the literature were used, ICER per QALY estimates were similar to the base-case estimates. However, the true cost of MM in the UK remains unclear and therefore a major audit is recommended to establish these costs and to include them in future economic models.

Observational studies and registry reports

Observational studies (essentially case series) included in the clinical effectiveness review rarely reported data by device. It is recommended that future publications from single centres should adhere to a more consistent reporting structure, clearly reporting by indication of device and by the device implanted, allowing for more consistent analyses in future reviews.

INTERMACS and IMACS registry reports remain the largest sources of LVAD patient data in the real world and they generally do not distinguish by device to avoid bias in favour of any particular manufacturer. However, they do often report the wider device type (e.g. continuous flow). Many INTERMACS reports were not included as they did not report by indication; therefore future registry analyses should focus on reporting this where available. However, it is important to note that due to the recent changes in the heart allocation system in the USA, almost all new implantations listed in INTERMACS are now for DT indication. This means that in the future, INTERMACS reports may be more reflective of the DT population than in earlier years, which were dominated by BTT indications.

Research into subgroups

Another key area that future research should focus on is the analysis of subgroups of LVAD patients. If LVADs are found to be more cost-effective in particular subgroups, such as certain INTERMACS profiles, select groups may then be recommended to receive LVADs. Therefore, future studies should focus on measuring and reporting results by INTERMACS profiles, as well as considering any other important subgroups.

While subgroups could be important, there is also the possibility of removing the indication labels of DT, BTT and BTC altogether and focusing on making implant decisions for individual patients based on suitability. This is currently in practice in other countries, such as Poland, and could be a consideration in the UK where only approximately 120 LVADs are implanted each year.

Patient and public involvement

Patient and public involvement were included throughout the project. The PPI group included both patient representatives as well as family members and carers to ensure a range of perspectives and experiences. The PPI group met several times throughout the study with members of the research team, including both clinicians and methodologists. The first meeting was held at the beginning of the research to convey the aims of the work and to allow PPI members to share their experiences to enable the non-clinical research team members to develop an understanding of living with HF and a LVAD. This meeting also offered the opportunity for PPI to comment on the proposed research and identify outcomes of importance regarding the systematic review of clinical effectiveness and aspects to be included in the economic evaluation. Two members were also invited to attend the wider steering group meetings for the project, to offer PPI insight and perspective.

Results of the research were conveyed to the PPI group during a meeting following submission of the report. Representatives also had the opportunity to comment on plain English summaries.

Conclusions

Findings from the clinical effectiveness review demonstrate that LVADs have significantly improved over time and the currently available HM3 LVAD is considered clinically effective in patients with end-stage HF ineligible for transplant, with the available evidence suggesting it may offer survival of over 75% at 2 years of follow-up with reduced complications and major events in comparison to older devices. However, there are no studies comparing the currently available device in the UK to MM.

Findings from the review of economic evaluations show that the estimates of the cost-effectiveness of a LVAD as DT vary widely depending on factors such as device, perspective, analysis approach and when and where studies were conducted. However, cost-effectiveness has improved over time, which may be explained by the increased life expectancy associated with newer generation devices and a reduction in adverse events and device costs. However, the estimated incremental cost per QALY gained compared to MM tended to remain higher than the accepted thresholds of cost-effectiveness applied in the UK.

Findings from the economic evaluation of LVADs compared to MM as DT amongst patients with AHF ineligible for a HT from the NHS perspective indicates that LVADs may not be cost-effective compared to MM with estimates of cost-effectiveness being just higher than current WTP thresholds recommended in the UK. Better data on outpatient costs for LVAD and MM patients are required, as these have an impact on the cost-effectiveness estimates,

While currently there is no evidence from studies directly comparing the HM3 device to MM, there is an ongoing RCT being undertaken in Sweden (SweVAD trial) comparing the two. The trial is due to complete final follow-up in December 2023. Hopefully, it should allow for relative effects of current device and current MM to be determined, which will enable more robust data to be used to update the current economic evaluation and the clinical effectiveness review, rather than relying upon indirect comparisons with wide uncertainty.

In addition, an audit of MM costs in DT patients in the UK is needed to reduce uncertainties in the economic evaluation. Finally, future trials and other studies should report results by patient severity profiles (e.g. INTERMACS classification), and if registry/observational studies, then also by device implanted, as these will aid in developing reliable subgroup analyses based on severity profiles to aid identification of whether a LVAD is (more) cost-effective for some groups of DT patients.

Additional information

Contributions of authors

Sophie Beese (https://orcid.org/0000-0001-6329-0779) (Research fellow, systematic reviews) led on the systematic review of clinical effectiveness (including search strategy development), jointly led on the systematic review of cost-effectiveness and worked on all aspects of each review; wrote the first draft of clinical effectiveness chapter and discussion chapter; wrote the scientific summary and was involved in the organisation of the project.

Tuba S Avşar (https://orcid.org/0000-0002-4143-3852) (Research fellow, health economics) led on the economic evaluation and model development, jointly led on the systematic review of cost-effectiveness; worked on both clinical and cost-effectiveness systematic reviews; wrote the first draft of the cost-effectiveness systematic review and economic evaluation chapters.

Malcolm Price (https://orcid.org/0000-0002-7352-3027) (Associate professor, biostatistics) led on the network meta-analysis as part of the systematic review of clinical effectiveness, and gave statistical input and advice for all research chapters with particular focus on the clinical review and economic evaluation.

David Quinn (https://orcid.org/0000-0003-2465-305X) (Cardiothoracic surgeon) made significant clinical input on all aspects of the project, worked on screening and selection for both systematic reviews; led on all aspects of patient and public involvement.

Hoong S Lim (https://orcid.org/0000-0002-6569-1805) (Consultant cardiologist) made significant clinical input on all aspects of the project, worked on screening of articles for both systematic reviews.

Janine Dretzke (https://orcid.org/0000-0002-2591-6918) (Senior research fellow, systematic reviews) contributed to the development of the search strategy, was involved in screening of articles for both systematic reviews, development of approach to inclusion and analysis of studies for the clinical review.

Chidubem O Ogwulu (https://orcid.org/0000-0002-8133-7021) (Research fellow, health economics) was involved in screening and selection of articles for both systematic reviews, carried out data extraction for review of clinical effectiveness.

Pelham Barton (https://orcid.org/0000-0002-0519-3724) (Honorary reader in mathematical modelling) gave overall economic input and advice on the systematic review of cost-effectiveness and the economic evaluation.

Louise J Jackson (https://orcid.org/0000-0001-8492-0020) (Associate professor, health economics) gave overall economic input and significant advice on the systematic review of cost-effectiveness and economic evaluation.

David Moore (https://orcid.org/0000-0002-4163-4080) (Associate professor, evidence synthesis) led the project overall, conceptualisation of project and funding acquisition, gave input and advice on all aspects of the project.

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Equality, diversity and inclusion

Participant representation: This study utilises publicly available research and therefore reflects the diversity of this evidence.

Research team and wider involvement: The research team were compiled for their relevant clinical and methodological expertise. They were employed by equal opportunities employers with active inclusive staff development programmes.

PPI members were approached for participation based on having received the intervention under consideration and on potential clinical similarity to those for whom the intervention is being considered in this report.

Data-sharing statement

This is a quantitative study using published and/or publicly available data. Data generated in the study are presented within the report. If required, further information can be obtained from the corresponding author.

Ethics statement

Ethical approval was not required for this study because it involves systematic reviews and an economic analysis using publicly available evidence.

Information Governance statement

This study did not utilise any personal information or data.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/MLFA4009.

Primary conflicts of interest: Hoong Sern Lim and David Quinn have received funding from the devices industry including from Abbot and Abiomed for payment or honoraria for lectures, as well as support for travel to meetings. No other conflicts of interest were noted.

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157. Goldstein DJ, Naka Y, Horstmanshof D, Ravichandran AK, Schroder J, Ransom J, *et al*. Association of clinical outcomes with left ventricular assist device use by bridge to transplant or destination therapy intent: the Multicenter Study of MagLev Technology in patients undergoing mechanical circulatory support therapy with HeartMate 3 (MOMENTUM 3) randomized clinical trial. *JAMA Cardiol* 2020;**5**:411–9. https://doi.org/10.1001/jamacardio.2019.5323

158. Jalowiec A, Grady KL, White-Williams C. Predictors of rehospitalization time during the first year after heart transplant. *Heart Lung* 2008;**37**:344–55. https://doi.org/10.1016/j.hrtlng.2007.10.007

159. Starling RC, Estep JD, Horstmanshof DA, Milano CA, Stehlik J, Shah KB, *et al*. ROADMAP Study Investigators. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: the ROADMAP study 2-year results. *JACC Heart Fail* 2017;**5**:518–27. https://doi.org/10.1016/j.jchf.2017.02.016

160. Tattevin P, Flécher E, Auffret V, Leclercq C, Boulé S, Vincentelli A, *et al*. Risk factors and prognostic impact of left ventricular assist device-associated infections. *Am Heart J* 2019;**214**:69–76. https://doi.org/10.1016/j.ahj.2019.04.021

161. Luengo-Fernandez R, Walli-Attaei M, Gray A, Torbica A, Maggioni AP, Huculeci R, *et al*. Economic burden of cardiovascular diseases in the European Union: a population-based cost study. *Eur Heart J* 2023;**44**:4752–67. https://doi.org/10.1093/eurheartj/ehad583

162. Jentzer JC, Schrage B, Holmes DR, Jr, Dabboura S, Anavekar NS, Kirchhof P, *et al*. Influence of age and shock severity on short-term survival in patients with cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:604–12. https://doi.org/10.1093/ehjacc/zuaa035

Appendix 1 An exploration of the data sets to provide further data relevant to left ventricular assist device as destination therapy

Several registries contain data on patients receiving mechanical circulatory support. Information on their contents and access arrangements were explored to determine their relevance and usefulness in providing additional information to this report.

The NHS Blood and Transplant service collects data in the context of LVADs as bridge to transplant only.[150]

The National Institute for Cardiovascular Outcomes Research (NICOR) and the Myocardial Ischemia National Audit Project do not routinely collect data on LVADs (personal communication with NICOR).[151,152]

The EUROMACS contains Europe-wide data including that on LVADs.[153] It does not contain much UK data at this time. Submission of patient data is not mandatory, and the extent of any long-term data is unclear.

There have been a number of publications reporting data and analyses from INTERMACS.[154] Some of these relate to DT. Relevant publications/data have been used in this report.

There have also been several publications reporting data and analyses from the IMACS, some of which contain DT data.[155] Relevant publications that reported DT-specific data have been used in this report.

Appendix 2 Search strategies

MEDLINE search strategy

Database: Ovid MEDLINE(R)

Search strategy:

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1 (left adj4 ventric* adj4 assist*).ti,ab.
2 Assisted Circulation/
3 (Assis* adj4 circulat*).ti,ab.
4 (heartware hvad or heartware vad or heartmate or ventracor ventrassist or jarvik or flowmaker or micromed debakey or debakey vad or reliantheart or heartassist or berlin incor or terumo duraheart or evaheart).ti,ab.
5 (LVAD or LVAS or HVAD or VAD).ti,ab.
6 Heart-Assist Devices/
7 (continuous-flow adj3 device?).ti,ab.
8 circulatory support device?.ti,ab.
9 (Heart* adj4 assist* adj4 (device* or system* or pump* or treat* or therap* or surg*)).ti,ab.
10 (axial-flow adj3 device?).ti,ab.
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp Heart Failure/
13 Shock, Cardiogenic/
14 (cardiogenic* adj3 shock*).ti,ab.
15 Cardiomyopathies/
16 (cardiomyopath* or myocardit*).ti,ab.
17 exp Ventricular Dysfunction/
18 (ventricul* adj4 dysfunct*).ti,ab.
19 Myocarditis/
20 myocardit*.ti,ab.
21 ((end-stage or endstage* or end stage* or advance* or acute) adj4 heart* adj4 failur*).ti,ab.
22 heart failure*.ti,ab.
23 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 ((Destinat* or permanent*) adj4 (therap* or treat* or surg*)).ti,ab.
25 DT.ab,ti.
26 ((long-term or longest-term) and (LVAD or HVAD or LVAS or VAD or treat? or device?)).ti,ab.
27 ((ineligible or 'not eligible' or 'not candidate$1' or non-candidate$1) adj4 transplant$).ti,ab.
31 BTT.ti,ab.
28 BTC.ti,ab.
29 (bridge adj3 (decision or transplant* or recover* or candidacy)).ti,ab.
30 or 25 or 26 or 27 or 28 or 29 or 30
31 11 and 23 and 31
31 animals/ not humans/
32 32 not 33

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EMBASE search strategy

Database: EMBASE

Search strategy:

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1 (left adj4 ventric* adj4 assist*).ti,ab.
2 assisted circulation/
3 (Assis* adj4 circulat*).ti,ab.
4 (heartware hvad or heartware vad or heartmate or ventracor ventrassist or jarvik or flowmaker or micromed debakey or debakey vad or reliantheart or heartassist or berlin incor or terumo duraheart or evaheart).ti,ab.
5 (LVAD or LVAS or HVAD or VAD).ti,ab.
6 heart assist device/
7 (continuous-flow adj3 device?).ti,ab.
8 circulatory support device?.ti,ab.
9 (Heart* adj4 assist* adj4 (device* or system* or pump* or treat* or therap* or surg*)).ti,ab.
10 (axial-flow adj3 device?).ti,ab.
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp heart failure/
13 cardiogenic shock/
14 (cardiogenic* adj3 shock*).ti,ab.
15 cardiomyopathy/
16 (cardiomyopath* or myocardit*).ti,ab.
17 exp heart ventricle function/
18 (ventricul* adj4 dysfunct*).ti,ab.
19 myocarditis/
20 myocardit*.ti,ab.
21 ((end-stage or endstage* or end stage* or advance* or acute) adj4 heart* adj4 failur*).ti,ab.
22 heart failure*.ti,ab.
23 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 ((Destinat* or permanent*) adj4 (therap* or treat* or surg*)).ti,ab.
25 DT.ab,ti.
26 ((long-term or longest-term) and (LVAD or HVAD or LVAS or VAD or treat? or device?)).ti,ab.
27 ((ineligible or 'not eligible' or 'not candidate$1' or non-candidate$1) adj4 transplant$).ti,ab.
28 BTT.ti,ab.
29 BTC.ti,ab.
30 (bridge adj3 (decision or transplant* or recover* or candidacy)).ti,ab.
31 24 or 25 or 26 or 27 or 28 or 29 or 30
32 11 and 23 and 31
33 exp animal/ not exp human/
34 32 not 33

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Cochrane CENTRAL search strategy:

ID Search hits

#1 (left NEAR/4 ventric* NEAR/4 assist*):ti,ab
#2 MeSH descriptor: [Assisted Circulation] explode all trees
#3 (Assis* NEAR/4 circulat*):ti,ab
#4 (heartware hvad or heartware vad or heartmate or ventracor ventrassist or jarvik or flowmaker or micromed debakey or debakey vad or reliantheart or heartassist or berlin incor or terumo duraheart or evaheart):ti,ab
#5 (LVAD or LVAS or HVAD or VAD):ti,ab
#6 MeSH descriptor: [Heart-Assist Devices] explode all trees
#7 (continuous-flow NEAR/3 device?):ti,ab
#8 'circulatory support device?':ti,ab
#9 (Heart* NEAR/4 assist* NEAR/4 (device* or system* or pump* or treat* or therap* or surg*)):ti,ab
#10 (axial-flow NEAR/3 device?):ti,ab
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 MeSH descriptor: [Heart Failure] explode all trees
#13 MeSH descriptor: [Shock, Cardiogenic] this term only
#14 (cardiogenic* NEAR/3 shock*):ti,ab
#15 MeSH descriptor: [Cardiomyopathies] this term only
#16 (cardiomyopath* or myocardit*):ti,ab
#17 MeSH descriptor: [Ventricular Dysfunction] explode all trees
#18 (ventricul* NEAR/4 dysfunct*):ti,ab
#19 MeSH descriptor: [Myocarditis] this term only
#20 myocardit*:ti,ab
#21 ((end-stage or endstage* or end stage* or advance* or acute) NEAR/4 heart* NEAR/4 failur*):ti,ab
#22 'heart failure*':ti,ab
#23 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24 ((Destinat* or permanent*) NEAR/4 (therap* or treat* or surg*)):ti,ab
#25 DT:ti,ab
#26 ((long-term or longest-term) and (LVAD or HVAD or LVAS or VAD or treat? or device?)):ti,ab
#27 ((ineligible or 'not eligible' or 'not candidate$1' or non-candidate$1) NEAR/4 transplant$):ti,ab
#28 BTT:ti,ab
#29 BTC:ti,ab
#30 (bridge NEAR/3 (decision or transplant* or recover* or candidacy)):ti,ab
#31 #24 or #25 or #26 or #27 or #28 or #29 or #30
#32 #11 and #23 and #31

EconLit search strategy:

TX left ventricular assist device OR TX LVAD OR TX assisted circulation OR TX ((LVAS or HVAD or VAD)) OR TX heart assist device OR TX ((heartware hvad or heatware vad or heartmate or ventracor ventrassist or jarvik or flowmaker or micromed debakey vad or reliantheart or heartassist or berlin incur or terumo duraheart or evaheart)) OR TX continuous flow device OR TX axial flow device OR TX continuous-flow LVAD

NHSEED search strategy:

#1 MeSH DESCRIPTOR Heart-Assist Devices EXPLODE ALL TRESS IN NHSEED
#2 ((lvad or hvad or lvas or vad)) OR ((left ventric* assist device* or heart assist device* or continuous flow device or axial flow device)) OR ((heartware hvad or heartware vad or heartmate or ventracor ventrassist or jarvik or flowmaker or micromed debakey or debakey vad or reliantheart or heartassist or berlin incur or terumo duraheart or evaheart)) IN NHSEED
#3 #1 OR #2

Appendix 3 Excluded studies

TABLE 29 Full text excluded studies with reasons

Study ID	Reason for exclusion
Abdalla S, Kaan A, Nazzari H, Ignaszewski A, Virani S, Toma M. Risk factors of neurological events in patients supported with continuous flow LVADs. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S398.	Do not report DT data
Abdeen MS, Albert A, Maxhera B, Hoffmann T, Petrov G, Sixt S, *et al.* Implanting permanent left ventricular assist devices in patients on veno-arterial extracorporeal membrane oxygenation support: do we really need a cardiopulmonary bypass machine? *Eur J Cardio-Thorac Surg* 2016;**50**:542–7.	< 50 DT patients
Ada Ip A, Roldan J, Moss N. Differences between ischemic and non-ischemic cardiomyopathy and its relationship with long-term outcomes following ventricular assist device placement. *Eur J Heart Fail* 2019;**21**(Suppl. 1):83.	Do not report DT data
Adachi I, Burki S, Horne D, Jeewa A, Elias B, McKenzie E, *et al.* Continuous flow VAD support at a tertiary pediatric center: compared to pedimacs data. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S280–1.	Paediatric population
Adachi I. Pediatric ventricular assist device support as a permanent therapy: clinical reality. *J Thorac Cardiovasc Surg* 2019;**158**:1438–41.	Paediatric population
Adamo L, Tang Y, Nassif ME, Novak E, Jones PG, LaRue S, *et al.* The HeartMate risk score identifies patients with similar mortality risk across all INTERMACS profiles in a large multicenter analysis. *JACC Heart Fail* 2016;**4**:950–8.	Do not report DT data
Adamson RM, Bower BL, Sundareswaran KS, Farrar DJ, Dembitsky WP. Radiologic assessment of HeartMate II position: minimal pump migration after long-term support. *J Heart Lung Transplant* 2015;**34**:1617–23.	Do not report DT data
Adamson RM, Dembitsky WP, Reichman RT, Moreno-Cabral RJ, Daily PO. Mechanical support: assist or nemesis? *J Thorac Cardiovasc Surg* 1989;**98**:915–20; discussion 920.	< 50 DT patients
Adamson RM, Stahovich M, Chillcott S, Baradarian S, Chammas J, Jaski B, *et al.* Clinical strategies and outcomes in advanced heart failure patients older than 70 years of age receiving the HeartMate II left ventricular assist device: a community hospital experience. *J Am Coll Cardiol* 2011;**57**:2487–95.	Do not report DT data
Adatya S, Egnaczyk G, Katz JN, Brieke A, Stulak J, Nathan S, *et al.* The effect of pre-existing hypercoagulable disorders on outcomes in patients with LVADS. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S11.	Do not report DT data
Adesiyun TA, McLean RC, Tedford RJ, Whitman GJR, Sciortino CM, Conte JV, *et al.* Long-term follow-up of continuous flow left ventricular assist devices: complications and predisposing risk factors. *Int J Artif Organs* 2017;**40**:622–8.	Do not report DT data
Adlbrecht C, Hulsmann M, Wurm R, Eskandary F, Neuhold S, Zuckermann A, *et al.* Outcome of conservative management vs. assist device implantation in patients with advanced refractory heart failure. *Eur J Clin Invest* 2016;**46**:34–41.	Duplicate record
Adnan Yousaf A, Mihiyaddin S, Aldweik M, Ashraf S. Prolonged use of Levitronix-right ventricular assist device (RVAD) in patients with long term left ventricular assist device (LVAD). *Eur J Heart Fail* 2018;**20**(Suppl. 1):87.	Do not report DT data
Afzal A, Nisar T, Jamil A, Kluger A, Felius J, Gong T, *et al.* Impact of renal dysfunction on patients undergoing left ventricular assist device implantation. *J Card Fail* 2019;**25**(8 Suppl.):S147.	Do not report DT data
Agrawal S, Garg L, Nanda S, Sharma A, Bhatia N, Manda Y, *et al.* The role of implantable cardioverter-defibrillators in patients with continuous flow left ventricular assist devices – a meta-analysis. *Int J Cardiol* 2016;**222**:379–84.	Do not report DT data
Ahmad T, Kelly JP, McGarrah RW, Hellkamp AS, Fiuzat M, Testani JM, *et al.* Prognostic implications of long-chain acylcarnitines in heart failure and reversibility with mechanical circulatory support. *J Am Coll Cardiol* 2016;**67**:291–9.	< 50 DT patients

continued

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Ahmed N, Gandhi H, Kim Y, Saeed O, Patel S, Murthy S, *et al.* Neutrophil to lymphocyte ratio at the time of LVAD implant predicts 30-day readmission. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S319.	Do not report DT data
Akdemir B, Jedeon Z, Cogswell R, Schultz J, Wald LV, John R, *et al.* Atrial fibrillation and mortality in patients with LVAD: a single center cohort. Circulation Conference: American Heart Association Scientific Sessions, AHA. 2019;140.	Do not report DT data
Akin S, Muslem R, Constantinescu AA, Manintveld OC, Birim O, Brugts JJ, *et al.* 18F-FDG PET/CT in the diagnosis and management of continuous flow left ventricular assist device infections: a case series and review of the literature. *ASAIO J* 2018;**64**:e11–9.	< 50 DT patients
Akiyama M, Kawatsu S, Yoshioka I, Adachi O, Kumagai K, Saiki Y. Comparison of renal function after implantation of continuous-flow and pulsatile left ventricular assist devices. *J Card Fail* 2017;**23**(10 Suppl. 1):S35–6.	Do not report DT data
Alba AC, McDonald M, Rao V, Ross HJ, Delgado DH. The effect of ventricular assist devices on long-term post-transplant outcomes: a systematic review of observational studies. *Eur J Heart Fail* 2011;**13**:785–95.	Do not report DT data
Aleksova N, Alba A, Fan CS, Amin F, Kiamanesh O, McGuinty C, *et al.* The effect of age on outcomes following destination therapy left ventricular assist device implantation: an analysis of the IMACS registry. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S37.	Do not report DT data
Alemany HS, Unlu O, Pabon M, Sobol I, Krishnan U, Goyal P, *et al.* Impact of intra-operative transfusions on post left ventricular assist device placement outcomes: a single center study. *J Am Coll Cardiol* 2020;**75**(11):980.	Do not report DT data
Alsara O, Reeves RK, Pyfferoen MD, Trenary TL, Engen DJ, Vitse ML, *et al.* Inpatient rehabilitation outcomes for patients receiving left ventricular assist device. *Am J Phys Med Rehabil* 2014;**93**:860–8.	Do not report DT data
Al-Sarie M, Rauf A, Kfoury AG, Catino A, Wever-Pinzon J, Bonios M, *et al.* Myocardial structural and functional response after long-term mechanical unloading with continuous flow left ventricular assist device: axial versus centrifugal flow. *JACC Heart Fail* 2016;**4**:570–6.	< 50 DT patients
Al-Sarie M, Rauf A, Wever-Pinzon J, Catino A, Stehlik J, Kfouri A, *et al.* Myocardial and end-organ response after long-term mechanical unloading with continuous-flow left ventricular assist device: axial-versus centrifugal-flow. *J Heart Lung Transplant* 2016;(1):S330–1.	Do not report DT data
Alvarez J, Duero Posada J, Moayedi Y, Alhussein M, Runeckles K, Ross H, *et al.* Clinical differences between contemporary continuous flow left ventricular assist devices: a single center comparison between heartware, heartmate II and heartmate 3. *Can J Cardiol* 2017;**33**(10 Suppl. 1):S70–1.	Do not report DT data
Amione-Guerra J, Bhimaraj A, Ashrith G, Bruckner B, Suarez EE, Park MH, *et al.* Implantation of continuous flow-left ventricular assist devices (CF-LVAD) in the extremely obese (BMI ≥ 40 kg/m^2): a single center experience. *J Heart Lung Transplant* 2016;**35**(Suppl.):S374.	Do not report DT data
Amione-Guerra J, Cordero-Reyes AM, Bhimaraj A, Trachtenberg BH, Torre-Amione G, Park MH, *et al.* Elevated transpulmonary gradient is a predictor of survival in patients with WHO Group II pulmonary hypertension treated with continuous-flow left ventricular assist devices (CF-LVAD). *J Heart Lung Transplant* 2016;**35**(Suppl.):S163–4.	Do not report DT data
Anderson RD, Lee G, Virk S, Bennett RG, Hayward CS, Muthiah K, *et al.* Catheter ablation of ventricular tachycardia in patients with a ventricular assist device: a systematic review of procedural characteristics and outcomes. *JACC Clin Electrophysiol* 2019;**5**:39–51.	< 50 DT patients
Andrews M, Wesner S, Watkins R, Katz JN. No distance is too great: a patient's commute to their implantation center is not associated with worse outcomes following placement of a left ventricular assist device. *J Heart Lung Transplant* 2016;**35**(Suppl.):S377.	Do not report DT data
Angermayr L, Velasco Garrido M, Busse R. Ventricular assist devices for heart failure. *GMS Health Technol Assess* 2007;**3**:Doc10.	Wrong study design
Ankersmit HJ, Tugulea S, Spanier T, Weinberg AD, Artrip JH, Burke EM, *et al.* Activation-induced T-cell death and immune dysfunction after implantation of left-ventricular assist device. *Lancet* 1999;**354**:550–5.	< 50 DT patients

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Anonymous. Corrections: short- and long-term outcomes of continuous-flow left ventricular assist device therapy in 79 patients with end-stage heart failure. *Pol Arch Intern Med* 2020;**130**:926–7.	Wrong patient population
Anonymous. Special report: cost-effectiveness of left-ventricular assist devices as destination therapy for end-stage heart failure. *Technol Eval Cent Assess Program Exec Summ* 2004;**19**:1.	Duplicate record
Anonymous. Special report: left ventricular assist devices as destination therapy for end-stage heart failure–cost-effectiveness analysis. TEC Bulletin [Electronic Resource] 2003;**20**:33–4.	Duplicate record
Ansari M, Garcia D. Intra-aortic balloon pump and peripheral LVAD for treatment of cardiogenic shock. *Catheter Cardiovasc Interv* 2017;**89**(Suppl. 2):S46.	Do not report DT data
Anselmi A, Galand V, Vincentelli A, Boule S, Dambrin C, Delmas C, *et al.* Current results of left ventricular assist device therapy in France: the ASSIST-ICD registry. *Eur J Cardio Thorac Surg* 2020;16.	Do not report DT data
Anselmi A, Galand V, Vincentelli A, Boule S, Dambrin C, Delmas C, *et al.* Current results of left ventricular assist device therapy in France: The ASSIST-ICD registry. *Eur J Cardio-Thorac Surg* 2020;**58**:112–20.	Do not report DT data
Anwer LA, Tchantchaleishvili V, Poddi S, Daly RC, Joyce LD, Kushwaha SS, *et al.* Atrial fibrillation should guide prophylactic tricuspid procedures during left ventricular assist device implantation. *ASAIO J* 2018;**64**:586–93.	Do not report DT data
Arabia FA, Smith RG, Jaffe C, Wild JC, Rose DS, Nelson RJ, *et al.* Cost analysis of the Novacor Left Ventricular Assist System as an outpatient bridge to heart transplantation. *ASAIO J* 1996;**42**:M546–9.	Wrong patient population
Araujo-Gutierrez R, Potter LM, Teigen L, Schultz J, Estep JD, John R, *et al.* Pre-operative pectoralis muscle quantity and attenuation by computed tomography are predictive of recurrent gastrointestinal bleeding on left ventricular assist device support: a multicenter analysis. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S396–7.	Do not report DT data
Asleh R, Schettle SS, Khan FW, Kushwaha SS. Left ventricular assist devices as destination therapy in stage D heart failure. *J Geriatr Cardiol* 2019;**16**:592–600.	Wrong study design
Asuka E, Pak S, Thiess AK, Torres A. Gastrointestinal bleeding as a complication in continuous flow ventricular assist devices: a systematic review with meta-analysis. *J Clin Med Res* 2020;**12**:543–59.	Do not report DT data
Atluri P, Fairman AS, MacArthur JW, Goldstone AB, Cohen JE, Howard JL, *et al.* Continuous flow left ventricular assist device implant significantly improves pulmonary hypertension, right ventricular contractility, and tricuspid valve competence. *J Card Surg* 2013;**28**:770–5.	Do not report DT data
Atluri P, Goldstone AB, Kobrin DM, Cohen JE, MacArthur JW, Howard JL, *et al.* Ventricular assist device implant in the elderly is associated with increased, but respectable risk: a multi-institutional study. *Ann Thorac Surg* 2013;**96**:141–7.	Do not report DT data
Aurora L, Ahluwalia G, Mahan M, Williams CT. Impact of social determinants on outcomes in patients with left ventricular assist devices. *J Card Fail* 2019;**25**(8 Suppl.):S127.	Do not report DT data
Aurora L, Sadiq O, Nemeh H, Williams C. Left ventricular assist devices complicated by gastrointestinal bleeding and outcomes on transplant. *Am J Transplant* 2018;**18**(Suppl. 4):651.	Do not report DT data
Auvil B, Chung J, Ameer A, Han J, Helmers M, Birati E, *et al.* Asymptomatic moderate aortic insufficiency with a left ventricular assist device portends a worse long-term survival. *ASAIO J* 2018;**64**(Suppl. 1):63.	Do not report DT data
Avancena AL, Peng DM, Lee J, Si M, Schumacher KR, Hutton DW. Cost-effectiveness of immediate ventricular assist device implantation in children with inotrope-dependent heart failure. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S87.	Paediatric population
Avramovic N, Dell'Aquila AM, Weckesser M, Milankovic D, Vrachimis A, Sindermann JR, *et al.* Metabolic volume performs better than SUVmax in the detection of left ventricular assist device driveline infection. *Eur J Nucl Med Mol Imaging* 2017;**44**:1870–7.	< 50 DT patients

continued

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Axelrad JE, Pinsino A, Trinh P, Colombo P, Yuzefpolskaya M, Gonda T. Endoscopic evaluation in patients with CF-LVADS and gastrointestinal bleeding: are we ready Q for a paradigm shift to improve care? *Am J Gastroenterol* 2017;**112**(Suppl. 1):S318.	Do not report DT data
Ayers BC, Wood K, Lee E, Bruckel J, Ling F, Kutyifa V, *et al.* PROMISing new tool correlates well with Kansas City cardiomyopathy questionnaire in left ventricular assist device patients. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S438.	Do not report DT data
Aymami M, Donal E, Guihaire J, Le Helloco A, Federspiel M, Galli E, *et al.* Rest and exercise adaptation of the right ventricular function in long-term left ventricular assist device patients: a prospective, pilot study. *J Card Fail* 2016;**22**:240–1.	Do not report DT data
Aymami M, Haddad F, Amsallem M, Marques M, Sallam K, Wheeler M, *et al.* External validation of right heart failure risk scores following LVAD implantation and evaluation of emerging echocardiographic indices. *Arch Cardiovasc Dis Suppl* 2017;**9**:46.	Do not report DT data
Aymami M, Haddad F, Wheeler M, Amsallem M, Marques M, Adams J, *et al.* External validation of right heart failure risk scores following left ventricular assist device implantation and evaluation of the role of emerging echocardiographic indices. Circulation Conference: American Heart Association's. 2016;134.	Do not report DT data
Baffy NJ, Horsley-Silva JL, Ramirez FC. Endoscopic management and outcomes of gastrointestinal bleeding in patients with left ventricular assist device (LVAD). *Gastrointest Endosc* 2018;**87**(6 Suppl. 1):AB422.	Do not report DT data
Baker WL, Radojevic J, Gluck JA. Systematic review of phosphodiesterase-5 inhibitor use in right ventricular failure following left ventricular assist device implantation. *Artif Organs* 2016;**40**:123–8.	< 50 DT patients
Balachandran IC, Kennedy K, Nunez JF, Kiernan M, Grandin E, Buxton AE, *et al.* The effect of digoxin use on outcomes in patients with durable LVADs: an intermacs analysis. *J Am Coll Cardiol* 2020;**75**(11):993.	Do not report DT data
Balakumaran K, Garcia RA, Schwab T, Gaznabi S, Dahm JT, Peng SL, *et al.* Predictive preoperative characteristics for right ventricular failure after left ventricle assist device placement. *J Card Fail* 2020;**26**(10 Suppl.):S128.	Do not report DT data
Bansal A, Akhtar F, Desai S. Post-approval experience with fully magnetically levitated continuous flow left ventricular assist device – single center experience. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S416.	Do not report DT data
Bansal A, Schexnayder D, Akhtar F, Bansal A, Velasco-Gonzalez C, Verma A, *et al.* Right heart failure in different left ventricular assist devices: single-center experience. *Ochsner J* 2019;**19**:194–8.	Do not report DT data
Bansal N, Hailpern SM, Katz R, Hall YN, Kurella Tamura M, Kreuter W, *et al.* Outcomes associated with left ventricular assist devices among recipients with and without end-stage renal disease. *JAMA Intern Med* 2018;**178**:204–9.	Do not report DT data
Bart NK, Malik S, Emmanuel S, Andresen D, Muthiah K, Hayward CS. Blood stream infection in patients with permanent mechanical circulatory support: risk factors for on-pump mortality. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S319.	Do not report DT data
Bedzra EKS, Dardas TF, Cheng RK, Pal JD, Mahr C, Smith JW, *et al.* Pulmonary function tests do not predict mortality in patients undergoing continuous-flow left ventricular assist device implantation. *J Thorac Cardiovasc Surg* 2017;**154**:1959–70.e1.	Do not report DT data
Bejko J, Toto F, Gregori D, Gerosa G, Bottio T. Left ventricle assist devices and driveline's infection incidence: a single-centre experience. *J Artif Organs* 2018;**21**:52–60.	< 50 DT patients
Bellavia D, Iacovoni A, Scardulla C, Moja L, Pilato M, Kushwaha SS, *et al.* Prediction of right ventricular failure after ventricular assist device implant: systematic review and meta-analysis of observational studies. *Eur J Heart Fail* 2017;**19**:926–46.	< 50 DT patients
Benedetti G, Mohite P, Smail H, Garcia Saez D, Patil NP, Husain M, *et al.* Long-term follow-up and predicting factors of de novo aortic regurgitation after LVAD implantation. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S291.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Benjamin MM, Garacci Z, Sundarajan S, Mohammed A. Longer duration of milrinone associated with higher risk for right ventricular failure following left ventricular assist device implantation in stage D heart failure patients. *J Card Fail* 2019;**25**(8 Suppl.):S47.	Do not report DT data
Beyersdorf F. Economics of ventricular assist devices: European view. *Ann Thorac Surg* 2001;**71**:S192–4; discussion S202.	Wrong study design
Bhat G, Kumar S, Aggarwal A, Pauwaa S, Rossell G, Kurien S, *et al.* Experience with noncardiac surgery in destination therapy left ventricular assist devices patients. *ASAIO J* 2012;**58**:396–401.	< 50 DT patients
Bielka A, Kalinowski M, Pacholewicz J, Antonczyk R, Zakliczynski M, Przybylowski P, *et al.* Left ventricular assist devices offer similar one-year survival to the heart transplant recipients – single center experience. *Kardiologia Polska* 2018;**76**(Suppl. 1):365–6.	Do not report DT data
Bielka A, Kalinowski M, Pacholewicz J, Malyszek-Tumidajewicz J, Waszak J, Copik I, *et al.* Short- and long-term outcomes of continuous-flow left ventricular assist device therapy in 79 patients with end-stage heart failure. *Pol Arch Intern Med* 2020;**130**:589–97.	Wrong patient population
Bielka A, Kalinowski M, Pacholewicz J. Erratum: short-and long-term outcomes of continuous-flow left ventricular assist device therapy in 79 patients with end-stage heart failure. *Pol Arch Intern Med* 2020;**130**:926–7.	Wrong patient population
Bieniarz MC, Delgado R. The financial burden of destination left ventricular assist device therapy: who and when? *Curr Cardiol Rep* 2007;**9**:194–9.	Wrong study design
Birati EY, Hanff TC, Maldonado D, Grandin EW, Kennel PJ, Mazurek JA, *et al.* Predicting long term outcome in patients treated with continuous flow left ventricular assist device: the Penn-Columbia Risk Score. *J Am Heart Assoc* 2018;**7**:e006408.	Do not report DT data
Birks EJ, Tansley PD, Yacoub MH, Bowles CT, Hipkin M, Hardy J, *et al.* Incidence and clinical management of life-threatening left ventricular assist device failure. *J Heart Lung Transplant* 2004;**23**:964–9.	Do not report DT data
Bishawi M, Bell S, Cai L, Landford W, Arif S, McLarty A, *et al.* Antibiotic prophylaxis strategies in LVAD implantation and LVAD infections: a systematic review of the literature. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S242.	Do not report DT data
Bishawi M, Joseph J, Patel C, Schroder J, Daneshmand M, Bowles D, *et al.* Risk factors for stroke on left ventricular assist devices. *J Card Surg* 2018;**33**:348–52.	Do not report DT data
Bjelic M, Ayers B, Paic F, Bernstein W, Barrus B, Chase K, *et al.* Study results suggest less invasive HeartMate 3 implantation is a safe and effective approach for obese patients. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 2021;**40**:990–7.	Do not report DT data
Blumer V, Hernandez G, Ortiz M, Cioff J, Chaparro S. Oncologic patients with advanced heart failure: to VAD or not to VAD? Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC. 2018;71.	Do not report DT data
Bobenko A, Schoenrath F, Knierim JH, Friede T, Verheyen N, Mehra MR, *et al.* Exercise training in patients with a left ventricular assist device (Ex-VAD): rationale and design of a multicentre, prospective, assessor-blinded, randomized, controlled trial. *Eur J Heart Fail* 2019;**21**:1152–9.	Wrong intervention
Boyle AJ, Ascheim DD, Russo MJ, Kormos RL, John R, Naka Y, *et al.* Clinical outcomes for continuous-flow left ventricular assist device patients stratified by pre-operative INTERMACS classification. *J Heart Lung Transplant* 2011;**30**:402–7.	Do not report DT data
Braun OO, Nilsson J, Gustafsson F, Dellgren G, Fiane AE, Lemstrom K, *et al.* Continuous-flow LVADs in the Nordic countries: complications and mortality and its predictors. *Scand Cardiovasc J* 2019;**53**:14–20.	< 50 DT patients
Brewer RJ, Cabrera R, El-Atrache M, Zafar A, Hrobowski TN, Nemeh HM, *et al.* Relationship of tricuspid repair at the time of left ventricular assist device implantation and survival. *Int J Artif Organs* 2014;**37**:834–8.	< 50 DT patients

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Brewer RJ, Lanfear DE, Sai-Sudhakar CB, Sundareswaran KS, Ravi Y, Farrar DJ, *et al.* Extremes of body mass index do not impact mid-term survival after continuous-flow left ventricular assist device implantation. *J Heart Lung Transplant* 2012;**31**:167–72.	Do not report DT data
Brinkley DM, Wang L, Yu C, Kiernan MS. The effect of renin-angiotensin-aldosterone system inhibition on morbidity and mortality during long-term continuous-flow left ventricular assist device support. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S132.	Do not report DT data
Brisco MA, Kimmel SE, Coca SG, Putt ME, Jessup M, Tang WW, *et al.* Prevalence and prognostic importance of changes in renal function after mechanical circulatory support. *Circ Heart Fail* 2014;**7**:68–75.	Wrong outcomes
Brisco MA, Sundareswaran KS, Milano CA, Feldman D, Testani JM, Ewald GA, *et al.* Incidence, risk, and consequences of atrial arrhythmias in patients with continuous-flow left ventricular assist devices. *J Card Surg* 2014;**29**:572–80.	Do not report DT data
Brozzi NA, Cifuentes RO, Saba IC, Macon C, Ghodsizad A, Andreopoulos F, *et al.* Long-term outcomes of elderly patients receiving continuous flow left ventricular support. *J Card Surg* 2020;**35**:3405–8.	Do not report DT data
Bruce CR, Minard CG, Wilhelms LA, Abraham M, Amione-Guerra J, Pham L, *et al.* Caregivers of patients with left ventricular assist devices: possible impacts on patients' mortality and interagency registry for mechanically assisted circulatory support-defined morbidity events. *Circ Cardiovasc Qual Outcomes* 2017;**10**:01.	Do not report DT data
Brush S, Budge D, Alharethi R, McCormick AJ, MacPherson JE, Reid BB, *et al.* End-of-life decision making and implementation in recipients of a destination left ventricular assist device. *J Heart Lung Transplant* 2010;**29**:1337–41.	< 50 DT patients
Bryce K, Pehote M, Lanfear D. Cognitive functioning and post-LVAD outcomes: influence of comorbidities and specific cognitive domains. *J Card Fail* 2016;**22**(Suppl. 8):S124.	Do not report DT data
Bunte MC, Blackstone EH, Thuita L, Fowler J, Joseph L, Ozaki A, *et al.* Major bleeding during HeartMate II support. *J Am Coll Cardiol* 2013;**62**:2188–96.	< 50 DT patients
Burke MA, Alexy T, Kamioka N, Shafi T, Turbyfield CT, Stowe J, *et al.* Outflow graft obstruction causing recurrent heart failure after left ventricular assist device implantation. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S98.	Do not report DT data
Cai J, Xia W, Akhabue E, Setoguchi S, Okwuosa I, Greenberg P. Primary causes of hospitalization among patients with left ventricular assist devices. *J Heart Lung Transplant* 2021;**40**(4 Suppl.):S418.	Do not report DT data
Casida J, Aikens J, Pagani F, Ewald G, Craddock H, Pavol M, *et al.* Advancing the science of self-management in adults with long-term left ventricular assist devices. *Artif Organs* 2018;**42**:1095–103.	< 50 DT patients
Casida J, Wu HS, Harden J, Chern J, Carie A. Development and initial evaluation of the psychometric properties of self-efficacy and adherence scales for patients with a left ventricular assist device. *Prog Transplant* 2015;**25**:107–15.	< 50 DT patients
Casida JM, Abshire M, Ghosh B, Yang JJ. The relationship of anxiety, depression, and quality of life in adults with left ventricular assist devices. *ASAIO J* 2018;**64**:515–20.	< 50 DT patients
Casida JM, Wu HS, Abshire M, Ghosh B, Yang JJ. Cognition and adherence are self-management factors predicting the quality of life of adults living with a left ventricular assist device. *J Heart Lung Transplant* 2017;**36**:325–30.	< 50 DT patients
Castedo E, Martinez Cabeza P, Perez de la Sota E, Sbraga F, Polo ML, Arribas JM, *et al.* First ESPAMACS official report: 369 mechanical circulatory support devices (October 2014–May 2016). *Cirugia Cardiovascular* 2016;**23**:15–21.	< 50 DT patients
Cavarretta E, Marullo AGM, Sciarretta S, Benedetto U, Greco E, Roever L, *et al.* A network meta-analysis of randomized trials and observational studies on left ventricular assist devices in adult patients with end-stage heart failure. *Eur J Cardio-Thorac Surg* 2019;**55**:461–7.	Wrong study design

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Chair SY, Cheng L. The effectiveness of cardiac rehabilitation in patients with left ventricular assist devices (LVADs): a systematic review and meta-analysis. *ASAIO J* 2018;**64**(Suppl. 1):70.	Do not report DT data
Chang HH, Chen PL, Chen IM, Kuo TT, Weng ZC, Huang PJ, *et al.* Cost–utility analysis of direct ventricular assist device vs double bridges to heart transplantation in patients with refractory heart failure. *Clin Transplant* 2017;31.	Wrong patient population
Chen S, Lin A, Liu E, Gowan M, May LJ, Doan LN, *et al.* Outpatient outcomes of pediatric patients with left ventricular assist devices. *ASAIO J* 2016;**62**:163–8.	Paediatric population
Chen S, Lin A, Liu E, May LJ, Doan LN, Maeda K, *et al.* Discharge outcomes in children supported with continuous flow left ventricular assist devices. *J Heart Lung Transplant* 2015;(1):S324.	Paediatric population
Cheng JM, den Uil CA, Hoeks SE, van der Ent M, Jewbali LS, van Domburg RT, *et al.* Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. *Eur Heart J* 2009;**30**:2102–8.	< 50 DT patients
Cheng JM, den Uil CA, Hoeks SE, van der Ent M, Jewbali LS, van Domburg RT, *et al.* Percutaneous left ventricular assist devices vs intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Database of Abstracts of Reviews of Effects (DARE). 2010.	Duplicate record
Chickerillo K, Andrade AA, Kukla L, Khan M, Hussain S, Krause N, *et al.* Chronic kidney disease and left ventricular assist device patients: a retrospective review. *J Card Fail* 2019;**25**(8 Suppl.):S152.	Do not report DT data
Chickerillo K, Andrade AA, Kukla L, Krause N, Aicher T, Paliga R, *et al.* 2-year outcomes of LVAD patients with chronic kidney disease. *ASAIO J* 2021;**67**(Suppl. 2):94.	Do not report DT data
ChiCtr, Teda International Cardiovascular Hospital Y. A clinical trial to evaluate the efficacy and safety of implantable magnetic fluid suspension ventricular assist device in patients with end-stage heart failure. 2019.	Do not report DT data
Chien CV, Gelow JM, Mudd JO, Davis J, Lee CS. Right atrial pressure is the best hemodynamic predictor of heart failure hospitalizations in patients on LVAD support. *J Card Fail* 2016;**22**(Suppl. 8):S22.	Do not report DT data
Choi JH, Luc JGY, Moncho Escrivá E, Phan K, Rizvi SSA, Patel S, *et al.* Impact of concomitant mitral valve surgery with LVAD placement: systematic review and meta-analysis. *Artif Organs* 2018;**42**:1139–47.	< 50 DT patients
Chou B, Lamba HK, Long G, Parikh V, Chatterjee S, George J, *et al.* Outcomes of LVAD implantation in ischemic versus nonischemic cardiomyopathy. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S449.	Do not report DT data
Chou BP, Lamba HK, Cheema FH, Civitello AB, Delgado RM, Simpson L, *et al.* Outcomes of repeat left ventricular assist device exchange. *ASAIO J* 2020;**66**:64–8.	< 50 DT patients
Christle JW, Moneghetti K, Haddad F, Myers J, Ashley EA, Wheeler M, *et al.* Serial echo-cardiopulmonary exercise test ramping for evaluation of patients with VAD. *Eur Heart J* 2018;**39**(Suppl. 1):386.	Do not report DT data
Christle JW, Moneghetti KJ, Ha R, Haddad F, Banerjee D, Wheeler MT. Combining echocardiography with cardiopulmonary exercise stress testing to evaluate recovery of systolic function in patients with left ventricular assist devices. *Eur J Heart Fail* 2017;**19**(Suppl. 1):112.	Do not report DT data
Chu JK, Sarda S, Falkenstrom K, Boydston W, Chern JJ. Ventricular access device infection rate: a retrospective study and review of the literature. *Child's Nerv Syst* 2014;**30**:1663–70.	Paediatric population
Chu SK, McCormick Z, Hwang S, Rydberg L. Outcomes of acute inpatient rehabilitation in patients with left ventricular assist devices. *PM&R* 2013;(1):S141.	< 50 DT patients
Chung JJ, Stetson R, Chen CW, Gaffey AC, Rame J, Acker MA, *et al.* Doing the math: the costs of long term mechanical circulatory support. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S287.	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Chung JJ, Stetson R, Gordon J, Chen CW, Gaffey AC, Rame JE, *et al.* Better with time: an economic assessment of long-term mechanical circulatory support in a population surviving at least 1 year with a left ventricular assist device. *Semin Thorac Cardiovasc Surg* 2018.	Wrong indication
Chung JJ, Stetson R, Gordon J, Chen CW, Gaffey AC, Rame JE, *et al.* Better with time: an economic assessment of long-term mechanical circulatory support in a population surviving at least 1 year with a left ventricular assist device. *Semin Thorac Cardiovasc Surg* 2020;**32**:738–46.	Do not report DT data
Chyou JY. Relationship of gender, baseline QRS duration, and composite of cardiovascular readmission and death in patients with left ventricular assist device. *Heart Rhythm* 2017;**14**(5 Suppl. 1):S578.	Do not report DT data
Clarke A, Pulikottil-Jacob R, Connock M, Suri G, Kandala NB, Maheswaran H, *et al.* Cost-effectiveness of left ventricular assist devices (LVADs) for patients with advanced heart failure: analysis of the British NHS bridge to transplant (BTT) program. *Int J Cardiol* 2014;**171**:338–45.	Wrong indication
Clarke N, Pruszynski JE, Drazner M, Huffman LC, Peltz M. Device choice does not influence outcomes after left ventricular assist device (LVAD) in patients bridged to transplant or destination therapy. *J Am Coll Surg* 2017;**225**(4 Suppl. 1):S28.	Do not report DT data
Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al.* The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. *Health Technol Assess (Winchester, England)* 2005;**9**:1–132, iii.	Wrong study design
Clegg AJ, Scott DA, Loveman E, Colquitt JL, Royle P, Bryant J. Clinical and cost-effectiveness of left ventricular assist devices as a bridge to heart transplantation for people with end-stage heart failure: a systematic review and economic evaluation. *Eur Heart J* 2006;**27**:2929–38.	Wrong indication
Cleveland JC, Jr, Naftel DC, Reece TB, Murray M, Antaki J, Pagani FD, *et al.* Survival after biventricular assist device implantation: an analysis of the Interagency Registry for Mechanically Assisted Circulatory Support database. *J Heart Lung Transplant* 2011;**30**:862–9.	Do not report DT data
Cogswell R, John R, Shultz J, Martin C, Thenappan T, Kamdar F, *et al.* Pre-operative pectoralis muscle quantity and attenuation by computed tomography are predictive of recurrent gastro-intestinal bleeding on left ventricular assist device support. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S73.	Do not report DT data
Cogswell R, Murray T, Araujo R, Teigen L, Trachtenberg B, Schultz J, *et al.* A novel model incorporating pectoralis muscle measures to predict mortality after ventricular assist device implantation. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S108.	Do not report DT data
Cogswell R, Murray T, Araujo R, Teigen L, Trachtenberg B, Schultz JN, *et al.* External validation of the Minnesota pectoralis muscle risk score to predict mortality after ventricular assist device implantation. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S37.	Do not report DT data
Cogswell R, Teigen L, Allen T, Estep J, Araujo R, Schultz J, *et al.* Measurement of pectoralis muscle quantity and attenuation by computed tomography using routinely available software is feasible and predicts mortality after LVAD implantation. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S445.	Do not report DT data
Cogswell R, Teigen L, Schultz J, Thenappan T, Lin L, Kealhofer J, *et al.* Pre-operative pectoralis muscle measures by computed tomography predict early right heart failure deaths after left ventricular assist device. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S468.	Do not report DT data
Connelly JH, Abrams J, Klima T, Vaughn WK, Frazier OH. Acquired commissural fusion of aortic valves in patients with left ventricular assist devices. *J Heart Lung Transplant* 2003;**22**:1291–5.	Wrong patient population
Cool JA, Parikh NS, Kamel H, Karas MG, Boehme AK. Stroke risk and mortality in patients with ventricular assist devices. Stroke Conference: American Heart Association/American Stroke Association. 2016;47.	Do not report DT data
Corral JE, Yarlagadda B, Kroner PT, Goswami R, Leoni-Moreno JC, Raimondo M, *et al.* Left ventricular assist device (LVAD), heart transplantation and acute pancreatitis: a retrospective cohort. *Gastroenterol* 2019;**156**(6 Suppl. 1):S-1036.	Do not report DT data
Cowger J, Pagani FD, Haft JW, Romano MA, Aaronson KD, Kolias TJ. The development of aortic insufficiency in left ventricular assist device-supported patients. *Circ Heart Fail* 2010;**3**:668–74.	< 50 DT patients

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Cowger JA, Aaronson KD, Romano MA, Haft J, Pagani FD. Consequences of aortic insufficiency during long-term axial continuous-flow left ventricular assist device support. *J Heart Lung Transplant* 2014;**33**:1233–40.	< 50 DT patients
Cowger JA, Naka Y, Aaronson K, Horstmanshoff D, Gulati S, Rinde-Hoffman D, *et al.* Quality of life and functional capacity assessment in the multicenter study of maglev technology in patients undergoing mechanical circulatory support therapy with Heartmate 3 (Momentum 3) pivotal trial. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S66–7.	Do not report DT data
Cowger JA, Shah P, Singh R, Pagani FD, Aaronson KD, Dardas TF, *et al.* Long term survivors of LVAD support: what attributes describe their survival advantage? *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S422.	Do not report DT data
Coyle L, Yost G, Gallagher C, Graney N, Siemeck R, Bhat G, *et al.* Impatct of morbid obesity after left ventricular assist device placement. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S182–3.	Do not report DT data
Critsinelis A, Lamba H, Volkovicher N, Kurihara C, Kawabori M, Sugiura T, *et al.* Effects of continuous flow left ventricular assist devices on long-term kidney function. *ASAIO J* 2018;**64**(Suppl. 1):75.	Do not report DT data
Critsinelis A, Lamba HK, Kurihara C, Kawabori M, Sugiura T, Santiago A, *et al.* Comparison of HMII and HVAD outcomes in patients supported for over two years. *ASAIO J* 2018;**64**(Suppl. 1):77.	Do not report DT data
Critsinelis AC, Kurihara C, Kawabori M, Sugiura T, Civitello AB, Morgan JA. Preoperative prealbumin level as a predictor of outcomes in patients who underwent left ventricular assist device implantation. *Am J Cardiol* 2017;**120**:1998–2002.	Do not report DT data
Crow S, John R, Boyle A, Shumway S, Liao K, Colvin-Adams M, *et al.* Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices. *J Thorac Cardiovasc Surg* 2009;**137**:208–15.	< 50 DT patients
Cruz RR, Teo L, Loh J, Chan L, Khoo CY, Ng CT, *et al.* The use of ARNI in the prevention of ventricular assist device implantation among patients with advanced heart failure: a single center experience. *Eur J Heart Fail* 2019;**21**(Suppl. 1):84–5.	Do not report DT data
Cushing K, Kushnir V. Gastrointestinal bleeding following LVAD placement from top to bottom. *Dig Dis Sci* 2016;**61**:1440–7.	Wrong study design
Dailey J, Nguyen LH, Kohli A, Ha J, Russell MB, Dhingra R, *et al.* 968 a Multi-center study of left ventricular assist device (LVAD)-related bleeding. *Gastrointest Endosc* 2020;**91**(6 Suppl.):AB84–5.	Do not report DT data
Daimee UA, Wang M, Papernov A, Sherazi S, McNitt S, Vidula H, *et al.* Renal function changes following left ventricular assist device implantation. *Am J Cardiol* 2017;**120**:2213–20.	Do not report DT data
Dang NC, Topkara VK, Leacche M, John R, Byrne JG, Naka Y. Left ventricular assist device implantation after acute anterior wall myocardial infarction and cardiogenic shock: a two-center study. *J Thorac Cardiovasc Surg* 2005;**130**:693–8.	Do not report DT data
de By TMMH, Castedo E, Krabatsch T, Mohacsi P, Meyns B, Netuka I, *et al.* The EUROMACS Registry of patients who receive mechanical circulatory support: role and perspectives. *Cir Cardiovascular* 2016;**23**:22–5.	Wrong intervention
Dean D, Kallel F, Ewald GA, Tatooles A, Sheridan BC, Brewer RJ, *et al.* Reduction in driveline infection rates: results from the HeartMate II Multicenter Driveline Silicone Skin Interface (SSI) Registry. *J Heart Lung Transplant* 2015;**34**:781–9.	Do not report DT data
DeFilippis E, Haythe J, Marshall D, Lin E, Axsom K, Truby L, *et al.* Sex differences in characteristics and outcomes following HeartMate 3 left ventricular assist device implantation. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S337.	Do not report DT data
Demirozu ZT, Critsinelis A, Cohn WE, Radovancevic R, Ho J, Hernandez R, *et al.* Experience with the HeartMate II left ventricular assist device in patients older than 60 years. *Heart Surg Forum* 2019;**22**:E124–30.	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Demirozu ZT, Radovancevic R, Hochman LF, Gregoric ID, Letsou GV, Kar B, *et al.* Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. *J Heart Lung Transplant Offi Publ Int Soc Heart Transplant* 2011;**30**:849–53.	Do not report DT data
Deng MC, Wilhelm MJ, Scheld HH. Effects of exercise during long-term support with a left ventricular assist device. *Circulation* 1998;**97**:1212–3.	Wrong study design
Deniz E, Hanke JS, Rojas SV, Egger C, Urribari A, Reiss N, *et al.* Predictors of thrombembolic events in left ventricular assist devices. *Eur Heart J* 2016;**37**(Suppl. 1):792.	Do not report DT data
Deo SV, Hasin T, Altarabsheh SE, McKellar SH, Shah IK, Durham L 3rd, *et al.* Concomitant tricuspid valve repair or replacement during left ventricular assist device implant demonstrates comparable outcomes in the long term. *J Card Surg* 2012;**27**:760–6.	< 50 DT patients
Deo SV, Sharma V, Altarabsheh SE, Hasin T, Dillon J, Shah IK, *et al.* Hepatic and renal function with successful long-term support on a continuous flow left ventricular assist device. *Heart Lung Circ* 2014;**23**:229–33.	< 50 DT patients
Deo SV, Sharma V, Cho YH, Shah IK, Park SJ. De novo aortic insufficiency during long-term support on a left ventricular assist device: a systematic review and meta-analysis. *ASAIO J (Am Soc Artif Intern Organs: 1992)* 2014;**60**:183–8.	< 50 DT patients
Deshmukh A, Anyanwu E, Uriel N, Jeevanandam V, Tung R, Ozcan C. Left atrial structural remodeling with ventricular assist device. Circulation Conference: American Heart Association's. 2016;134.	Do not report DT data
Deshmukh A, Kim G, Moss JD, Nayak HM, Burke M, Jeevanandam V, *et al.* Atrial arrhythmias and clinical outcomes in patients with left ventricular assist devices. *Heart Rhythm* 2016;(1):S588.	Do not report DT data
Diakos N, Taleb I, Pinzon OW, Javan H, Kfoury A, Stehlik J, *et al.* BIUx2 × 2. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S252.	Do not report DT data
Dobbels F, Mauthner O, Milisen K. Frailty in left ventricular assist device destination therapy: putting a new motor in a rickety old car running out of gas? *J Heart Lung Transplant* 2014;**33**:347–9.	Wrong study design
Donahey EE, Polly DM, Vega JD, Lyon M, Butler J, Nguyen D, *et al.* Multidrug-resistant organism infections in patients with left ventricular assist devices. *Tex Heart Inst J* 2015;**42**:522–7.	< 50 DT patients
Dong T, Doshi N, Steinberg R, Nayak A, O'Connell C, Howser J, *et al.* SIPAT B score predicts mortality in both BTT and DT male LVAD patients. *J Card Fail* 2019;**25**(8 Suppl.):S157.	Do not report DT data
Downs EA, Johnston LE, LaPar DJ, Yarboro LT, Kern JA, Kirby JL, *et al.* Impact of preoperative glycemic control on long-term mechanical circulatory support device implantation. *J Heart Lung Transplant* 2016;(1):S377.	Do not report DT data
Drews T, Dandel M, Krabatsch T, Potapov E, Stepanenko A, Hennig E, *et al.* Long-term mechanical circulatory support in 198 patients: largest single-center experience worldwide. *ASAIO J* 2011;**57**:9–16.	Do not report DT data
Drews T, Jurmann M, Michael D, Miralem P, Weng Y, Hetzer R. Differences in pulsatile and non-pulsatile mechanical circulatory support in long-term use. *J Heart Lung Transplant* 2008;**27**:1096–101.	< 50 DT patients
Drews T, Stepanenko A, Dandel M, Buz S, Lehmkuhl HB, Hetzer R. Mechanical circulatory support in patients of advanced age. *Eur J Heart Fail* 2010;**12**:990–4.	Do not report DT data
Drks, Klinik für Herzchirurgie R-KCBNN. Clinical course and prognostic significance of mitral valve insufficiency under LVAD (left ventricular assist device) therapy. 2020.	Do not report DT data
Duran A, Guha A, Bhimaraj A, Trachtenberg B, Park MH, Estep J, *et al.* Outcomes associated with complete versus partial LV unloading in patients with LVAD. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S458.	Do not report DT data
Elkaryoni A, Khan MS, Al Badarin F, Poonia J, Potturi N, Ellakany K, *et al.* An implantable cardioverter defibrillator is not associated with a reduction in mortality in advanced heart failure patients with continuous flow left ventricular assist device: a systematic review and meta-analysis. *Circ Conf* 2018;138.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Elzeneini M, Mahmoud A, Elsayed AH, Mahtta D, Al-Ani M, Aranda J, *et al.* Preoperative bleeding and blood product transfusion association with the preoperative use of aspirin and heparin in left ventricular assist device implantation. *J Card Fail* 2019;**25**(8 Suppl.):S148.	Do not report DT data
Emerson D, Chikwe J, Catarino P, Hassanein M, Deng L, Cantor RS, *et al.* Contemporary left ventricular assist device outcomes in an aging population: an STS INTERMACS analysis. *J Am Coll Cardiol* 2021;**78**(9):883–94.	Do not report DT data
Ensor CR, Paciullo CA, Cahoon WD, Jr, Nolan PE, Jr. Pharmacotherapy for mechanical circulatory support: a comprehensive review. *Ann Pharmacother* 2011;**45**:60–77.	Wrong study design
Evans RW. Costs and insurance coverage associated with permanent mechanical cardiac assist/replacement devices in the United States. *J Card Surg* 2001;**16**:280–93.	Wrong study design
Evans RW. Economic impact of mechanical cardiac assistance. *Prog Cardiovasc Dis* 2000;**43**:81–94.	Wrong study design
Exarchos TP, Rigas G, Goletsis Y, Stefanou K, Jacobs S, Trivella MG, et al. A dynamic Bayesian network approach for time-specific survival probability prediction in patients after ventricular assist device implantation. Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine & Biology Society 2014;2014:3172–5.	Do not report DT data
Fang JC. Rise of the machines–left ventricular assist devices as permanent therapy for advanced heart failure. *N Engl J Med* 2009;**361**:2282–5.	Wrong study design
Felix S, Oerlemans M, Ramjankhan F, Buijsrogge M, Kirkels H, De Jonge N. Further improvement of exercise capacity one year after implantation of a CF-left ventricular assist device. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S129.	Do not report DT data
Felix S, Oerlemans MIF, Asselbergs FW, Van Laake LW, De Jonge N. Predictors of late right heart failure after mechanical circulatory support. *Eur Heart J* 2020;**41**(Suppl. 2):1101.	Do not report DT data
Felix SE, Ramjankhan FZ, De Heer F, De Jonge N, Buijsrogge MP, Suyker WJ. Mid term results of mechanical circulatory support in the Netherlands, a single centre experience from the university medical centre Utrecht (UMCU). *J Heart Lung Transplant* 2016;(1):S332.	Do not report DT data
Felix SEA, Oerlemans MIF, Van Laake LW, Ramjankhan FZ, Buijsrogge MP, Kirkels JH, *et al.* Increasing exercise capacity in the first year after implantation of a CF-left ventricular assist device. *Eur J Heart Fail* 2018;**20**(Suppl. 1):259.	Do not report DT data
Felix SEA, Ramjankhan FZ, De Heer F, Buijsrogge MP, Suyker WJL, Hulstein N, *et al.* Single center long term results of mechanical circulatory support in the Netherlands. *Eur J Heart Fail* 2016;(1):374–5.	Do not report DT data
Feller ED, Sorensen EN, Haddad M, Pierson RN, 3rd, Johnson FL, Brown JM, *et al.* Clinical outcomes are similar in pulsatile and nonpulsatile left ventricular assist device recipients. *Ann Thorac Surg* 2007;**83**:1082–8.	< 50 DT patients
Fendler TJ, Nassif ME, Kennedy KF, Joseph SM, Silvestry SC, Ewald GA, *et al.* Global outcome in patients with left ventricular assist devices. *Am J Cardiol* 2017;**119**:1069–73.	Do not report DT data
Fick A, Tymkew HA, Deters ML, Martin K, Ratermann JD, Reilly A, *et al.* Functional status and discharge location of patients post LVAD surgery in the acute care setting. *Cardiopulm Phys Ther J* 2021;**32**(3):e8.	Do not report DT data
Fine NM, Park SJ, Stulak JM, Topilsky Y, Daly RC, Joyce LD, *et al.* Proximal thoracic aorta dimensions after continuous-flow left ventricular assist device implantation: longitudinal changes and relation to aortic valve insufficiency. *J Heart Lung Transplant* 2016;**35**:423–32.	Wrong outcomes
Fitzpatrick JR, 3rd, Frederick JR, Hsu VM, Kozin ED, O'Hara ML, Howell E, *et al.* Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support. *J Heart Lung Transplant* 2008;**27**:1286–92.	Do not report DT data
Flint KM, Matlock DD, Lindenfeld J, Allen LA. Frailty and the selection of patients for destination therapy left ventricular assist device. *Circ Heart Fail* 2012;5:286–93.	Wrong study design

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Florisson DS, Conte SM, De Bono JA, Newcomb AE. Do patients with the centrifugal flow HeartMate 3 or HeartWare left ventricular assist device have better outcomes compared to those with axial flow HeartMate II? *Interact Cardiovasc Thorac Surg* 2019;**29**:844–51.	< 50 DT patients
Forest SJ, Bello R, Friedmann P, Casazza D, Nucci C, Shin JJ, *et al.* Readmissions after ventricular assist device: etiologies, patterns, and days out of hospital. *Ann Thorac Surg* 2013;**95**:1276–81.	< 50 DT patients
Forni A, Chiominto B, Faggian G. Surgical therapy in end stage heart failure: should we change our vision? *J Heart Lung Transplant* 2016;**35**(4 Suppl.):S278.	< 50 DT patients
Frankfurter C, Molinero M, Vishram-Nielsen JKK, Foroutan F, Mak S, Rao V, *et al.* Predicting the risk of right ventricular failure in patients undergoing left ventricular assist device implantation: a systematic review. *Circ Heart Fail* 2020:CIRCHEARTFAILURE120006994.	Do not report DT data
Friedman JA. Experiences of left ventricular assist device-destination therapy recipients: a systematic review and meta-synthesis. *Heart Lung* 2020.	Wrong study design
Fujino T, Imamura T, Nitta D, Rodgers D, Nguyen A, Chung B, *et al.* Longitudinal trend of tricuspid regurgitation following left ventricular assist device implantation. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S70–1.	Do not report DT data
Fukuhara S, Ikegami H, Polanco AR, Song JJ, Han J, Takeda K, *et al.* Concomitant repair for mild aortic insufficiency and continuous-flow left ventricular assist devices. *Eur J Cardio-Thorac Surg* 2017;**52**:1062–8.	< 50 DT patients
Fukuhara S, Takeda K, Chiuzan C, Han J, Kurlansky PA, Takayama H, *et al.* Concomitant mitral repair and continuous-flow left ventricular assist devices: is it warranted? *J Thorac Cardiovasc Surg* 2017;**154**:1303–12.e4.	< 50 DT patients
Gaffey AC, Chen CW, Chung JJ, Han J, Bermudez CA, Wald J, *et al.* Is there a difference in bleeding after left ventricular assist device implant: centrifugal versus axial? *J Cardiothorac Surg* 2018;**13**:22.	Do not report DT data
Gaffey AC, Chen CW, Han J, Rame JE, Kiernan MS, Chung J, *et al.* Should aggressive implantation of a temporary RVAD be utilized as means of recovery for RV function to allow for long-term left ventricular assist device therapy. Circulation Conference: American Heart Association's. 2016;134.	Do not report DT data
Galand V, Auffret V, Flecher E, Pichard C, Boule S, Vincentelli A, *et al.* Occurrence of early ventricular arrhythmias after left ventricular assist device implantation is the strongest predictor of post-operative mortality: new insight from the assist-Icd study. *Heart Rhythm* 2019;**16**(5 Suppl.):385–6.	Duplicate record
Galand V, Flecher E, Auffret V, Pichard C, Boule S, Vincentelli A, *et al.* Early ventricular arrhythmias after LVAD implantation is the strongest predictor of 30-day post-operative mortality. *JACC Clin Electrophysiol* 2019;**5**:944–54.	Do not report DT data
Galand V, Flecher E, Chabanne C, Lelong B, Goeminne C, Vincentelli A, *et al.* Outcomes of left ventricular assist device implantation in patients with uncommon etiology cardiomyopathy. *Am J Cardiol* 2020;**125**:1421–8.	Do not report DT data
Gallo M, Valadon CL, Trivedi JR, Slaughter MS. Reduced pulsatility during continuous flow left ventricular assist device does not affect kidney function. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S118.	Do not report DT data
Galvao M, Immekus J, Saeed O, Fida N, Browne A, Goldstein DJ, *et al.* An international survey to assess referral thresholds for destination therapy in non-inotrope dependent patients: results of the consensus-DT study. *J Heart Lung Transplant* 2013;(1):S131–2.	Wrong study design
Galvao M, Saeed O, Immekus J, Goldstein DJ, Maybaum S. An international survey to assess referral thresholds for destination therapy in non-inotrope-dependent patients: results of the CONSENSUS-DT study. *J Card Fail* 2014;**20**:492–7.	Wrong study design
Ganga HV, Leung A, Jantz J, Choudhary G, Stabile L, Levine DJ, *et al.* Supervised exercise training versus usual care in ambulatory patients with left ventricular assist devices: a systematic review. *PLOS ONE* 2017;**12**:e0174323.	< 50 DT patients

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Garan AR, Levin AP, Topkara V, Thomas SS, Yuzefpolskaya M, Colombo PC, *et al.* Early post-operative ventricular arrhythmias in patients with continuous-flow left ventricular assist devices. *J Heart Lung Transplant* 2015;**34**:1611–6.	Do not report DT data
Garcia RA, Balakumaran K, Schwab T, Gaznabi S, Dahm J, Peng SL, *et al.* Short and long term mortality in patients with right heart failure after left ventricular assist device placement. *J Card Fail* 2020;**26**(10 Suppl.):S136.	Do not report DT data
Gelijns AC, Richards AF, Williams DL, Oz MC, Oliveira J, Moskowitz AJ. Evolving costs of long-term left ventricular assist device implantation. *Ann Thorac Surg* 1997;**64**:1312–9.	Wrong indication
Gelijns AC, Russo MJ, Hong KN, Brown LD, Ascheim DD, Moskowitz AJ. Dynamics of device innovation: implications for assessing value. *Int J Technol Assess Health Care* 2013;**29**:365–73.	Wrong study design
Genev I, Yost G, Gregory M, Gomez K, Pappas P, Tatooles A, *et al.* Improved nutrition status in patients with advanced heart failure implanted with a left ventricular assist device. *Nutr Clin Pract* 2019;**34**:444–9.	Do not report DT data
Genovese EA, Dew MA, Teuteberg JJ, Simon MA, Bhama JK, Bermudez CA, *et al.* Early adverse events as predictors of 1-year mortality during mechanical circulatory support. *J Heart Lung Transplant* 2010;**29**:981–8.	< 50 DT patients
George I, Xydas S, Topkara VK, Ferdinando C, Barnwell EC, Gableman L, *et al.* Clinical indication for use and outcomes after inhaled nitric oxide therapy. *Ann Thorac Surg* 2006;**82**:2161–9.	Do not report DT data
Gibreal M, Katugaha S, Abdullah K, Stulak J, Cowger JA, Salerno C, *et al.* Bloodstream infection in patients with LVAD and CIED. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S39–40.	Do not report DT data
Goda A, Takayama H, Pak SW, Uriel N, Mancini D, Naka Y, *et al.* Aortic valve procedures at the time of ventricular assist device placement. *Ann Thorac Surg* 2011;**91**:750–4.	< 50 DT patients
Goldenthal I, Hickey KT, Colombo PC, Naka Y, Garan AR, Yuzefpolskaya M, *et al.* Atrial fibrillation is associated with recurrent ventricular arrhythmias after LVAD implant: incidence and impact in a consecutive series. Circulation Conference: American Heart Association Scientific Sessions, AHA. 2019;140.	Do not report DT data
Goldstein DJ, Maybaum S, MacGillivray TE, Moore SA, Bogaev R, Farrar DJ, *et al.* Young patients with nonischemic cardiomyopathy have higher likelihood of left ventricular recovery during left ventricular assist device support. *J Card Fail* 2012;**18**:392–5.	Do not report DT data
Gosev I, Kiernan MS, Eckman P, Soleimani B, Kilic A, Uriel N, *et al.* Long-term survival in patients receiving a continuous-flow left ventricular assist device. *Ann Thorac Surg* 2018;**105**:696–701.	Do not report DT data
Grady KL, Andrei AC, Xu Y, Petty MG, Kao A, Hsich EM, *et al.* Change in caregiver burden from before to early after surgery: findings from the sustaining quality of life of the aged: transplant or mechanical support (SUSTAIN-IT) study. Circulation Conference: American Heart Association Scientific Sessions, AHA. 2019;140.	Do not report DT data
Grady KL, Jackson K, Wortman K, Buono S, Beiser D, Murks C, *et al.* Self-reported physical health with a left ventricular assist device: findings from the mechanical circulatory support measures of adjustment and quality of life (MCS A-QOL) study. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S437–8.	Do not report DT data
Grady KL, Meyer PM, Mattea A, Dressler D, Ormaza S, White-Williams C, *et al.* Change in quality of life from before to after discharge following left ventricular assist device implantation. *J Heart Lung Transplant* 2003;**22**:322–33.	Do not report DT data
Grady KL, Okwuosa I, Petty M, Adam H, Pollan L, Andrei AC, *et al.* Sustaining quality of life of the aged: transplant or mechanical support: baseline caregiver quality of life. Circulation Conference. 2018;138.	Do not report DT data
Grady KL, Sherri W, Naftel DC, Myers S, Gelijins A, Moskowitz A, *et al.* Age and gender differences and factors related to change in health-related quality of life from before to 6 months after left ventricular assist device implantation: findings from interagency registry for mechanically assisted circulatory support. *J Heart Lung Transplant* 2016;**35**:777–88.	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Grady KL, Xu Y, Andrei A, Warzecha A, Kao A, Hsich EM, *et al.* Both patient and caregiver factors are related to patient health-related quality of life before surgery. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S92–3.	Do not report DT data
Grinstein J, Kadakkal A, Rodrigo M, Hofmeyer M, Mohammed S, Butt N, *et al.* Early renal recovery after left ventricular assist device implantation is associated with improved clinical outcomes in patients with kidney disease at baseline. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S359.	Do not report DT data
Grupper A, Park SJ, Pereira NL, Schettle SD, Gerber Y, Topilsky Y, *et al.* Role of ventricular assist therapy for patients with heart failure and restrictive physiology: Improving outcomes for a lethal disease. *J Heart Lung Transplant* 2015;**34**:1042–9.	< 50 DT patients
Guenther SP, Fong R, Abovwe N, Shad R, MacArthur JW, Teuteberg J, *et al.* A decade of ***single center HeartWare™ HVAD™ Experience. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S339.	Do not report DT data
Guidi JL, Troutman G, Birati EY, Wald J, Fox A, Ortega-Legaspi J, *et al.* Survival in intermacs 1 & 2 patients after LVAD therapy: does chronicity of heart failure matter? *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S128.	Do not report DT data
Gulati G, Grandin EW, Kennedy KF, Cabezas F, DeNofrio D, Kociol R, *et al.* Pre-implant phosphodiesterase-5 inhibitor use is associated with higher rates of severe early right heart failure after IVAD implantation: an INTERMACS analysis. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S195.	Do not report DT data
Gunasingam N, Williams D. Bleeding in patients with left ventricular assist devices: The experience of a single centre. *J Gastroenterol Hepatol (Australia)* 2016;**31**(Suppl. 2):34.	Do not report DT data
Gupta S, Roy S, Cogswell R, Thenappan T, Liao K, John R. Readmission within 30 days after left ventricular assist device implantation is associated with increased long-term mortality. *J Heart Lung Transplant* 2016;(1):S259–60.	Do not report DT data
Gupta S, Roy S, John R, Cogswell R. Sodium nadir during left ventricular assist device implantation is not associated with increased mortality. *J Heart Lung Transplant* 2016;(1):S339–40.	Do not report DT data
Halkar M, Nowacki AS, Kendall K, Efeovbokhan N, Gorodeski EZ, Moazami N, *et al.* Utility of the psychosocial assessment of candidates for transplantation in patients undergoing continuous-flow left ventricular assist device implantation. *Prog Transplant* 2018;**28**:220–5.	Do not report DT data
Hamdan R, Fakih S, Mohammad M, Charif F, Abdallah H, Safa S, *et al.* The Lebanese left ventricular assist device experience, a success story despite the odds. *J Cardiothorac Surg* 2020;15:192.	< 50 DT patients
Hamed S, Schmack B, Mueller F, Ehlermann P, Hittmann D, Ruhparwar A, *et al.* Implementation of an intensified outpatient follow-up protocol improves outcomes in patients with ventricular assist devices. *Clin Res Cardiol* 2019;**108**:1197–207.	< 50 DT patients
Han J, Mauro CM, Kurlansky PA, Fukuhara S, Yuzefpolskaya M, Topkara VK, *et al.* Impact of obesity on readmission in patients with left ventricular assist devices. *Ann Thorac Surg* 2018;**105**:1192–8.	Do not report DT data
Han J, Pinsino A, Royzman E, Gaudig A, Mabasa M, Takayama H, *et al.* Predictors of postoperative vasoplegia in patients receiving left ventricular assist devices. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S127–8.	Do not report DT data
Han J, Takayama H, Kurlansky PA, Garan AR, Yuzefpolskaya M, Topkara VK, *et al.* Outcomes of multiple concomitant valve procedures in patients receiving continuous-flow left ventricular assist device. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S30.	Do not report DT data
Han J, Takeda K, Takayama H, Kurlansky PA, Mauro CM, Colombo PC, *et al.* Durability and clinical impact of tricuspid valve procedures in patients receiving a continuous-flow left ventricular assist device. *J Thorac Cardiovasc Surg* 2016;**151**:520–7.e1.	Do not report DT data
Han JJ, Chung J, Chen CW, Gaffey AC, Sotolongo A, Justice C, *et al.* Different clinical course and complications in Interagency Registry for Mechanically Assisted Circulatory Support 1 (INTERMACS) patients managed with or without extracorporeal membrane oxygenation. *ASAIO J* 2018;**64**:318–22.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Han JJ, Iyengar A, Patrick WL, Goldenring J, Molina M, Ameer A, *et al.* Impact of socioeconomic status on outcomes post-ventricular assist device implantation. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S128–9.	Do not report DT data
Han JJ, Sooppan R, Johnson AP, Chen CW, Gaffey AC, Phillips EC, *et al.* Higher body mass index increases risk of HeartMate II pump thrombosis but does not adversely affect long-term survival. *Circ J* 2017;**81**:213–9.	Do not report DT data
Hanff TC, Mazurek JA, Grandin EW, Padegimas A, Howard J, Forde-McLean R, *et al.* The anemic stress index – a novel index that predicts short and long term mortality of patients on continuous flow ventricular assist devices. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S173–4.	Do not report DT data
Hashim T, Sanam K, Revilla-Martinez M, Morgan CJ, Tallaj JA, Pamboukian SV, *et al.* Clinical characteristics and outcomes of intravenous inotropic therapy in advanced heart failure. *Circ Heart Fail* 2015;**8**:880–6.	Wrong study design
Hasin T, Deo S, Maleszewski JJ, Topilsky Y, Edwards BS, Pereira NL, *et al.* The role of medical management for acute intravascular hemolysis in patients supported on axial flow LVAD. *ASAIO J* 2014;**60**:9–14.	Do not report DT data
Hasin T, Grupper A, Dillon JJ, Maleszewski JJ, Li Z, Topilsky Y, *et al.* Early gains in renal function following implantation of HeartMate II left ventricular assist devices may not persist to one year. *ASAIO J* 2017;**63**:401–7.	< 50 DT patients
Hasin T, Topilsky Y, Schirger JA, Li Z, Zhao Y, Boilson BA, *et al.* Changes in renal function after implantation of continuous-flow left ventricular assist devices. *J Am Coll Cardiol* 2012;**59**:26–36.	< 50 DT patients
Heaton J, Li M. Adverse events of third generation left ventricular assist devices: insights from the manufacturer and user facility device experience (Maude) database. *J Am Coll Cardiol* 2021;**77**(18 Suppl. 1):645.	Do not report DT data
Heilmann C, Kuijpers N, Beyersdorf F, Trummer G, Berchtold-Herz M, Zeh W, *et al.* Does listing for heart transplant for longer than 30 days before ventricular assist device implantation influence utilization of psychotherapeutic support and outcome? *Eur J Cardio-Thorac Surg* 2012;**41**:1371–6; discussion 1376.	< 50 DT patients
Hernandez AF, Shea AM, Milano CA, Rogers JG, Hammill BG, O'Connor CM, *et al.* Long-term outcomes and costs of ventricular assist devices among Medicare beneficiaries. *JAMA* 2008;**300**:2398–406.	Wrong patient population
Hernandez-Montfort JA, Ton VK, Xie R, Fisher A, Meyns B, Nakatani T, *et al.* Longitudinal impact of temporary mechanical circulatory support on durable left ventricular assist device outcomes: an IMACS registry analysis. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S33.	Do not report DT data
Hetzer R, Kaufmann MF, Potapov E, Krabatsch T, Delmo Walter EM. Rotary blood pumps as long-term mechanical circulatory support: a review of a 15-year Berlin experience. *Semin Thorac Cardiovasc Surg* 2016;**28**:12–23.	Do not report DT data
Hickey K, Garan H, Mancini DM, Colombo PC, Sciacca RR, Abrams MP, *et al.* Atrial fibrillation in patients with left ventricular assist devices. *Heart Rhythm* 2016;(1):S220.	Do not report DT data
Hickey KT, Garan H, Mancini DM, Colombo PC, Naka Y, Sciacca RR, *et al.* Atrial fibrillation in patients with left ventricular assist devices: incidence, predictors, and clinical outcomes. *JACC Clin Electrophysiol* 2016;**2**:793–8.	Do not report DT data
Hickey KT, Reading M, Flannery MA, Te-Frey RT, Pineda MT, Ross KA, *et al.* Changes in the clinical characteristics of LVAD patients. *ASAIO J* 2018;**64**(Suppl. 1):103.	Do not report DT data
Hirji SA, Sabatino ME, Minhas AMK, Okoh AK, Fudim M, Vaduganathan M, *et al.* Contemporary nationwide heart transplantation and left ventricular assist device outcomes in patients with histories of bariatric surgery. *J Card Fail* 2021.	Do not report DT data
Holley CT, Fitzpatrick M, Roy SS, Alraies MC, Cogswell R, Souslian L, *et al.* Aortic insufficiency in continuous-flow left ventricular assist device support patients is common but does not impact long-term mortality. *J Heart Lung Transplant* 2017;**36**:91–6.	< 50 DT patients

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Holman WL, Naftel DC, Eckert CE, Kormos RL, Goldstein DJ, Kirklin JK. Durability of left ventricular assist devices: Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) 2006 to 2011. *J Thorac Cardiovasc Surg* 2013;**146**:437–41.e1.	Do not report DT data
Holmberg E, Ahn H, Peterzen B. More than 20 years' experience of left ventricular assist device implantation at a non-transplant Centre. *Scand Cardiovasc J* 2017;**51**:293–8.	< 50 DT patients
Holtz JE, Potter AN, Macpherson NC, Nguyen D, Kormos RL, Teuteberg JJ, *et al.* Worsening renal function after ventricular assist device placement is associated with twice the risk of death over 3 years. *J Heart Lung Transplant* 2016;(1):S263.	Do not report DT data
Hong Y, Dufendach K, Wang Y, Thoma F, Kilic A. Impact of hepatic steatosis on outcomes after left ventricular assist device implantation. *J Card Surg* 2021;**36**:2277–83.	Do not report DT data
Horsley-Silva JL, Noelting J, Love WT, Zawadowski G, Octavio P, Hardaway B, *et al.* Gastrointestinal bleeding in patients with left ventricular assist devices – a single center retrospective cohort study. *Gastrointest Endosc* 2016;(1):AB470.	Do not report DT data
Horton SC, Khodaverdian R, Chatelain P, McIntosh ML, Horne BD, Muhlestein JB, *et al.* Left ventricular assist device malfunction: an approach to diagnosis by echocardiography. *J Am Coll Cardiol* 2005;**45**:1435–40.	< 50 DT patients
Hulman M, Ondrusek M, de By T, Antonides CFJ, Artemiou P, Hudec V, *et al.* Single centre 12 year experience with durable mechanical circulatory support: comparison with the EUROMACS registry. *Bratisl Lek Listy* 2021;**122**:371–8.	Do not report DT data
Hutchinson OZ, Oz MC, Ascherman JA. The use of muscle flaps to treat left ventricular assist device infections. *Plast Reconstr Surg* 2001;**107**:364–73.	Do not report DT data
Ibrahim M, Cortesi C, Croix GS, Chaparro S. Renal dysfunction and outcomes after left ventricular assist device: a systematic review. *J Card Fail* 2019;**25**(8 Suppl.):S160–1.	Do not report DT data
Idris A, Al-Khadra Y, Kabach A, Darmoch F, Moussa Pacha H, Soud M, *et al.* The impact of peripheral arterial disease on advanced heart failure patients undergoing left ventricular assist device surgery. *Eur Heart J* 2018;**39**(Suppl. 1):386.	Do not report DT data
Imamura T, Kinugawa K, Nitta D, Inaba T, Maki H, Hatano M, *et al.* Readmission due to driveline infection can be predicted by new score by using serum albumin and body mass index during long-term left ventricular assist device support. *J Artif Organs* 2015;**18**:120–7.	< 50 DT patients
Imamura T, Kinugawa K, Shiga T, Endo M, Kato N, Inaba T, *et al.* Preoperative levels of bilirubin or creatinine adjusted by age can predict their reversibility after implantation of left ventricular assist device. *Circ J* 2013;**77**:96–104.	Do not report DT data
Ivak P, Pirk J, Tucanova Z, Maly J, Szarszoi O, Melenovsky V, *et al.* A single-center experience with magnetically levitated left ventricular assist device for treatment of end-stage heart failure. *Clin Exp Surg* 2020;**8**:7–16.	Do not report DT data
Ivak P, Pitha J, Wohlfahrt P, Kralova Lesna I, Stavek P, Dorazilova Z, *et al.* Endothelial dysfunction expressed as endothelial microparticles in patients with end-stage heart failure. *Physiol Res* 2014;**63**(Suppl. 3):S369–73.	< 50 DT patients
Iyengar A, Kwon OJ, Tamrat M, Salimbangon A, Satou N, Benharash P, *et al.* The in-hospital cost of ventricular assist device therapy: implications for patient selection. *ASAIO J* 2017;**63**:725–30.	Wrong indication
Izzy S, Renault S, Rubin D, Vaitkevicius H, Smallwood J, Givertz MM, *et al.* Neurovascular complications during long-term left ventricular assist device (LVAD) support: Single center experience. Stroke Conference: American Heart Association/American Stroke Association. 2016;47.	Do not report DT data
Izzy S, Rubin DB, Ahmed FS, Akbik F, Renault S, Sylvester KW, *et al.* Cerebrovascular accidents during mechanical circulatory support: new predictors of ischemic and hemorrhagic strokes and outcome. *Stroke* 2018;**49**:1197–203.	Do not report DT data
Jacobs S, Verhoeven J, Geens J, Rega F, Meyns B. One-year cost comparison between cardiac transplantation and LVAD therapy. *Int J Artif Organs* 2011;**34**(8):608.	Wrong patient population
Jacobs S, Verhoeven J, Meyns B. LVAD therapy becomes less expensive than transplantation after 29 months. *Artif Organs* 2012;**36**(5):A37.	Wrong patient population

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Jaiswal A, Truby LK, Chichra A, Jain R, Myers L, Patel N, *et al.* Impact of obesity on ventricular assist device outcomes. *J Card Fail* 2020;**26**:287–97.	Do not report DT data
Jaiswal A, Truby LK, Chichra A, Jain R, Myers L, Patel N, *et al.* Impact of obesity on ventricular assist device outcomes: obesity and VAD outcomes. *J Card Fail* 2020;**26**:287–97.	Do not report DT data
Jaworska E, Wlodarczyk A, Budasz-Swiderska M. Clinical and cost-effectiveness of third-generation, implantable left ventricular assist devices for people with end-stage heart failure: a systematic review. *Value Health* 2012;**15**(7):A345.	Wrong indication
Jedeon Z, Cogswell R, Schultz J, John R, Roukoz H. Beta blocker and renin-angiotensin system inhibitors are associated with decreased mortality in patients with left ventricular assist devices. Circulation Conference: American Heart Association Scientific Sessions, AHA. 2019;140.	Do not report DT data
Jennings DL, Wagner JL, To L, Nemerovski CW, Kalus JS, Morgan JA, *et al.* Epidemiology and outcomes associated with anemia during long-term support with continuous-flow left ventricular assist devices. *J Card Fail* 2014;**20**:387–91.	Wrong outcomes
John F, Sembrano R, Roy S, Gupta S, Nayak R, Plack D, *et al.* Pre-operative predictors for admission to a rehabilitation facility after LVAD implantation and its impact on long term survival. *J Heart Lung Transplant* 2016;(1):S165.	< 50 DT patients
John R, Kamdar F, Eckman P, Colvin-Adams M, Boyle A, Shumway S, *et al.* Lessons learned from experience with over 100 consecutive HeartMate II left ventricular assist devices. *Ann Thorac Surg* 2011;**92**:1593–9; discussion 1599.	< 50 DT patients
John R, Naka Y, Park SJ, Sai-Sudhakar C, Salerno C, Sundareswaran KS, *et al.* Impact of concurrent surgical valve procedures in patients receiving continuous-flow devices. *J Thorac Cardiovasc Surg* 2014;**147**:581–9; discussion 589.	Do not report DT data
Johnson BV, Rao S, Kurcik KL, Mazurek JA, Tanna MS, Atluri P, *et al.* Aortic valve thickening as a novel risk factor for development of aortic incompetence after left ventricular assist device implantation. *J Card Fail* 2019;**25**(8 Suppl.):S161.	Do not report DT data
Johnson MR. The benefits and risks of left ventricular assist device implantation; where is the point of clinical equipoise? *Cardiology (Switzerland)* 2016;**134**(Suppl. 1):284.	Do not report DT data
Jonida Bejko J, Bottio T, Carrozzini M, Comisso M, Toto F, Tarzia V, *et al.* Propensity matched comparison of two different continuous-flow left ventricular assist devices. A matter of device? *Eur J Heart Fail* 2017;**19**(Suppl. 1):114.	Do not report DT data
Jorde U, Siddiqi N, Luke A, Sims DB, Saeed O, Patel SR, *et al.* Effect of a multifaceted team management approach on survival and stroke rates in heartmate 2 recipients. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S423.	Do not report DT data
Jorde UP, Shah AM, Sims DB, Madan S, Siddiqi N, Luke A, *et al.* Continuous-flow left ventricular assist device survival improves with multidisciplinary approach. *Ann Thorac Surg* 2019;**108**:508–16.	Do not report DT data
Jorde UP, Uriel N, Nahumi N, Bejar D, Gonzalez-Costello J, Thomas SS, *et al.* Prevalence, significance, and management of aortic insufficiency in continuous flow left ventricular assist device recipients. *Circ Heart Fail* 2014;**7**:310–9.	Do not report DT data
Joseph SM, Hall SA, Lima B, Robertson JO, Naftel DC, Myers S, *et al.* Does inotrope dependence make a difference in outcome in patients receiving left ventricular assist device? comparison between intermacs profiles 3 vs 4/5 from the intermacs registry. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S139–40.	Do not report DT data
Joshi Y, Borie M, Aissaoui N, Bel A, Latremoullie C, Jouan J. Experience with true percutaneous veno-pulmonary extracorporeal membrane oxygenation as right ventricular temporary support following left ventricular assist device insertion. *Artif Organs* 2020;**44**(3):E65–6.	Do not report DT data
Jprn U, Hokkaido University Hospital N, Osaka University Hospital Tokyo University H. A multicenter prospective study on prediction of right heart failure and prognosis in patients with severe heart failure after left ventricular assist device implantation. Japan: National Institute of Public Health; 2015.	Do not report DT data

continued

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Jprn U, Osaka University hospital Y. Clinical research of the left ventricular assist device with post-auricular connector. Japan: National Institute of Public Health; 2017.	< 50 DT patients
Kalathiya RJ, Houston BA, Chaisson JM, Grimm JC, Stevens GR, Sciortino CM, *et al.* Cardiac index declines during long-term left ventricular device support. *Artif Organs* 2016;**40**:1105–12.	< 50 DT patients
Kalavrouziotis D, Tong MZ, Starling RC, Massiello A, Soltesz E, Smedira NG, *et al.* Percutaneous lead dysfunction in the HeartMate II left ventricular assist device. *Ann Thorac Surg* 2014; **97**:1373–8.	Wrong outcomes
Kalinowski M, Kothari S, Kobeszko M, Josephson G, Cotts W, Pauwaa S, *et al.* Investigation of gastrointestinal bleeding among left ventricular assist device recipients. *Am J Gastroenterol* 2019;**114**(Suppl.):S338–9.	Do not report DT data
Kalinowski M, Kothari S, Kobeszko M, Josephson G, Cotts W, Pauwaa S, *et al.* Investigation of repeat gastrointestinal bleeding among continuous flow left ventricular assist device recipients. *Gastroenterology* 2020;**158**(6 Suppl. 1):S-248.	Do not report DT data
Kalinowski M, Kothari S, Kobeszko M, Josephson G, Cotts W, Pauwaa S, *et al.* A comparison of characteristics in left ventricular assist device patients with and without gastrointestinal bleeding. *J Investig Med* 2019;**67**(5):903–4.	Do not report DT data
Kalinowski M, Kothari S, Kobeszko M, Josephson G, Cotts W, Pauwaa S, *et al.* A comparison of characteristics in left ventricular assist device patients with and without gastrointestinal bleeding. *Gastroenterology* 2019;**156**(6 Suppl. 1):S–253.	Do not report DT data
Kalinowski M, Kothari S, Kobeszko M, Josephson G, Cotts W, Pauwaa S, *et al.* An institutional review of gastrointestinal bleeding among 563 continuous flow left ventricular assist device recipients. *Gastrointest Endosc* 2020;**91**:AB605–6.	Do not report DT data
Kalya AV, Tector AJ, Crouch JD, Downey FX, McDonald ML, Anderson AJ, *et al.* Comparison of Novacor and HeartMate vented electric left ventricular assist devices in a single institution. *J Heart Lung Transplant* 2005;**24**:1973–5.	Do not report DT data
Kanwar M, Khoo C, Lohmueller L, Bailey S, Murali S, Antaki J. Predicting post LVAD acute severe right heart failure using Bayesian analysis. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S357.	Do not report DT data
Kanwar MK, Lohmueller LC, Teuteberg J, Kormos RL, Rogers JG, Benza RL, *et al.* Risk assessment in patients with a left ventricular assist device across INTERMACS profiles using Bayesian analysis. *ASAIO J* 2019;**65**:436–41.	Wrong outcomes
Kapelios CJ, Lund LH, Selzman CH, Meyers SL, Koliopoulou A, Stehlik J, *et al.* Early and late right heart failure following LVAD implantation: epidemiology, natural history and outcomes. An analysis of the STS INTERMACS database. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S20.	Do not report DT data
Karen Booth K, Urban M, Robinson-Smith N, Woods A, Wrightson N, Scheuler S, *et al.* Right heart failure post LVAD therapy-timing of RVAD placement predicts survival. *Eur J Heart Fail* 2016;(1):480.	Do not report DT data
Karmpalioti M, Soyama Y, Huntjens P, Raymer D, LaRue S, Itoh A, *et al.* Clinical and echocardiographic prognostic markers of right ventricular failure after left ventricular assist device. *J Am Coll Cardiol* 2020;**75**(11):991.	Do not report DT data
Kassi M, Eshelbrenner C, Amione-Guerra J, Estep J. Utility of echocardiography in defining inflow cannula malposition in left ventricular assist device and the association with adverse outcome. *J Heart Lung Transplant* 2016;(1):S97.	Do not report DT data
Kato TS, Schulze PC, Yang J, Chan E, Shahzad K, Takayama H, *et al.* Pre-operative and post-operative risk factors associated with neurologic complications in patients with advanced heart failure supported by a left ventricular assist device. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 2012;**31**:1–8.	Do not report DT data
Katz JN, Adamson RM, John R, Tatooles A, Sundareswaran K, Kallel F, *et al.* Safety of reduced anti-thrombotic strategies in HeartMate II patients: a one-year analysis of the US-TRACE study. *J Heart Lung Transplant* 2015;**34**:1542–8.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Katz JN, Jensen BC, Chang PP, Myers SL, Pagani FD, Kirklin JK. A multicenter analysis of clinical hemolysis in patients supported with durable, long-term left ventricular assist device therapy. *J Heart Lung Transplant* 2015;**34**:701–9.	Do not report DT data
Kawabori M, Kurihara C, Critsinelis A, Chou BP, Zhang Q, Kaku Y, *et al.* Effect of cardiac arrest with aortic cross-clamping during left ventricular assist device implantation. *Interact Cardiovasc Thorac Surg* 2020;**30**:47–53.	Do not report DT data
Kawabori M, Kurihara C, Critsinelis AC, Sugiura T, Kaku Y, Civitello AB, *et al.* Gastrointestinal bleeding after HeartMate II or HVAD implantation: incidence, location, etiology, and effect on survival. *ASAIO J* 2020;**66**:283–90.	Do not report DT data
Kawabori M, Kurihara C, Sugiura T, Civitello AB, Cohn WE, Fraizer OH, *et al.* Effect of preoperative small left ventricle on patients with chronic heart failure undergoing implantation of long-term continuous flow ventricular assist devices: comparative analysis of heartmate II and heartware devices. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S340–1.	Do not report DT data
Kawabori M, Kurihara C, Sugiura T, Cohn WE, Civitello AB, Frazier OH, *et al.* Continuous-flow left ventricular assist device implantation in patients with a small left ventricle. *Ann Thorac Surg* 2018;**105**:799–806.	Do not report DT data
Kawabori M, Kurihara C, Sugiura T, Delgado MR, Simpson L, Nair AP, *et al.* Effect of aortic cross-clamping during left ventricular assist device implantation: a single institutional 13-year experience over 500 implantations. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S481.	Do not report DT data
Kawabori M, Soffer J, Mastorianni M, Zhan Y, Warner KG, Rastegar H, *et al.* The effect of postoperative vasoplegia to the survival of LVAD recipients. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S360.	Do not report DT data
Kervan U, Kocabeyoglu SS, Aygun E, Demirkan B, Sert D, Akin Y, *et al.* Is tricuspid annular plane systolic excursion (TAPSE) predictor for out patients with LVAD right ventricular failure in LVAD patients with preoperative low value TAPSE on mild-term follow-up. *Transplantation* 2018;**102**(7 Suppl. 1):S836.	Do not report DT data
Khan A, Fan H, Sparrow C, Raymer D, Nassif M, Ewald G, *et al.* Cancer in patients with left ventricular assist devices. *J Card Fail* 2016;**22**(Suppl. 8):S126.	Do not report DT data
Khan MS, Yuzefpolskaya M, Memon MM, Usman MS, Garan AR, Demmer RT, *et al.* Outcomes associated with obesity in patients undergoing left ventricular assist device implantation: a meta-analysis. *Circ Conf* 2018;138.	Do not report DT data
Khan MS, Yuzefpolskaya M, Memon MM, Usman MS, Yamani N, Garan AR, *et al.* Outcomes associated with obesity in patients undergoing left ventricular assist device implantation: a systematic review and meta-analysis. *ASAIO J* 2020;**66**:401–8.	Do not report DT data
Khazanie P, Hammill BG, Patel CB, Eapen ZJ, Peterson ED, Rogers JG, *et al.* Trends in the use and outcomes of ventricular assist devices among Medicare beneficiaries, 2006 through 2011. *J Am Coll Cardiol* 2014;**63**:1395–404.	Wrong indication
Kiernan MS, Sundareswaran KS, Pham DT, Kapur NK, Pereira NL, Strueber M, *et al.* Preoperative determinants of quality of life and functional capacity response to left ventricular assist device therapy. *J Card Fail* 2016;**22**:797–805.	Do not report DT data
Kilic A, Katz JN, Joseph SM, Brisco-Bacik MA, Uriel N, Lima B, *et al.* Changes in pulmonary artery pressure before and after left ventricular assist device implantation in patients utilizing remote haemodynamic monitoring. *ESC Heart Fail* 2019;**6**:138–45.	Do not report DT data
Kilic A, Pagani FD, Likosky DS, Seese LM, Althouse AD, Kormos RL. Identifying temporal relationships between adverse events following implantation of durable left ventricular assist devices. *Circ Conf* 2018;138.	Do not report DT data
Kilic A, Phillips G, Chimanji N, Sai-Sudhakar CB, Hasan A, Higgins RSD, *et al.* Cost comparison between heart transplantation and left ventricular assist device implantation. *J Card Fail* 2014;(1):S84.	Wrong patient population

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Kilic A, Sultan I, Yuh DD, Shah AS, Baumgartner WA, Cameron DE, *et al.* Ventricular assist device implantation in the elderly: nationwide outcomes in the United States. *J Card Surg* 2013;**28**:183–9.	Wrong indication
Kim M, Lamba HK, Chou B, Civitello AB, Delgado RM, Simpson L, *et al.* Outcomes and predictors of postoperative atrial fibrillation in patients with left ventricular assist devices. Stroke Conference: American Heart Association/American Stroke Association. 2019;50.	Do not report DT data
Kimura M, Nawata K, Kinoshita O, Yamauchi H, Itoda Y, Imamura T, *et al.* Cerebrovascular accident rate is different between centrifugal and axial-flow pumps, but survival and driveline infection rates are similar. *Transplant Proc* 2017;**49**:121–4.	Do not report DT data
Kitahara H, Najjar S, Ahmed S, Lam PH, Kadakkal A, Mohammed S, *et al.* One-year survival rate after thoracotomy for left ventricular assist device implantation compared with sternotomy. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S440-S1.	Do not report DT data
Kocabeyoglu S, Pac M, Kervan U, Karahan M, Aygun E, Beyazal O, *et al.* Preoperative patient optimization using low dose levosimendan improves outcomes of patients after left ventricular assist device implantation. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S484-S5.	Do not report DT data
Kociol RD. Time for MADIT-VAD?: ICDs among LVAD patients. *JACC Heart Fail* 2016;**4**:780–2.	Wrong study design
Koratala A, Olaoye OA, Kazory A. AKI and renal replacement therapy after implantation of left ventricular assist device. *J Am Soc Nephrol* 2017;**28**:975.	Wrong study design
Kormos RL, Cowger J, Pagani FD, Teuteberg JJ, Goldstein DJ, Jacobs JP, *et al.* The society of thoracic surgeons intermacs database annual report: evolving indications, outcomes, and scientific partnerships. *Ann Thorac Surg* 2019;**107**:341–53.	Duplicate record
Kugler C, Malehsa D, Schrader E, Tegtbur U, Guetzlaff E, Haverich A, *et al.* A multi-modal intervention in management of left ventricular assist device outpatients: dietary counselling, controlled exercise and psychosocial support. *Eur J Cardio-Thorac Surg* 2012;**42**:1026–32.	Do not report DT data
Kumar A, Shivamurthy P, Gluck J, Kluger J. Single center experience of ventricular arrhythmias in left ventricular assist device patients. Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC. 2018;71.	Do not report DT data
Kumar S, Rivas-Lasarte M, Rashid SM, Scatola A, Rochlani Y, Murthy S, *et al.* External validation and comparison of the EUROMACS and right ventricular failure risk score for right ventricular failure prediction after left ventricular assist device. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S38.	Do not report DT data
Kurihara C, Cohn WE, Kawabori M, Sugiura T, Civitello AB, Morgan JA. Long-term continuous-flow left ventricular assist device support after left ventricular outflow tract closure. *ASAIO J* 2019;**65**:558–64.	Do not report DT data
Kurihara C, Critsinelis A, Kawabori M, Sugiura T, Civitello AB, Morgan JA. Effect of preoperative atrial fibrillation on patients with chronic heart failure who undergo long-term continuous-flow LVAD implantation. *ASAIO J* 2018;**64**:594–600.	Do not report DT data
Kurihara C, Critsinelis AC, Kawabori M, Sugiura T, Loor G, Civitello AB, *et al.* Frequency and consequences of right-sided heart failure after continuous-flow left ventricular assist device implantation. *Am J Cardiol* 2018;**121**:336–42.	Do not report DT data
Kurihara C, Kawabori M, Critsinelis A, Sugiura T, Civitello AB, Simpson L, *et al.* Incidence and impact of severe LVAD-related infections requiring surgical treatment in obesity patients on long-term heartmate II and heartware support. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S361–2.	Do not report DT data
Kurihara C, Kawabori M, Sugiura T, Critsinelis AC, Wang S, Cohn WE, *et al.* Bridging to a long-term ventricular assist device with short-term mechanical circulatory support. *Artif Organs* 2018;**42**:589–96.	Do not report DT data
Kyo S, Nishimura T. Destination therapy by implantable LVAD: agenda for introduction of DT in Japan. *J Card Fail* 2016;**22**(9 Suppl. 1):S158.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Kyvernitakis A, Pappas O, Farmakiotis D, Mahale P, Horn E, Murali S, *et al.* Predictors and clinical implications of bloodstream infections in continuous flow left ventricular assist device recipients: a single institutional experience of 212 patients. *Open Forum Infect Dis* 2017;**4**(Suppl. 1):S548–9.	Do not report DT data
LaBuhn C, Uriel N, Sayer G, Kim G, Kalantari S, Raikhelkar J, *et al.* Surgical and nursing management in the care of patients post LVAD implant without the use of blood products. *ASAIO J* 2018;**64**(Suppl. 1):113.	< 50 DT patients
LaBuhn CJ, Jeevanandam V, Rodgers D, Ota T, Sayer G, Kim G, *et al.* Life during long term LVAD support. *J Heart Lung Transplant*. 2018;**37**(4 Suppl. 1):S476.	Do not report DT data
Lagrue S, Roussoulieres A, Dewachter C, Rimouche A, Cullus P, Luc Vachiery J. Pulmonary hypertension does not influence outcome following implantation of a left-ventricular assist device. *Acta Cardiol* 2019;**74**(Suppl. 1):24–5.	Do not report DT data
Lahpor J, Khaghani A, Hetzer R, Pavie A, Friedrich I, Sander K, *et al.* European results with a continuous-flow ventricular assist device for advanced heart-failure patients. *Eur J Cardio-Thorac Surg* 2010;**37**:357–61.	Do not report DT data
Lai GYY, Kesavabhotla K, Potts M, Jahromi B. Outcomes and management of intracranial hemorrhage (ICH) in patients with ventricular assist devices (VAD) Louise Eisenhardt Travel Scholarship. *J Neurosurg* 2018;**128**(4):44.	Do not report DT data
Lamba HK, Kim M, Hart L, Chou B, Rao C, Chatterjee S, *et al.* Different risk factors for ischemic and hemorrhagic stroke on continuous flow left ventricular assist device support. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S171–2.	Do not report DT data
Lampropulos JF, Kim N, Wang Y, Desai MM, Barreto-Filho JAS, Dodson JA, *et al.* Trends in left ventricular assist device use and outcomes among Medicare beneficiaries, 2004–2011. *Open Heart* 2014;1(1) (no pagination).	Wrong patient population
Lampropulos JF, Kim N, Wang Y, Krumholz HM. Trends in 1-year hospitalizations and costs from 2004 to 2010 among Medicare fee-for-service beneficiaries with LVADs. Circulation: Cardiovascular Quality and Outcomes Conference: American Heart Association's Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke. 2013;6.	Wrong patient population
Lander BS, Patel K, Blackstone EH, Nordseth T, Starling RC, Gorodeski EZ. Post-acute care trajectories in the first year following hospital discharge after left ventricular assist device implantation. *J Am Med Dir Assoc* 2016;**17**:908–12.	Do not report DT data
Lander MM, Kunz N, Dunn E, Althouse AD, Lockard K, Shullo MA, *et al.* Substantial reduction in driveline infection rates with the modification of driveline dressing protocol. *J Card Fail* 2018;**24**:746–52.	Do not report DT data
Landis ZC, Soleimani B, Stephenson ER, El-Banayosy A, Pae WE. Severity of end-organ damage as a predictor of outcomes after implantation of left ventricular assist device. *ASAIO J* 2015;**61**:127–32.	< 50 DT patients
Lei L, Mansoor E, Cooper GS, Wong RC. Epidemiology and risk factors of upper gastrointestinal bleeding after ventricular assist devices implantation in the United States. *Gastroenterology* 2018;**154**(6 Suppl. 1):S-698.	Do not report DT data
Lenartova K, Vila P, Williamson S, Moravcova S, Wypych-Zych A, Stevens K, *et al.* LVAD, heart failure journey continues. *J Cardiothorac Vasc Anesth* 2020;**34**(Suppl. 1):S10.	Do not report DT data
Letsou GV, Ho JK, Musfee FI, Frazier OH, Wang N. Causes of mortality in patients undergoing continuous-flow LVAD implantation. *ASAIO J* 2020;**66**(Suppl. 2):3.	Do not report DT data
Letsou GV, Ho JK, Musfee FI, Frazier OH, Wang N. Post-transplant survival after continuous-flow LVAD implantation is superior to survival after pulsatile-flow LVAD implantation. *ASAIO Journal* 2020;**66**(Suppl. 2):37.	Do not report DT data
Leuck A, Schultz J, Mazzulla F, John R, Spratt J, Walts AN, *et al.* Bridge to transplant status is associated with improved survival after the development of left ventricular assist device infection. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S259.	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Levin AP, Uriel N, Takayama H, Mody KP, Ota T, Yuzefpolskaya M, *et al.* Device exchange in HeartMate II recipients: long-term outcomes and risk of thrombosis recurrence. *ASAIO J* 2015;**61**:144–9.	< 50 DT patients
Levin L, Wieselthaler G, Aras M, Klein L. Malnutrition is associated with right ventricular failure at the time of left ventricular device implantation. *Artif Organs* 2020;**44**(3):E122–3.	Do not report DT data
Lietz K, Branch A, McGrath M, Herre J. Relationship between the cost and cause of hospital readmissions after LVAD implantation. *J Heart Lung Transplant* 2014;(1):S101–2.	Wrong patient population
Lim S, Chue CD, Ranasinghe A, Mascaro JG. Discontinuation of aspirin in HeartMate 3: long-term outcomes. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S48.	Do not report DT data
Lochel S, Maukel LM, Weidner G, de By TMMH, Spaderna H. Gender differences in psychosocial and clinical characteristics in the European Registry for Patients with Mechanical Circulatory Support. *Heart Lung* 2021;**50**(6):845–52.	Do not report DT data
Loehn T, Mierke J, Kuehns C, Schweigler T, Pfluecke C, Youssef A, *et al.* Long-term survival after early vs. late initiation of percutaneous mechanical support in infarct-related cardiogenic shock. *Eur Heart J* 2018;**39**(Suppl. 1):624.	Do not report DT data
Loforte A, Gliozzi G, Mariani C, De By T, Schonrath F, Potapov E, *et al.* Concomitant cardiac procedures during implantation of long-term continuous-flow LVADs: a European registry for patients with mechanical circulatory support (EUROMACS) analysis. *Artif Organs* 2020;**44**(3):E75.	Do not report DT data
Loforte A, Gliozzi G, Mariani C, De By T, Schonrath F, Potapov E, *et al.* Concomitant mitral valve surgery in left ventricular assist device recipients: a European registry for patients with mechanical circulatory support (EUROMACS) analysis. *Artif Organs* 2020;**44**(3):E125.	Do not report DT data
Loforte A, Montalto A, Lilla della Monica P, Lappa A, Contento C, Menichetti A, *et al.* Mechanical circulatory support in advanced heart failure: single-center experience. *Transplant Proc* 2014;**46**:1476–80.	< 50 DT patients
Loforte A, Montalto A, Musumeci F, Mariani C, Polizzi V, Lilla Della Monica P, *et al.* A novel risk model to predict right ventricular failure after continuous flow left ventricular assist device implantation. *J Heart Lung Transplant* 2018;**37**(4 Suppl.):S370.	Do not report DT data
Loforte A, Musumeci F, Montalto A, Pilato E, Lilla Della Monica P, Grigioni F, *et al.* Use of mechanical circulatory support devices in end-stage heart failure patients. *J Card Surg* 2014;**29**:717–22.	< 50 DT patients
Loghmanpour NA, Kanwar MK, Druzdzel MJ, Benza RL, Murali S, Antaki JF. A new Bayesian network-based risk stratification model for prediction of short-term and long-term LVAD mortality. *ASAIO J* 2015;**61**:313–23.	Do not report DT data
Logstrup BB, Nemec P, Schoenrath F, Gummert J, Pya Y, Potapov E, *et al.* Heart failure etiology and risk of right heart failure in adult left ventricular assist device support: the European Registry for Patients with Mechanical Circulatory Support (EUROMACS). *Scand Cardiovasc J* 2020;**54**:306–14.	Do not report DT data
Lolay GAK, Guglin M, George B, Kido K. The value of N. terminal pro. brain natriuretic peptide after LVAD implantation. *J Am Coll Cardiol* 2016;(1):1371.	Do not report DT data
Louis C, Gosev I, McNitt S, Prasad S, Vidula H, Alexis J, *et al.* Risk of adverse events in patients undergoing left ventricular assist device implantation in cardiogenic shock. *ASAIO J* 2019;**65**(Suppl. 1):46.	Do not report DT data
Louis C. Risk of adverse events with left ventricular assist devicein cardiogenic shock patients. Circulation Conference: American Heart Association's. 2019;140.	Do not report DT data
Love WT, Zawadowski GM, Noelting J, Horsley-Silva JL, Staley LL, Amity ME, *et al.* Increased risk of gastrointestinal bleeding in heartmate II compared to heartware left ventricular assist devices – a single center retrospective cohort. *J Heart Lung Transplant* 2016;(1):S79.	Do not report DT data
Luc JGY, Tchantchaleishvili V, Phan K, Dunlay SM, Maltais S, Stulak JM. Medical therapy compared with surgical device exchange for left ventricular assist device thrombosis: a systematic review and meta-analysis. *ASAIO J (Am Soc Artif Intern Organs: 1992)* 2019;**65**:307–17.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Luigi Adamo L, Tang Y, Nassif M, Novak E, Jones PG, Larue S, *et al.* The heart mate risk score identifies patients with similar mortality risk across all INTERMACS classes in a large multi-center analysis: low INTERMACS class should not be a contraindication to LVAD. *Eur J Heart Fail* 2016;(1):307.	Do not report DT data
Lundgren S, High R, Poon C, Raichlin E, Zolty R, Burdorf A, *et al.* Psychosocial factors and outcomes with left ventricular assist device therapy. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S338.	Do not report DT data
Lundgren S, Stoller D, Lyden E, Burdorf A, Hyden M, Zolty R, *et al.* Outcomes in patients on digoxin following LVAD implantation. *J Card Fail* 2019;**25**(8 Suppl.):S165–6.	Do not report DT data
Magnetta DA, Kang J, Wearden PD, Smith KJ, Feingold B. Cost-effectiveness of ventricular assist device destination therapy for advanced heart failure in Duchenne muscular dystrophy. *J Heart Lung Transplant* 2016;(1):S353.	Wrong patient population
Magnetta DA, Kang J, Wearden PD, Smith KJ, Feingold B. Cost-effectiveness of ventricular assist device destination therapy for advanced heart failure in Duchenne Muscular Dystrophy. *Pediatr Cardiol* 2018;**39**:1242–8.	Paediatric population
Maharaj V, Masotti M, Schultz J, Martin CM, John R, Alexy T, *et al.* Trends in renal function prior to and after LVAD placement and association with post LVAD mortality. *J Heart Lung Transplant* 2021;**40**(4 Suppl.):S422.	Do not report DT data
Maharaj V, Schultz J, Charpentier V, Duval S, John R, Shaffer A, *et al.* Higher body mass index is associated with end stage renal failure after left ventricular assist device implantation. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S410.	Do not report DT data
Mahfood Haddad T, Saurav A, Smer A, Azzouz MS, Akinapelli A, Williams MA, *et al.* Cardiac rehabilitation in patients with left ventricular assist device: a systematic review and meta-analysis. *J Cardiopulm Rehabil Prev* 2017;**37**:390–6.	Do not report DT data
Mahr C, McGee E, Cheung A, Mokadam NA, Strueber M, Slaughter MS, *et al.* Cost-effectiveness of thoracotomy approach for the implantation of a small intrapericardial centrifugal LVAD. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S366.	Wrong patient population
Mahr C, McGee E, Cheung A, Mokadam NA, Strueber M, Slaughter MS, *et al.* Cost-effectiveness of thoracotomy approach for the implantation of a centrifugal left ventricular assist device. *ASAIO J* 1992.	Duplicate record
Mahr C, McGee E, Cheung A, Mokadam NA, Strueber M, Slaughter MS, *et al.* Cost-effectiveness of thoracotomy approach for the implantation of a centrifugal left ventricular assist device. *ASAIO J (Am Soc Artif Intern Organs: 1992)* 2020;**66**:855–61.	Wrong patient population
Mai X, Clerkin K, Topkara VK, Takeda K, Demmer R, Yuzefpolskaya M, *et al.* Comparison of survival and modes of death by ICD status among LVAD recipients. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S182.	Do not report DT data
Mai X, Topkara VK, Wong K, Castagna F, Trinh PN, Sreekanth S, *et al.* Long-term outcomes in continuous-flow left ventricular assist device patients with and without ICD. *J Heart Lung Transplant* 2016;(1):S24.	Do not report DT data
Majeed F, Kop WJ, Poston RS, Kallam S, Mehra MR. Prospective, observational study of anti-platelet and coagulation biomarkers as predictors of thromboembolic events after implantation of ventricular assist devices. *Nat Clin Pract Cardiovasc Med* 2009;**6**:147–57.	< 50 DT patients
Makki N, Mesubi O, Steyers C, Olshansky B, Abraham WT. Meta-analysis of the relation of ventricular arrhythmias to all-cause mortality after implantation of a left ventricular assist device. *Am J Cardiol* 2015;**116**:1385–90.	< 50 DT patients
Makki N, Mesubi O, Steyers C, Olshansky B. Ventricular arrhythmias and mortality after left ventricular assist devices implantation: a meta-analysis. Circulation Conference: American Heart Association's. 2014;130.	Do not report DT data
Malick A, Naka Y, Sanchez J, Butler C, Ning Y, Kurlansky P, *et al.* Development of De Novo aortic insufficiency in patients with HeartMate 3. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S406–7.	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Malik S, Raichlin E, Lyden E, Hewlett A. Gastrointestinal bleeding in patients with left ventricular assist devices; whereas the leak and what are the outcomes? *Gastrointest Endosc* 2017;**85**(5 Suppl. 1):AB447.	Do not report DT data
Maltais S, Anwer LA, Haglund NA, Cowger J, Shah P, Aaronson KD, *et al.* Temporal differences in outcomes during long-term mechanical circulatory support. *J Card Fail* 2017;**23**:852–8.	Do not report DT data
Maltais S, Anwer LA, Tchantchaleishvili V, Haglund NA, Dunlay SM, Aaronson KD, *et al.* Left lateral thoracotomy for centrifugal continuous-flow left ventricular assist device placement: an analysis from the mechanical circulatory support research network. *ASAIO J* 2018;**64**:715–20.	Do not report DT data
Maltais S, Haglund N, Shah P, Cowger J, Aaronson KA, Pagani F, *et al.* Lessons learned from over 250 continuous-low centrifugal left ventricular assist device implantation: growing experience and outcomes in alternative approaches era. *J Heart Lung Transplant* 2016;(1):S39.	Do not report DT data
Maltais S, Haglund NA, Davis ME, Cowger J, Shah P, Pagani FD, *et al.* Heart failure etiology influences outcomes after continuous-flow LVAD implantation. *J Heart Lung Transplant* 2016;(1):S110–1.	Do not report DT data
Maltais S, Tchantchaleishvili V, Daly RC, Joyce DL, Joyce LD, Kushwaha SS, *et al.* Should prophylactic tricuspid valve surgery be considered in patients with atrial fibrillation undergoing LVAD implantation? *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S29–30.	Do not report DT data
Marasco SF, Summerhayes R, Quayle M, McGiffin D, Luthe M. Cost comparison of heart transplant vs. left ventricular assist device therapy at one year. *Clin Transplant* 2016;**30**:598–605.	Wrong indication
Mariani S, Dogan G, Hanke JS, Wendl RM, Chatterjee A, Deniz E, *et al.* Left ventricular assist device implantation via left thoracotomy and upper hemisternotomy: long-term follow-up of 111 patients. *Int J Artif Organs* 2019;**42**(8):413.	Do not report DT data
Mariani S, Li T, Bounader K, Boethig D, Schode A, Hanke JS, *et al.* Sex differences in outcomes following less-invasive left ventricular assist device implantation. *Ann Cardiothorac Surg* 2021;**10**:255–67.	Do not report DT data
Mariani S, Michaelis J, Dogan G, Hanke J, Chatterjee A, Bothig D, *et al.* Minimally invasive implatation of left ventricular assist devices: a tool to increase survival in women. *Artif Organs* 2020;**44**(3):E63.	Do not report DT data
Markham R, Challa A, Cafaro J, Bancroft J, Wockner L, Kyranis S, *et al.* Comparison of CoaguChek XS INR and laboratory inr in patients with a Heartware continuous flow left ventricular assist device. *Heart Lung Circ* 2016;**25**(Suppl. 2):S260.	Wrong indication
Martin SI, Wellington L, Stevenson KB, Mangino JE, Sai-Sudhakar CB, Firstenberg MS, *et al.* Effect of body mass index and device type on infection in left ventricular assist device support beyond 30 days. *Interact Cardiovasc Thorac Surg* 2010;**11**:20–3.	Do not report DT data
Masashi Kawabori M, Lofftus S, Vest A, Pramil V, Zhan Y, Warner KG, *et al.* Preoperative geriatric nutrition risk index scoring is predictive of survival in LVAD recipients. *Eur J Heart Fail* 2019;**21**(Suppl. 1):83–4.	Do not report DT data
McIlvennan CK, Bryce K, Lindenfeld J, Allen LA, Lanfear DE. Assessment of cognitive function prior to and after implantation of left ventricular assist device. *J Heart Lung Transplant* 2016;(1):S165–6.	Do not report DT data
McIlvennan CK, Thompson JS, Matlock DD, Cleveland JC, Jr, Dunlay SM, LaRue SJ, *et al.* A multicenter trial of a shared decision support intervention for patients and their caregivers offered destination therapy for advanced heart failure: DECIDE-LVAD: rationale, design, and pilot data. *J Cardiovasc Nurs* 2016;**31**:E8–20.	Wrong intervention
McKellar SH, Deo S, Daly RC, Durham LA, 3rd, Joyce LD, Stulak JM, *et al.* Durability of central aortic valve closure in patients with continuous flow left ventricular assist devices. *J Thorac Cardiovasc Surg* 2014;**147**:344–8.	Do not report DT data
Meehan K, Graney N, Combs P, Andrade A, Macaluso G, Tatooles A, *et al.* Outcomes of mechanical circulatory support in women in a single center. *Int J Artif Organs* 2018;**41**(9):540.	Do not report DT data
Mehta P, Imamura T, Belkin MN, Rodgers D, Sarswat N, Kim G, *et al.* Neurohormonal blockade reduces adverse events during LVAD support. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S180–1.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Melehy A, Seres D, Mullen H, Sanchez J, Kurlanksy P, Garan R, *et al.* Comprehensive nutrition assessment before left ventricular assist device implantation in chronically Ill hospitalized patients. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S82.	Do not report DT data
Melnikov S, Abuhazira M, Golobov D, Yaari V, Jaarsma T, Ben Gal T. Depression and anxiety moderate the relationship between body image and personal well-being among patients with an implanted left ventricular assist device. *J Cardiovasc Nurs* 2020;**35**:149–55.	Wrong study design
Menon AK, Baranski SK, Unterkofler J, Autschbach R, Moza AK, Goetzenich A, *et al.* Special treatment and wound care of the driveline exit site after left ventricular assist device implantation. *Thorac Cardiovasc Surgeon* 2015;**63**:670–4.	< 50 DT patients
Meyer AL, Malehsa D, Bara C, Budde U, Slaughter MS, Haverich A, *et al.* Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. *Circ Heart Fail* 2010;**3**:675–81.	< 50 DT patients
Meyer AL, Malehsa D, Bara C, Haverich A, Strueber M. Implantation of rotary blood pumps into 115 patients: a single-centre experience. *Eur J Cardio-Thorac Surg* 2013;**43**:1233–6.	< 50 DT patients
Meyns B, Jacobs S, Van Den Bossche K, Verhoeven J, Bostic RR, Vanhaecke J, *et al.* Cost of 1-year LVAD destination therapy in chronic heart failure: a comparison with heart transplantation. *J Heart Lung Transplant* 2013;(1):S98–9.	< 50 DT patients
Mihalj M, Heinisch PP, Schober P, Dobner S, Fuerholz M, Martinelli M, *et al.* Third generation continuous flow left ventricular assist devices: a comparative outcome analysis by device type. *Eur Heart J* 2021;42(Suppl. 1):946.	< 50 DT patients
Milgrom A, Collins A, Grubbs JA, Derrick C, Logan K, Edelson W, *et al.* Determinants of infection at a nontransplanting cardiothoracic LVAD program. *Open Forum Infect Dis* 2019;**6**(Suppl. 2):S450.	Do not report DT data
Miller LW, Lietz K. Candidate selection for long-term left ventricular assist device therapy for refractory heart failure. *J Heart Lung Transplant* 2006;**25**:756–64.	Wrong study design
Mirza KK, Xie R, Cowger J, Kirklin JK, Meyns B, Gustafsson F, *et al.* Comparative analysis of regional outcomes and adverse events after continuous-flow left ventricular assist device implantation: an IMACS analysis. *J Heart Lung Transplant* 2020;**39**:904–14.	Do not report DT data
Mishra V, Fiane AE, Winsnes BA, Geiran O, Sorensen G, Hagen TP, *et al.* Cardiac replacement therapies: outcomes and costs for heart transplantation versus circulatory assist. *Scand Cardiovasc J* 2017;**51**:1–7.	Wrong indication
Moayedifar R, Sandner S, Riebandt J, Wiedemann D, Haberl T, Schloeglhofer T, *et al.* Renal function after ventricular assist device implantation. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S347–8.	Do not report DT data
Moazami N, Ewald GA, Pagani FD, John R, MacGillivray TE, Chen L, *et al.* Clinical durability and low incidence of pump replacement of a continuous-flow left ventricular assist device. *J Heart Lung Transplant* 2009;(1):S207.	Wrong indication
Moazami N, Milano CA, John R, Sun B, Adamson RM, Pagani FD, *et al.* Pump replacement for left ventricular assist device failure can be done safely and is associated with low mortality. *Ann Thorac Surg* 2013;**95**:500–5.	Do not report DT data
Mohamedali B, Bhat G, Yost G, Tatooles A. Changes in spirometry after left ventricular assist device implantation. *Artif Organs* 2015;39:1046–50.	Do not report DT data
Mohamedali B, Bhat G. The influence of pre-left ventricular assist device (LVAD) implantation glomerular filtration rate on long-term LVAD outcomes. *Heart Lung Circ* 2017;26:1216–23.	Do not report DT data
Mohamedali B, Yost G, Bhat G. Is diabetes mellitus a risk factor for poor outcomes after left ventricular assist device placement? *Tex Heart Inst J* 2017;44:115–9.	Do not report DT data
Mohamedali B, Yost G, Bhat G. Mechanical circulatory support improves diabetic control in patients with advanced heart failure. *Eur J Heart Fail* 2014;16:1120–4.	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Mohamedali B, Yost G, Bhat G. Obesity as a risk factor for consideration for left ventricular assist devices. *J Card Fail* 2015;**21**:800–5.	Do not report DT data
Mohiyaddin S, Yousaf A, Hailan A, Aldweik M. Prolonged use of levitronix right ventricular assist device (RVAD) in patients with long term left ventricular assist device (LVAD). Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC. 2018;71.	Do not report DT data
Molfetta A, Casadio L, Fresiello L, Iacobelli R, Filippelli S, Perri G, *et al.* Short-and long-term changes in ventricular loading conditions in LVAD patients: pulsatile vs continuous flow LVAD. *J Cardiovasc Transl Res* 2018;**11**(1):69–70.	Paediatric population
Molina EJ, Najjar SS, Ahmed S, Rodrigo ME, Hofmeyer M, Kadakkal A, *et al.* Real world experience with the HeartMate 3 (HM3) Left Ventricular Assist Device (LVAD): analysis of the first 125 consecutive patients at a single institution. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S338.	Do not report DT data
Molina EJ, Najjar SS, Ahmed S, Rodrigo ME, Hofmeyer M, Kadakkal A, *et al.* Real world experience with the HeartMate 3 (HM3) Left Ventricular Assist Device (LVAD): analysis of the first 125 consecutive patients at a single institution. *J Heart Lung Transplant* 2020;**39**:S338.	Do not report DT data
Mondellini GM, Pinsino A, Braghieri L, Javaid A, Lin EF, Cagliostro B, *et al.* Serum cystatin C as a predictor of early outcomes and long-term mortality in contemporary LVAD patients. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S182.	Do not report DT data
Moreno L, Leblanc M, Gurley M, McCarthy P, Paganini EP. Dialytic support in patients with acute renal failure with implantable left ventricular assist devices. *J Intensive Care Med* 1997;**12**:33–9.	< 50 DT patients
Moreno SG. Letter by moreno regarding article, 'cost-effectiveness analysis of continuous flow left ventricular assist devices as destination therapy'. *Circ Heart Fail* 2012;**5**:e50.	Wrong study design
Morgan JA, Paone G, Nemeh HW, Henry SE, Gerlach B, Williams CT, *et al.* Non-cardiac surgery in patients on long-term left ventricular assist device support. *J Heart Lung Transplant* 2012;**31**:757–63.	< 50 DT patients
Morgan JA, Paone G, Nemeh HW, Henry SE, Patel R, Vavra J, *et al.* Gastrointestinal bleeding with the HeartMate II left ventricular assist device. *J Heart Lung Transplant* 2012;**31**:715–8.	< 50 DT patients
Morgan JA, Paone G, Nemeh HW, Murthy R, Williams CT, Lanfear DE, *et al.* Impact of continuous-flow left ventricular assist device support on right ventricular function. *J Heart Lung Transplant* 2013;**32**:398–403.	Do not report DT data
Morgan JA, Tsiouris A, Nemeh HW, Hodari A, Karam J, Brewer RJ, *et al.* Impact of concomitant cardiac procedures performed during implantation of long-term left ventricular assist devices. *J Heart Lung Transplant* 2013;**32**:1255–61.	Do not report DT data
Morreale C, Paliga R, Kothari S, Meehan K, Coyle L, Morack M, *et al.* Psychosocial characteristics and outcomes in patients with ventricular assist device. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S448.	Do not report DT data
Morris KL, Haleem A, Patel A, Garcia-Cortes R, Chaudhry S, Zanotti G, *et al.* Increased Right Heart Failure (RHF) in high BMI LVAD recipients. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S38.	Do not report DT data
Morrissey O, Xie R, Schaenman J, Husain S, Mooney M, Nakatani T, *et al.* Epidemiology of fungal infections (FI) in mechanical circulatory support device (MCSD) recipients: analysis of IMACS registry 2013-2015. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S27.	Do not report DT data
Morshuis M, Garbade J, Zimpfer D, Shaw S, Lavee J, Gustafsson F, *et al.* Clinical outcomes with heartmate 3™ left ventricular assist device as treatment for advanced heart failure: 12-month outcomes from the ELEVATE registry. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S84.	Do not report DT data
Movahedi F, Carey L, Zhang Y, Padman R, Antaki J, Kanwar M. Analysis of post-LVAD clinical pathways. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S352.	Do not report DT data
Movahedi F, Lohmueller L, Zhang Y, Padman R, Antaki J. Clinical journey of severe heart failure patients after left ventricular assistance device implant. *J Card Fail* 2017;**23**(8 Suppl. 1):S107.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Mulloy DP, Bhamidipati CM, Stone ML, Ailawadi G, Kron IL, Kern JA. Orthotopic heart transplant versus left ventricular assist device: a national comparison of cost and survival. *J Thorac Cardiovasc Surg* 2013;**145**:566–74.	Wrong indication
Murphy M, Foster M, Wald J, Marble J, Rao SD, Atluri P, *et al.* Partial recovery of ejection fraction with neurohormonal blockade improves long-term event free survival for patients with continuous flow LVAD. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S132–3.	Do not report DT data
Musa T, Chue C, Lim HS. Renal recovery following use of left ventricular assist device in advanced heart failure patients. *Heart* 2017;**103**(Suppl. 5):A16.	Do not report DT data
Muslem R, Akin S, Constantinescu AA, Manintveld O, Brugts JJ, van der Heiden CW, *et al.* Long-term mechanical durability of left ventricular assist devices: an urgent call for periodic assessment of technical integrity. *ASAIO J* 2018;**64**:521–8.	Do not report DT data
Muslem R, Caliskan K, Akin S, Yasar YE, Sharma K, Gilotra NA, *et al.* Effect of age and renal function on survival after left ventricular assist device implantation. *Am J Cardiol* 2017;**120**:2221–5.	Do not report DT data
Muslem R, Ong CS, Tomashitis B, Schultz J, Ramu B, Craig ML, *et al.* Pulmonary arterial elastance and INTERMACS-defined right heart failure following left ventricular assist device. *Circ Heart Fail* 2019;**12**:e005923.	Do not report DT data
Myers TJ, Macris MP. Clinical experience with the HeartMate left ventricular assist device. *Heart Failure* 1994;**10**:247–56 + 58.	Wrong indication
Nadziakiewicz P, Pacholewicz J, Zakliczynski M, Niklewski T, Borkowski J, Hrapkowicz T, *et al.* Comparison of mechanical circulatory support by the use of pulsatile left ventricular assist devices polvad MEV and continuous flow heart ware and Heart Mate II in a single-center experience. *Transplant Proc* 2016;**48**:1770–4.	< 50 DT patients
Naik A, Akhter SA, Fedson S, Jeevanandam V, Rich JD, Koyner JL. Acute kidney injury and mortality following ventricular assist device implantation. *Am J Nephrol* 2014;**39**:195–203.	Do not report DT data
Nakagawa S, Luna JM, Topkara VK, Yuzefpolskaya M, Vawdrey D, Garan AR, *et al.* Novel palliative care integration program increases days alive and out of hospital and reduces inpatient direct costs among left ventricular assist device patients. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S173.	Wrong patient population
Nakanishi K, Homma S, Han J, Takayama H, Colombo PC, Yuzefpolskaya M, *et al.* Prevalence, predictors, and prognostic value of residual tricuspid regurgitation in patients with left ventricular assist device. *J Am Heart Assoc* 2018;**7**:24.	Do not report DT data
Namn Y, Cohen-Mekelburg S, Sherman Z, Crawford CV. Predictors of gastrointestinal rebleed events in patients with a ventricular assist device (VAD). *Am J Gastroenterol* 2017;**112**(Suppl. 1):S303–4.	Do not report DT data
Nativi-Nicolau J, Healy A, Abdelrahman S, Jaramillo J, Elmer A, Tagge S, *et al.* Readmission rates in patients with left ventricular assist devices. *J Heart Lung Transplant* 2016;(1):S335.	Do not report DT data
Nayak A, Neill C, Kormos RL, Lagazzi L, Halder I, McTiernan C, *et al.* Chemokine receptor patterns and right heart failure in mechanical circulatory support. *J Heart Lung Transplant* 2017;**36**:657–65.	< 50 DT patients
NCT, Abbott Medical Devices Y, Thoratec C. *PREVENtion of HeartMate II Pump Thrombosis* 2014. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02158403 (accessed September 2020).	Do not report DT data
NCT, Abbott Medical Devices Y, Thoratec Corporation Yes 29/10/ NCT. *Thoratec HeartMate II Left Ventricular Assist System (LVAS) for Destination Therapy*. 2005. URL: https://classic.clinicaltrials.gov/ct2/show/NCT00121485 (accessed September 2020).	Duplicate record
NCT, Abbott Medical Devices Y. *Implantation of the HeartMate 3 in Subjects with Heart Failure Using Surgical SWIFT HM3 PMS*. 2020. URL: https://classic.clinicaltrials.gov/ct2/show/NCT04548128 (accessed September 2020).	< 50 DT patients
NCT, Joe Elie Salem N. *Medical Care versus Ventricular Assist Device for the Management of Endstage Heart Failure (MEVADE)*. 2017. URL: https://classic.clinicaltrials.gov/ct2/show/NCT03105726 (accessed September 2020).	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
NCT, Medtronic Cardiac R, Heart Failure Y. *A Clinical Trial to Evaluate the HeartWare™ VentricularAssist System (ENDURANCE SUPPLEMENTAL TRIAL)*. 2013. URL: https://classic.clinicaltrials.gov/ct2/show/NCT01966458 (accessed September 2020).	Duplicate record
NCT, Medtronic Cardiac R, Heart Failure Y. *Post-approval Study on Patients Who Received a HeartWare HVAD® During IDE Trials*. 2013. URL: https://classic.clinicaltrials.gov/ct2/show/NCT01832610	Wrong patient population
NCT, Medtronic Cardiac R, Heart Failure Y. *The HeartWare™ Ventricular Assist System as Destination Therapy of Advanced Heart Failure: The ENDURANCE Trial*. 2010. URL: https://classic.clinicaltrials.gov/ct2/show/NCT01166347	Duplicate record
NCT, Thomas Jefferson University Y, Thoratec C, National Skeletal Muscle Research C, Greater New York Geriatric Cardiology C. *Frailty: Prevalence and Response to Left Ventricular Assist Device Therapy in Older Heart Failure Patients*. 2014. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02156583	< 50 DT patients
NCT, Vastra Gotaland Region Y, Karolinska University H, University Hospital L, Skane University H, Uppsala University H, *et al. Swedish Evaluation of Left Ventricular Assist Device as Permanent Treatment in End-stage Heart Failure*. 2015. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02592499	Duplicate record
NCT, Ventracor Y, International Center for Health O, Innovation R. *VentrAssistTM LVAD for the Treatment of Advanced Heart Failure – Destination Therapy*. 2007. URL: https://classic.clinicaltrials.gov/ct2/show/NCT00490321	Do not report DT data
NCT. *Dabigatran as an Alternative Anticoagulant in Patients With Left Ventricular Assist Device (LVAD)*. 2016. URL: https://classic.clinicaltrials.gov/ct2/show/NCT02872649.	Wrong intervention
NCT. *Evaluation of the Jarvik 2000 Left Ventricular Assist System with Post-auricular Connector–Destination Therapy Study*. 2012. URL: https://clinicaltrialsgov/show/NCT01627821.	Duplicate record
NCT. *LVAD in Non Cardiac Transplant Candidates and Non Responders to Resynchronization*. 2010. URL: https://clinicaltrialsgov/show/NCT01126944.	< 50 DT patients
NCT. LVAD *versus* GDMT *in Ambulatory Advanced Heart Failure Patients*. 2021. URL: https://clinicaltrialsgov/show/NCT04768322.	Duplicate record
NCT. *Self-management App for Patients with Left-ventricular Assist Devices*. 2017. URL: https://clinicaltrialsgov/show/NCT03049748.	< 50 DT patients
NCT. *VentrAssistTM LVAD for the Treatment of Advanced Heart Failure – Destination Therapy*. 2007. URL: https://clinicaltrialsgov/show/NCT00490321.	< 50 DT patients
Nelson T, George S, Phancao A, El Banayosy A, Long JW. Effects of residential distance from LVAD implanting center on survival. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S345.	Do not report DT data
Neo CL, Kerk KL, Tay JH, Tan JL, Leam JL, Tan TE, *et al.* Functional recovery post left ventricular assist device implantation in INTERMACS profile 1 population. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S352.	Do not report DT data
Nitta D, Kinugawa K, Imamura T, Amiya E, Hatano M, Kinoshita O, *et al.* A Useful scoring system for predicting right ventricular assist device requirement among patients with a paracorporeal left ventricular assist device. *Int Heart J* 2018;**59**:983–90.	Do not report DT data
Nowacka A, Hullin R, Tozzi P, Barras N, Regamey J, Yerly P, *et al.* Short-term single-centre experience with the HeartMate 3 left ventricular assist device for advanced heart failure. *Eur J Cardio Thorac Surg Off J Eur Assoc Cardio Thorac Surg*. 2020;01.	< 50 DT patients
Numan L, Ramjankhan FZ, Oberski DL, Oerlemans MIFJ, Aarts E, Gianoli M, *et al.* Propensity score-based analysis of long-term outcome of patients on HeartWare and HeartMate 3 left ventricular assist device support. *ESC Heart Fail* 2021;**8**:1596–603.	Do not report DT data
Numan L, Ramjankhan FZ, Oberski DL, Oerlemans MIFJ, Aarts E, Gianoli M, *et al.* Propensity score-based analysis of long-term outcome of patients on HeartWare and HeartMate 3 left ventricular assist device support. *ESC Heart Fail* 2021;**8**(2):1596–603.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Numan L, Ramjankhan FZ, Oberski DL, Oerlemans MIFJ, Aarts E, Gianoli M, *et al.* Long-term outcome of patients on HeartWare and HeartMate 3 support in a single centre: a propensity score-based analysis. *Eur J Heart Fail* 2021;**23**(Suppl. 2):148–9.	Do not report DT data
Nunes AJ, MacArthur RG, Klarenbach SW. Cost of ventricular assist device therapy at a large canadian transplantation centre. *Can J Cardiol* 2012;(1):S267.	< 50 DT patients
Nunes AJ, Wiebe N, Chatterley P, MacArthur RG, Klarenbach SW. Systematic review of the cost-effectiveness of mechanical circulatory support. *Can J Cardiol* 2012;(1):S176–7.	Wrong indication
O'Horo JC, Abu Saleh OM, Stulak JM, Wilhelm MP, Baddour LM, Rizwan Sohail M. Left ventricular assist device infections: a systematic review. *ASAIO J* 2018;**64**:287–94.	Do not report DT data
Okoh AK, Chan O, Schultheis M, Fugar S, Kang N, Kaplon S, *et al.* Racial disparities and outcomes after left ventricular assist device implantation as bridge to transplantation or destination therapy. *Innov Technol Tech Cardiothorac Vasc Surg* 2019;**14**:236–42.	Do not report DT data
Okwuosa I, Anderson AS, Petty M, Hubert A, Pollan L, Andrei AC, *et al.* Sustaining quality of life of the aged: transplant or mechanical support (sustain-it): baseline caregiver burden. *Circ Conf* 2018;138.	Do not report DT data
Okwuosa IS, Xu Y, Andrei A, Warzecha A, Kao A, Hsich E, *et al.* Sustaining quality of life of the aged: transplant or mechanical support (Sustain-It): caregiver perceived burden. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S34–5.	Do not report DT data
Olagoke OO, Ezegwu O, Olagoke AA, Golzar Y. Incidence, trends and predictors of palliative care consultation among patients admitted for LVAD implantation in the United States. *J Card Fail* 2019;**25**(8 Suppl.):S59.	Do not report DT data
Oliveira GH, Dupont M, Naftel D, Myers SL, Yuan Y, Tang WH, *et al.* Increased need for right ventricular support in patients with chemotherapy-induced cardiomyopathy undergoing mechanical circulatory support: outcomes from the INTERMACS Registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol* 2014;**63**:240–8.	Do not report DT data
Olmsted RZ, Critsinelis A, Kurihara C, Kawabori M, Sugiura T, Civitello AB, *et al.* Severe LVAD-related infections requiring surgical treatment: incidence, predictors, effect on survival, and impact of device selection. *J Card Surg* 2019;**34**(2):82–91.	Duplicate record
Olsen C, Mandawat A, Triana T, Samsky MD, Chiswell K, Ravi K. Recovery of left ventricular function on LVAD support is associated with improved outcomes. Circulation Conference: American Heart Association Scientific Sessions, AHA. 2020;142.	Do not report DT data
Osaki S, Edwards NM, Velez M, Johnson MR, Murray MA, Hoffmann JA, *et al.* Improved survival in patients with ventricular assist device therapy: the University of Wisconsin experience. *Eur J Cardio-Thorac Surg* 2008;**34**:281–8.	< 50 DT patients
Oswald H, Schultz-Wildelau C, Gardiwal A, Lüsebrink U, König T, Meyer A, *et al.* Implantable defibrillator therapy for ventricular tachyarrhythmia in left ventricular assist device patients. *Eur J Heart Fail* 2010;**12**:593–9.	Do not report DT data
Otten A, Kurz S, Anwar S, Potapov E, Krall C, O'Brien B, *et al.* Prognostic value of 3-dimensional echocardiographical heart volume assessment in patients scheduled for left ventricular assist device implantation. *Eur J Cardio-Thorac Surg* 2018;**54**:169–75.	Do not report DT data
Oz MC, Argenziano M, Catanese KA, Gardocki MT, Goldstein DJ, Ashton RC, *et al.* Bridge experience with long-term implantable left ventricular assist devices. Are they an alternative to transplantation? *Circulation* 1997;**95**:1844–52.	Do not report DT data
Oz MC, Goldstein DJ, Pepino P, Weinberg AD, Thompson SM, Catanese KA, *et al.* Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. *Circulation* 1995;**92**:II169–73.	Do not report DT data
Pagani FD, Long JW, Dembitsky WP, Joyce LD, Miller LW. Improved mechanical reliability of the HeartMate XVE left ventricular assist system. *Ann Thorac Surg* 2006;**82**:1413–8.	< 50 DT patients

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Parikh U, Lamba H, Vincent J, Civitello AB, Nair A, Taimeh Z, *et al.* Pre-operative hyponatremia as a risk factor for mortality in patients after left ventricular assist device implantation. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S430–1.	Do not report DT data
Park CJ, Murray M, Kohmoto T, Lushaj E. Impact of distance from implant center on mechanical circulatory device patient outcomes. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S458–9.	Do not report DT data
Park JR, Brady PA, Clavell A, Maleszewski J, Nkomo V, Pislaru S, *et al.* Predictors and impact of de novo aortic regurgitation in patients with continuous flow left ventricular assist devices. Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC. 2018;71.	Do not report DT data
Patel N, Bandyopadhyay D, Chakraborty S, Amgai B, Kumari A, Patel Z, *et al.* National gender-based in-hospital mortality and outcome in patients with left ventricular assist device: 2008-2014 National Inpatient Sample trend analysis. *J Am Coll Cardiol* 2020;**75**(11):1507.	Do not report DT data
Patel N, Gluck JA, Radojevic J, Coleman CI, Baker WL. Left ventricular assist device implantation improves glycaemic control: a systematic review and meta-analysis. *ESC Heart Fail* 2018;**5**:1141–9.	Do not report DT data
Patel N, Kalra R, Doshi R, Joly J, Bajaj NS, Arora G, *et al.* Costs and in-hospital mortality associated with orthotopic heart transplants and left ventricular assist devices: national inpatient sample 2009–2014. Circulation Conference: Resuscitation Science Symposium, ReSS. 2017;136.	Wrong patient population
Patel S, Choi JH, Moncho Escrivá E, Rizvi SSA, Maynes EJ, Samuels LE, *et al.* Single versus multi-drug antimicrobial surgical infection prophylaxis for left ventricular assist devices: a systematic review and meta-analysis. *Artif Organs* 2019;**43**:E124–38.	Do not report DT data
Pelletier D, Radio SJ. Characterization of LVAD ventricular and aortic interfaces: potential role in device thrombosis. *Lab Invest* 2016;(1):83A.	Do not report DT data
Pendyal A, Gelow JM. Hepatitis c virus infection does not impact survival following continuous-flow left ventricular assist device implantation. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S28.	Do not report DT data
Pennings K, Van De Vosse F, De Mol B, Rutten M. Estimation of left ventricular pressure with the pump as 'pressure sensor' in patients with a continuous flow LVAD. *Int J Artif Organs* 2015;**38**(7):378.	Do not report DT data
Pennington DG, Oaks TE, Lohmann DP. Permanent ventricular assist device support versus cardiac transplantation. *Ann Thorac Surg* 1999;**68**:729–33.	Wrong patient population
Peters A, Smith L, Kennedy J, Abuannadi M, Bergin J, Mazimba S. Comparative analysis of established risk scores and novel hemodynamic metrics in predicting right ventricular failure in left ventricular assist device patients. Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC. 2018;71.	Do not report DT data
Peters AE, Smith LA, Ababio P, Breathett K, McMurry TL, Kennedy JLW, *et al.* Comparative analysis of established risk scores and novel hemodynamic metrics in predicting right ventricular failure in left ventricular assist device patients. *J Card Fail* 2019;**25**:620–8.	< 50 DT patients
Petty MG, Yao X, Andrei A, Warzecha A, Kao A, Hsich E, *et al.* Caregiver comorbidities and anxiety are related to caregiver quality of life: findings from the sustaining quallty of life of the aged: HT or MCS study. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S93.	Do not report DT data
Phan K, Haswell JM, Xu J, Assem Y, Mick SL, Kapadia SR, *et al.* Percutaneous transcatheter interventions for aortic insufficiency in continuous-flow left ventricular assist device patients: a systematic review and meta-analysis. *ASAIO J* 2017;**63**:117–22.	Do not report DT data
Phan K, Huo YR, Zhao DF, Yan TD, Tchantchaleishvili V. Ventricular recovery and pump explantation in patients supported by left ventricular assist devices: a systematic review. *ASAIO J* 2016;**62**:219–31.	Do not report DT data
Philip S, Chapnick E, Ghitan M, Lin YS, Kuhn-Basti M. Blood stream infection in LVAD recipients: more than meets the eye. *Open Forum Infect Dis* 2017;**4**(Suppl. 1):S546–7.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Pilarczyk K, Carstens H, Heckmann J, Kamler M, Koch A, Jakob H, et al. Left ventricular assist device implantation in patients with cardiogenic shock: is prior stabilization with Extracorporeal Life Support beneficial? Intensive Care Medicine Experimental Conference: 31st European Society of Intensive Care Medicine Annual Congress, ESICM. 2018;6.	Do not report DT data
Pitha J, Dorazilova Z, Melenovsky V, Kralova Lesna I, Stavek P, Stepankova J, *et al.* The impact of left ventricle assist device on circulating endothelial microparticles – pilot study. *Neuroendocrinol Lett* 2012;**33**(Suppl. 2):68–72.	< 50 DT patients
Poddi S, Maltais S, Asleh R, Schettle SD, Rosenbaum AN, Behfar A, *et al.* Analyzing the value of the pulmonary artery pulsatility index beyond predicting right heart failure. *ASAIO J* 2018;**64**(Suppl. 1):89.	Do not report DT data
Poddi S, Tchantchaleishvili V, Daly RC, Dunlay SM, Maltais S, Stulak JM. Age-related risk of adverse events after left ventricular assist device implantation: a device-specific comparison. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S367–8.	Do not report DT data
Popov AF, Hosseini MT, Zych B, Mohite P, Hards R, Krueger H, *et al.* Clinical experience with HeartWare left ventricular assist device in patients with end-stage heart failure. *Ann Thorac Surg* 2012;**93**:810–5.	< 50 DT patients
Potapov EV, Loforte A, Weng Y, Jurmann M, Pasic M, Drews T, *et al.* Experience with over 1000 implanted ventricular assist devices. *J Card Surg* 2008;**23**:185–94.	Wrong outcomes
Potapov EV, Nersesian G, Lewin D, Ozbaran M, De By TMMH, Stein J, *et al.* Propensity score-based analysis of long-term follow-up in patients supported with durable centrifugal left ventricular assist devices: the EUROMACS analysis. *Eur J Cardio-Thorac Surg* 2021;**60**(3):579–87	Do not report DT data
Prichard RA, Kershaw L, Goodall S, Davidson PM, Macdonald P, Newton P, *et al.* Bottom up costing ventricular assist device therapy and optimal medical management-first steps to establishing cost-effectiveness. Circulation: Cardiovascular Quality and Outcomes Conference: American Heart Association's Quality of Care and Outcomes Research. 2014;7.	Wrong patient population
Pulikottil-Jacob R, Suri G, Connock M, Kandala NB, Sutcliffe P, Maheswaran H, *et al.* Comparative cost-effectiveness of the HeartWare versus HeartMate II left ventricular assist devices used in the United Kingdom National Health Service bridge-to-transplant program for patients with heart failure. *J Heart Lung Transplant* 2014;**33**:350–8.	Wrong indication
Pya Y, Bekbossynova M, Jetybayeva S, Bekbossynov S, Andossova S, Salov R, *et al.* Initial 3-year outcomes with left ventricular assist devices in a country with a nascent heart transplantation program. *ESC Heart Fail* 2016;**3**:26–34.	Do not report DT data
Raikhelkar J, Fried J, Sumzin N, Clerkin K, Griffin J, Sanchez J, *et al.* Heartmate 3 implantation in cancer survivors with advanced heart failure. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S183.	Do not report DT data
Raitz G, Maning J, Macedo G, Blume V, Chaparro S. Device differences in LVAD pump thrombosis: a systematic review. *ASAIO J* 2019;**65**(Suppl. 1):70.	Do not report DT data
Rajagopal K, Daneshmand MA, Patel CB, Ganapathi AM, Schechter MA, Rogers JG, *et al.* Natural history and clinical effect of aortic valve regurgitation after left ventricular assist device implantation. *J Thorac Cardiovasc Surg* 2013;**145**:1373–9.	Do not report DT data
Rajapreyar I, Rame JE. Cost-effectiveness of long-term left ventricular assist device support: is the extra-welfarist model suitable for advanced heart failure? *ASAIO J* 2020;**66**:871–4.	Wrong study design
Rajaratnam A, El-Swais A, McTiernan C, Al Ghouleh I. Persistence of pulmonary hypertension in patients with ventricular assist devices. *J Am Coll Cardiol* 2021;**77**(18 Suppl. 1):759.	Do not report DT data
Rampa S, Nalliah R, Kyeong Lee M, Allareddy V, Auslender M. The rise of the machines: infections are the achilles' heel! *Crit Care Med* 2016;**44**(12 Suppl. 1):121.	Do not report DT data
Randhawa VK, Lin W, Sabe MA, Bullen JA, Soltesz EG, Tang WHW, *et al.* Mitral regurgitation severity after continuous-flow LVAD implantation as ot associated with adverse long-term clinical outcomes. *J Card Fail* 2020;**26**(10 Suppl.):S147.	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Randhawa VK, Soltesz EG, Faulkenberg KD, Wang Q, Wolski KE, Tong MZ, *et al.* Safety and impact of direct left atrial pressure monitoring in patients undergoing continuous-flow left ventricular assist device implantation. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S443–4.	Do not report DT data
Rao V, Oz MC, Flannery MA, Idrissi KA, Argenziano M, Edwards NM, *et al.* Changing trends in mechanical circulatory assistance. *J Card Surg* 2004;**19**:361–6.	Wrong patient population
Ravichandran AK, Shah P, Singh R, Aaronson KD, Pagani FD, Stulak J, *et al.* Impact of patient distance from ventricular assist device-implanting center on short- and long-term outcomes. *ASAIO J* 2018;**64**:721–6.	Do not report DT data
Raymer D, Vader J, Platts A, Nassif M, Silvestry S, Ewald G, *et al.* Health literacy as a predictor of adverse outcomes after implantation of left ventricular assist device. *J Card Fail* 2015;(1):S98.	Wrong setting
Refaat M, Chemaly E, Lebeche D, Gwathmey JK, Hajjar RJ. Ventricular arrhythmias after left ventricular assist device implantation. *Pacing Clin Electrophysiol* 2008;**31**:1246–52.	< 50 DT patients
Rehman AU, Birks EJ, Winters SJ. Amiodarone-induced hyperthyroidism in patients with heart failure with and without a left ventricular assist device. Endocrine Reviews Conference: 99th Annual Meeting of the Endocrine Society, ENDO. 2017;38.	Do not report DT data
Reynard AK, Butler RS, McKee MG, Starling RC, Gorodeski EZ. Impact of continuous flow left ventricular assist device therapy on depression and anxiety. *J Am Coll Cardiol* 2013;(1):E771.	Do not report DT data
Riebandt J, Moayedifar R, Wiedemann D, Schloglhofer T, Dimitrov K, Rajek A, *et al.* Less invasive left ventricular assist device implantation-5-year survival and post transplant outcomes. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S480.	Do not report DT data
Rivas-Lasarte M, Kumar S, Derbala MH, Ferrall J, Cefalu M, Rashid SM, *et al.* Prediction of right heart failure after left ventricular assist implantation: external validation of the EUROMACS right-sided heart failure risk score. *J Heart Lung Transplant* 2021;**40**(4 Suppl.):S168–9.	Do not report DT data
Roberts SC, Rich JD, Pham DT, Harap R, Stosor V. A spectrum of infectious complications in continuous-flow ventricular assist devices: a single-center longitudinal cohort. *Open Forum Infect Dis* 2019;**6**(Suppl. 2):S421–2.	Do not report DT data
Rockman HA, Adamson RM, Dembitsky WP, Bonar JW, Jaski BE. Acute fulminant myocarditis: long-term follow-up after circulatory support with left ventricular assist device. *Am Heart J* 1991;**121**:922–6.	Do not report DT data
Rodriguez DC, Algodi M, Berardi C, Makkiya M, Cyrille N, Saeed O, *et al.* Persistent hyponatremia early after LVAD implantation does not result in poor long-term outcomes. *J Heart Lung Transplant* 2016;(1):S332.	Do not report DT data
Rogers JG, Butler J, Lansman SL, Gass A, Portner PM, Pasque MK, *et al.* Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTrEPID Trial. *J Am Coll Cardiol* 2007;**50**:741–7.	< 50 DT patients
Rosenbaum AN, John R, Liao KK, Adatya S, Colvin-Adams MM, Pritzker M, *et al.* Survival in elderly patients supported with continuous flow left ventricular assist device as bridge to transplantation or destination therapy. *J Card Fail* 2014;**20**:161–7.	< 50 DT patients
Rosenbaum AN, Ternus BW, Pahwa S, Stulak JM, Clavell AL, Schettle SD, *et al.* Risk of liver dysfunction after left ventricular assist device implantation. *Ann Thorac Surg.* 2021.	Wrong outcomes
Rossi M, Serraino GF, Jiritano F, Renzulli A. What is the optimal anticoagulation in patients with a left ventricular assist device? *Interact Cardiovasc Thorac Surg* 2012;**15**:733–40.	< 50 DT patients
Roukoz H, Bhan A, Ravichandran A, Ahmed MM, Bhat G, Cowger J, *et al.* Continued versus suspended cardiac resynchronization therapy after left ventricular assist device implantation. *Sci Rep* 2020;**10**:2573.	Do not report DT data
Roukoz H, Jedeon ZA, Wald LV, John R, Cogswell R. The effect of ventricular arrhythmias and Vt ablation on thrombotic events in patients with left ventricular assist device. *Heart Rhythm* 2019;**16**(5 Suppl.):485.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Roukoz H, Sathnur N, Bhan AK, Ravichandran A, Ahmed MM, Bhat G, *et al.* Continued CRT versus turning off LV lead after left ventricular assist device implant: a multicenter experience. *Heart Rhythm* 2018;**15**(5 Suppl. 1):S48.	Do not report DT data
Russo MARK, Akhter S, Pisarski R, Iribarne A, Raman J, Anderson A, *et al.* Intermacs score predicts post-implant survival and resource utilization. *Eur Heart J* 2011;(1):81.	Wrong patient population
Sadigov A, Demir E, Nalbantgil S, Demirci C, Engin C, Yagdi T, *et al.* The influence of left ventricular assist device implantation on short-term and long-term renal functions in end-stage heart failure patients. *J Am Soc Nephrol* 2019;**30**:441.	Do not report DT data
Saeed D, Garbade J, Gustafsson F, Lavee J, Morshuis M, Zimpfer D, *et al.* Two-year outcomes in real world patients treated with Heartmate 3™ left ventricular assist device for advanced heart failure: data from the ELEVATE Registry. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S67.	Do not report DT data
Saeed D, Kidambi T, Shalli S, Lapin B, Malaisrie SC, Lee R, *et al.* Tricuspid valve repair with left ventricular assist device implantation: is it warranted? *J Heart Lung Transplant* 2011;**30**:530–5.	Do not report DT data
Saeed O, Colombo PC, Mehra MR, Uriel N, Goldstein DJ, Cleveland J, *et al.* Effect of aspirin dose on hemocompatibility-related outcomes with a magnetically levitated left ventricular assist device: an analysis from the MOMENTUM 3 study. *J Heart Lung Transplant* 2020;**39**:518–25.	Do not report DT data
Saing S, van der Linden N, Hayward CS, Goodall S. Cost-effectiveness of left ventricular assist devices in end stage heart failure using state transition modelling based on registry data. *Value Health* 2018;**21**(Suppl. 3):S261.	Wrong indication
Saito S, Nishinaka T, Yamazaki K. Long-term circulatory support with a left ventricular assist device therapy in Japan. *Circ J* 2010;**74**:624–5.	Wrong study design
Sajgalik P, Kim CH, Stulak JM, Kushwaha SS, Maltais S, Joyce DL, *et al.* Pulmonary function assessment post-left ventricular assist device implantation. *ESC Heart Fail* 2019;**6**:53–61.	Do not report DT data
Salih M, Ayan M, Ogunbayo G, Elghezewi A, Guglin M. Heartmate II versus heartware for heart failure: a meta-analysis. Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC. 2018;71.	Do not report DT data
Santiago A, Lamba H, Hart L, Nguyen M, Alnajar A, Nair A, *et al.* Significant decrease in HgA1c levels in diabetics after continuous-flow left ventricular assist device implantation. *ASAIO J* 2018;**64**(Suppl. 1):65.	Do not report DT data
Sas G, Chakor H, Bogaty P, Boothroyd L, Guertin J, Lambert L, *et al.* Évaluation des données probantes sur les dispositifs d'assistance ventriculaire gauche HeartMate II® et HeartWare® pour le traitement de l'insuffisance cardiaque chronique terminale [Implantable ventricular assist devices: assessment of evidence and required elements to establish a clinical registry in Québec]. *HTA Database.* 2012.	Duplicate record
Sato T, Seguchi O, Iwashima Y, Yanase M, Nakajima S, Hieda M, *et al.* Serum vrain natriuretic peptide concentration 60 days after surgery as a predictor of long-term prognosis in patients implanted with a left ventricular assist device. *ASAIO J* 2015;**61**:373–8.	Do not report DT data
Schaffer JM, Allen JG, Weiss ES, Arnaoutakis GJ, Patel ND, Russell SD, *et al.* Infectious complications after pulsatile-flow and continuous-flow left ventricular assist device implantation. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 2011;**30**:164–74.	< 50 DT patients
Schaffer JM, Allen JG, Weiss ES, Patel ND, Russell SD, Shah AS, *et al.* Evaluation of risk indices in continuous-flow left ventricular assist device patients. *Ann Thorac Surg* 2009;**88**:1889–96.	< 50 DT patients
Schaffer JM, Arnaoutakis GJ, Allen JG, Weiss ES, Patel ND, Russell SD, *et al.* Bleeding complications and blood product utilization with left ventricular assist device implantation. *Ann Thorac Surg* 2011;**91**:740–7; discussion 747.	< 50 DT patients
Scheiderer R, Belden C, Schwab D, Haney C, Paz J. Exercise guidelines for inpatients following ventricular assist device placement: a systematic review of the literature. *Cardiopulm Phys Ther J* 2013;**24**:35–42.	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Schenk S, McCarthy PM, Blackstone EH, Feng J, Starling RC, Navia JL, *et al.* Duration of inotropic support after left ventricular assist device implantation: risk factors and impact on outcome. *J Thorac Cardiovasc Surg* 2006;**131**:447–54.	Do not report DT data
Schettle S, Alnsasra H, Clavell A, Daly R, Glasgow A, Habermann E, *et al.* Opioid usage in patients undergoing left ventricular assist device implantation: correlation to patient characteristics and outcomes? *ASAIO J* 2019;**65**(Suppl. 1):99.	Do not report DT data
Schettle S, Pereira N, Kushwaha S, Daly R, Joyce D, Joyce L, *et al.* Morbidity risks with long term left ventricular assist device (LVAD) support. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S419.	Do not report DT data
Schettle S, Shahin Y, Rosenbaum A, Schirger J, Weber M, Tchantchaleishvili V, *et al.* Heart failure duration association with gastrointestinal bleeding post left ventricular assist device. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S394–5.	Do not report DT data
Schettle S, Shanin Y, Schirger J, Pahwa S, Weber M, Tchantchaleishvili V, *et al.* Impact of gastrointestinal bleeding burden with subsequent outcomes after left ventricular assist device implant. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S399–S400.	Do not report DT data
Schlensak C, Benk C, Siepe M, Heilmann C, Beyersdorf F. Clinical experience with the VentrAssist left ventricular assist device. *Thorac Cardiovasc Surg* 2010;**58**(Suppl. 2):S198–201.	Do not report DT data
Schloglhofer T, Blood M, Pietropaolo J, Lantz J. Alleviation of VAD coordinator time burden and empowerment of HVAD patients in order to improve outcomes. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S294–5.	Do not report DT data
Schmidt S, Reichart D, Brand C, Wagner F, Bernhardt A, Blankenberg S, *et al.* 2-year follow-up after minimally-invasive left ventricular assist device implantation – a single center experience. *Transpl Int* 2017;**30**(Suppl. 4):43.	Do not report DT data
Schmidt T, Bjarnason-Wehrens B, Bartsch P, Deniz E, Schmitto J, Schulte-Eistrup S, *et al.* Exercise capacity and functional performance in heart failure patients supported by a left ventricular assist device at discharge from inpatient rehabilitation. *Artif Organs* 2018;**42**:22–30.	< 50 DT patients
Schmidt T, Bjarnason-Wehrens B, Mommertz S, Hannig M, Schulte-Eistrup S, Willemsen D, *et al.* Changes in total cardiac output and oxygen extraction during exercise in patients supported with an HVAD left ventricular assist device. *Artif Organs* 2018;**42**:686–94.	< 50 DT patients
Schmitto J, Dogan G, Hanke SJ, Riebandt J, Ozbaran M, Engin C, *et al.* A multicenter analysis of implantation via a thoracotomy approach of a left ventricular assist system for the treatment of advanced heart failure. Thoracic and Cardiovascular Surgeon Conference: 48th Annual Meeting German Society for Thoracic, Cardiac, and Vascular Surgery Germany. 2019;67.	Do not report DT data
Schrage B, Rubsamen N, Magnussen C, Gummert J, Schonrath F, de By T, *et al.* Derivation and validation of the EUROMACS left ventricular assist device score for long-term outcome - the EUROMACS-LVAD-score. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S107–8.	Do not report DT data
Schramm R, Zittermann A, Morshuis M, Schoenbrodt M, Rossing Freifrau EV, Hakim-Meibodi K, *et al.* Short-term outcome after centrifugal continuous flow left ventricular assist device implantation comparing the HeartWare, HVAD, and Abbot HeartMate III. Thoracic and Cardiovascular Surgeon Conference: 48th Annual Meeting German Society for Thoracic, Cardiac, and Vascular Surgery Germany. 2019;67.	Do not report DT data
Schramm R, Zittermann A, Morshuis M, Schoenbrodt M, von Roessing E, von Dossow V, *et al.* Comparing short-term outcome after implantation of the HeartWare HVAD and the Abbott HeartMate 3. *ESC Heart Fail* 2020.	Do not report DT data
Schultz J, Masotti M, Maharaj V, El Rafei A, Shaffer A, John R, *et al.* Impact of acute liver injury prior to left ventricular assist device therapy. *J Heart Lung Transplant* 2021;**40**(4 Suppl.):S437.	Do not report DT data
Schultz JN, Goodwin K, John R, Alexy T, Kamdar F, Martin C, *et al.* Association between angiotensin II receptor blockade and recurrent gastrointestinal bleeding on left ventricular assist device support. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S163.	Do not report DT data
Schultz JN, John R, Martin CM, Pritzker M, Missov E, Thenappan T, *et al.* Impact of evaluation of left ventricular apical core pathology obtained at time of LVAD implantation. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S82–3.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Seguchi O, Fujita T, Nakajima S, Sato T, Sunami H, Yanase M, *et al.* Left ventricular assist device therapy for burned-out phase of hypertrophic cardiomyopathy. *Eur Heart J* 2016;**37**(Suppl. 1):537.	Do not report DT data
Sharples LD, Dyer M, Cafferty F, Demiris N, Freeman C, Banner NR, *et al.* Cost-effectiveness of ventricular assist device use in the United Kingdom: results from the Evaluation of Ventricular Assist Device Programme in the UK (EVAD-UK). *J Heart Lung Transplant* 2006;**25**:1336–43.	Wrong patient population
Shatla I, Abumoawad A, Cheng AL, Lopez Candales A. Impact of kidney disease on left ventricular assisted device outcomes: insight from National Readmission Database. *Eur Heart J* 2021;**42**(Suppl. 1):944.	Do not report DT data
Sheikh FH, Ahmed S, Rodrigo ME, Hofmeyer M, Kadakkal A, Grinstein J, *et al.* Long term outcomes of African-American LVAD recipients. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S338–9.	Do not report DT data
Sheikh FH, Majure DT, Ahmed S, Rodrigo ME, Jani SM, Hofmeyer M, *et al.* Obesity does not impact 1 year survival after LVAD implantation. *J Card Fail* 2016;**22** Suppl. 8):S110.	Do not report DT data
Sheikh FH, Majure DT, Rodrigo ME, Jani SM, Hofmeyer M, Boyce SW, *et al.* Characteristics and outcomes of African American LVAD recipients: a single center experience. *J Heart Lung Transplant* 2016;(1):S125.	Do not report DT data
Sherazi S, Ayers B, Polonsky B, McNitt S, Kutyifa V, Alexis J, *et al.* Association of cardiac rehabilitation with improved gealthcare utilization and long-term survival after left ventricular assist device implantation. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S110.	Do not report DT data
Shurrab M, Pettit S, Park S, Atturman S, Sbaih A, Khaleel G, *et al.* Is there a role for ICDs in LVAD patients? A meta-analysis. *Eur Heart J* 2016:103.	Do not report DT data
Siegenthaler MP, Frazier OH, Beyersdorf F, Martin J, Laks H, Elefteriades J, *et al.* Mechanical reliability of the Jarvik 2000 Heart. *Ann Thorac Surg* 2006;**81**:1752–8; discussion 1758.	< 50 DT patients
Silver SA, Long J, Zheng Y, Chertow GM. Outcomes after left ventricular assist device implantation in patients with AKI. *J Am Soc Nephrol* 2018;**29**:32.	Do not report DT data
Silvestry SC, Mahr C, Slaughter MS, Levy WC, Cheng RK, May DM, *et al.* Cost-effectiveness of a small intrapericardial centrifugal left ventricular assist device. *ASAIO J* 2020;**66**:862–70.	Duplicate record
Sims DB, Luke A, Rangasamy S, Borukhov E, Saeed O, Murthy S, *et al.* Reducing 30-day hospital readmission rate in left ventricular assist device patients with a structured readmission improvement plan. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S197–8.	Do not report DT data
Sladen RN, Shulman MA, Javaid A, Hodgson C, Myles PS, McGiffin D, *et al.* Postdischarge functional capacity, health-related quality of life, depression, anxiety, and post-traumatic stress disorder in patients receiving a long-term left ventricular assist device. *J Card Fail.* 2021.	Do not report DT data
Slaughter MS. Destination therapy: the future is arriving. *Congest Heart Fail* 2005;**11**:155–6.	Wrong study design
Slivnick J, Lampert B, Xu Y, Andrei A, Warzecha A, Kao A, *et al.* Association of patient health-related quality of life and caregiver burden in older heart failure patients receiving advanced therapies: findings from the SustaInIng QualItY of Life of the Aged: Transplant or Mechanical Support (SustAIn-it) study. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S438.	Do not report DT data
Smedira NG, Hoercher KJ, Lima B, Mountis MM, Starling RC, Thuita L, *et al.* Unplanned hospital readmissions after HeartMate II implantation: frequency, risk factors, and impact on resource use and survival. *JACC Heart Fail* 2013;**1**:31–9.	< 50 DT patients
Solanki M, Dobson L, Alwair H, Ghafghazi S, Wysoczynski M, Slaughter MS, *et al.* Association of temporal trends in neutrophil lymphocyte ratio on left ventricular assist device patient outcomes. *Artif Organs* 2021;**45**:742–7.	Do not report DT data
Soleimani B, Haouzi A, Manoskey A, Stephenson ER, El-Banayosy A, Pae WE. Development of aortic insufficiency in patients supported with continuous flow left ventricular assist devices. *ASAIO J* 2012;**58**:326–9.	< 50 DT patients

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Soliman OII, Akin S, Muslem R, Boersma E, Manintveld OC, Krabatsch T, *et al.* Derivation and validation of a novel right-sided heart failure model after implantation of continuous flow left ventricular assist devices: the EUROMACS (European Registry for Patients with Mechanical Circulatory Support) right-sided heart failure risk score. *Circulation* 2018;**137**:891–906.	Do not report DT data
Soni M, Birati EY, Marble J, Eckman P, Garberich R, Weaver C, *et al.* Gender and spirituality influence patient care decisions after LVAD. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S441.	Do not report DT data
Sotolongo A. High grade mitral regurgitation after a left ventricular assist device may adversely affect survival. *J Heart Lung Transplant* 2017;36(4 Suppl. 1):S344.	Do not report DT data
Sparrow CT, Raymer DS, Radhakrishnan SL, Nassif ME, Vader JM, LaRue SJ, *et al.* The effect of pump speed settings on suspected pump thrombosis in patients supported with continuous-flow left ventricular assist devices. *J Card Fail* 2016;**22**(Suppl. 8):S108–9.	Do not report DT data
Spratt JR, Roy S, Plack D, John R, Liao K, Cogswell RJ. Survival and driveline infection rates in patients on chronic immunosuppressive therapy who undergo left ventricular assist device implantation. *J Heart Lung Transplant* 2016;(1):S265.	Do not report DT data
Stawiarski K, Agboola O, Jacoby D, Bellumkonda L, Ahmad T, Sugeng L, *et al.* Chloride homeostasis in end stage heart failure and LVAD recipients. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S382–3.	Do not report DT data
Stawiarski K, Zogg C, Park J, Jacoby D, Bellumkonda L, Chen M, *et al.* Gender and diastolic dysfunction may be the driver of failure of myocardial recovery following LVAD implantation. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S311.	Do not report DT data
Stern B, Maheshwari P, Gorrepati VS, Chintanaboina J, Bethards D, Boehmer J, *et al.* Predictors of index gastrointestinal bleed in left ventricular assist device (LVAD) patients. *Gastrointest Endosc* 2020;**91**(6 Suppl.):AB569–70.	Do not report DT data
Strout S, Veasey T, Rieger K, Floroff C, Wray D, Brisco M, *et al.* Suppressive antibiotics for LVAD-associated infections: are they helpful or harmful? *J Heart Lung Transplant* 2016;(1):S75–6.	Do not report DT data
Stulak JM, Davis ME, Haglund N, Dunlay S, Cowger J, Shah P, *et al.* Adverse events in contemporary continuous-flow left ventricular assist devices: a multi-institutional comparison shows significant differences. *J Thorac Cardiovasc Surg* 2016;**151**:177–89.	Do not report DT data
Stulak JM, Tchantchaleishvili V, Dunlay S, Sharma S, Joyce LD, Joyce DL, *et al.* Association of late aortic and tricuspid valve regurgitation and outcomes while on left ventricular assist device therapy. *J Heart Lung Transplant* 2016;(1):S127.	Do not report DT data
Suboc TMB, Ahmed K, Kabir C, Graney N, Paliga R, Meehan K, *et al.* Elderly heart failure patients with left ventricular assist device: mortality, hospital readmission, length of stay, and adverse events. Circulation Conference: Resuscitation Science Symposium, ReSS. 2017;136.	Do not report DT data
Sugiura T, Kurihara C, Kawabori M, Cohn WE, Civitello AB, Frazier OH, *et al.* Concomitant valve procedures are not associated with higher perioperative mortality. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S171–2.	Do not report DT data
Sugiura T, Kurihara C, Kawabori M, Cohn WE, Civitello AB, Frazier OH, *et al.* Readmission within 30 days after continuous flow ventricular assist devices implantation-comparative analysis of heartmate II and heartware devices. *J Heart Lung Transplant* 2017;**36** 4 Suppl. 1):S425.	Do not report DT data
Sugiura T, Kurihara C, Kawabori M, Critsinelis AC, Wang S, Civitello AB, *et al.* Concomitant valve procedures in patients undergoing continuous-flow left ventricular assist device implantation: a single-center experience. *J Thorac Cardiovasc Surg* 2019;**158**:1083–9.e1.	Do not report DT data
Sultan M, Flores E, Verma D, Argarwal S, Rayyan E, Loli A, *et al.* Incidence and current management of left ventricular assist device thrombus. *Eur Heart J* 2017;**38**(Suppl. 1):1046–7.	Do not report DT data
Sundararajan S, Kiernan MS, DeNofrio D, Vest AR. Cachexia is common in ventricular assist device recipients but not predictive of mortality. *J Card Fail* 2016;**22**(Suppl. 8):S57–8.	Do not report DT data
Suzuki K, Yoshioka D, Toda K, Miyagawa S, Yoshikawa Y, Hata H, *et al.* Outcomes of left ventricular assist device for patients with hypertrophic cardiomyopathy. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S153.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Szentmihalyi I, Barabas JI, Bali A, Kapus G, Tamas C, Sax B, *et al.* [Heart transplantation and long-term lvad support cost-effectiveness model]. *Magyar Sebeszet* 2016;**69**:186–93.	Wrong study design
Takeda K, Naka Y, Yang JA, Uriel N, Colombo PC, Jorde UP, *et al.* Outcome of unplanned right ventricular assist device support for severe right heart failure after implantable left ventricular assist device insertion. *J Heart Lung Transplant* 2014;**33**:141–8.	Do not report DT data
Takeda K, Takayama H, Garan RA, Topkara VK, Han J, Fukuhara S, *et al.* Contemporary outcome of unplanned right ventricular assist device for severe right heart failure after continuous flow left ventricular assist device insertion. *J Heart Lung Transplant* 2016;(1):S55.	Do not report DT data
Takeda K, Takayama H, Kalesan B, Uriel N, Colombo PC, Jorde UP, *et al.* Long-term outcome of patients on continuous-flow left ventricular assist device support. *J Thorac Cardiovasc Surg* 2014;**148**:1606–14.	< 50 DT patients
Taleb I, Wever-Pinzon O, Alharethi R, Overton S, Nativi-Nicolau J, Dranow E, *et al.* Predicting right ventricular failure in chronic heart failure patients receiving left ventricular assist device. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S426.	Do not report DT data
Taleb I, Yin M, Koliopoulou A, Taleb M, Dranow E, Kemeyou L, *et al.* Cardiac reverse remodeling and recovery in dilated cardiomyopathy medication-naive patients requiring durable left ventricular assist device support. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S125.	Do not report DT data
Taleb I, Yin MY, Koliopoulou AG, Taleb M, Dranow E, Kemeyou L, *et al.* Cardiac reverse remodeling and recovery in dilated cardiomyopathy medication-naive patients requiring durable left ventricular assist device support. *Eur Heart J* 2019;**40**(Suppl. 1):3305.	Do not report DT data
Tam MC, Patel VN, Weinberg RL, Hulten EA, Aaronson KD, Pagani FD, *et al.* Diagnostic Accuracy of FDG PET/CT in suspected LVAD infections: a case series, systematic review, and meta-analysis. *JACC Cardiovasc Imaging* 2019;**13**:1191–202.	Wrong study design
Tantrachoti P, Klomjit S, Vutthikraivit W, Prieto S, Gongora E, Nair N. Impact of preoperative atrial fibrillation in patients with left ventricular assist device: a systematic review and meta-analysis. *Artif Organs* 2019;**43**:1135–43.	Do not report DT data
Tarzia V, Di Giammarco G, Bagozzi L, Bortolussi G, Maccherini M, Marinelli D, *et al.* From bench to bedside: impact of left ventricular assist device outflow conduit anastomosis position on outcome. *Artif Organs* 2021;**45**:236–43.	Do not report DT data
Tarzia V, Di Giammarco G, Di Mauro M, Bortolussi G, Maccherini M, Tursi V, *et al.* From bench to bedside: can the improvements in left ventricular assist device design mitigate adverse events and increase survival? *J Thorac Cardiovasc Surg* 2016;**151**:213–7.	Do not report DT data
Tarzia V, Di Giammarco G, Maccherini M, Maiani M, Agostoni P, Bagozzi L, *et al.* Technology and techniques: tools to mitigate adverse events and improve survival in left ventricular assist device patients. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S441–2.	Do not report DT data
Tarzia V, Di Mauro M, Bortolussi G, Bejko J, Marinelli D, Foschi M, *et al.* Access matters: survival advantage with minimally invasive implantation of LVAD as destination therapy. *J Heart Lung Transplant* 2016;(1):S53.	Do not report DT data
Tarzia V, Di Mauro M, Bortolussi G, Bejko J, Marinelli D, Foschi M, *et al.* Access matters: survival advantage with minimally invasive implantation of LVAD as destination therapy. *J Heart Lung Transplant* 2016;**35**(4 Suppl.):S53.	Do not report DT data
Tchantchaleishvili V, Luc JGY, Haswell J, Hallian W, Massey HT. Subxiphoid exchange of HeartMate II left ventricular assist device. *ASAIO J* 2017;**63**:414–8.	Do not report DT data
Teigen LM, Earthman CP, Hodges J, Shultz J, Martin C, John R, *et al.* A risk model incorporating pectoralis muscle measures more accurately risk predicts mortality after left ventricular assist device implantation. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S463.	Do not report DT data
Ternus B, Behfar A, Schirger J, Maltais S, Barsness G, Stulak J, *et al.* Pressure adjusted heart rate as a predictor of adverse outcomes after left ventricular assist device implantation. Circulation Conference. 2018;138.	Do not report DT data

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Teuteberg J, Kormos RL, Pagani FD, Kiernan MS, Naftel DC, Myers SL, *et al.* New definition, same old problem: characterizing the condition of right heart failure in INTERMACS. *J Heart Lung Transplant* 2016;(1):S266–7.	Do not report DT data
Teuteberg J, Studdard G, Pagani F, Kiernan M, Oliveria G, Rame E, *et al.* The ebb and flow of right heart failure in INTERMACS: does right heart failure get better or worse over time? *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S377–8.	Do not report DT data
Teuteberg JJ, Studdard G, Pagani F, Kiernan M, Oliveria G, Rame E, *et al.* The incidence of early and late clinical right heart failure and the impact on survival after continuous flow mechanical support: insights from the new intermacs definition of right heart failure. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S141.	Do not report DT data
Tigges-Limmer K, Kugler C, Brocks Y, Winkler Y, Rehn E, Morshuis M, *et al.* Psychosocial and sexual functioning in patients on ventricular assist device support – a crosssectional pilot study. *Transpl Int* 2016;**29**(Suppl. 3):49–50.	Do not report DT data
Toda K, Fujita T, Domae K, Shimahara Y, Kobayashi J, Nakatani T. Late aortic insufficiency related to poor prognosis during left ventricular assist device support. *Ann Thorac Surg* 2011;**92**:929–34.	Do not report DT data
Topilsky Y, Hasin T, Oh JK, Borgeson DD, Boilson BA, Schirger JA, *et al.* Echocardiographic variables after left ventricular assist device implantation associated with adverse outcome. *Circ Cardiovasc Imaging* 2011;**4**:648–61.	< 50 DT patients
Topilsky Y, Oh JK, Shah DK, Boilson BA, Schirger JA, Kushwaha SS, *et al.* Echocardiographic predictors of adverse outcomes after continuous left ventricular assist device implantation. *Jacc: Cardiovasc Imaging* 2011;**4**:211–22.	Do not report DT data
Topilsky Y, Pereira NL, Shah DK, Boilson B, Schirger JA, Kushwaha SS, *et al.* Left ventricular assist device therapy in patients with restrictive and hypertrophic cardiomyopathy. *Circ Heart Fail* 2011;**4**:266–75.	Do not report DT data
Topkara VK, Dang NC, Barili F, Cheema FH, Martens TP, George I, *et al.* Predictors and outcomes of continuous veno-venous hemodialysis use after implantation of a left ventricular assist device. *J Heart Lung Transplant* 2006;**25**:404–8.	Do not report DT data
Topkara VK, Kondareddy S, Malik F, Wang IW, Mann DL, Ewald GA, *et al.* Infectious complications in patients with left ventricular assist device: etiology and outcomes in the continuous-flow era. *Ann Thorac Surg* 2010;**90**:1270–7.	< 50 DT patients
Tremblay PL, Herman CR, Baskett RJ. Reversibility of pulmonary hypertension with LVAD support; a meta-analysis of published reports. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S492.	Do not report DT data
Tremblay PL, Stewart SA, Baskett RJ. The effect of Left Ventricular Assist Devices (LVAD) on pulmonary hypertension: a single center review. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S491–2.	Do not report DT data
Tripathi B, Schneider M, Rizwan T, Arora S, Dave M, Shah H, et al. National trends in the utilization, cost burden and outcomes associated with use of long-term mechanical circulatory support: 10-year experience. Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC. 2018;71.	Do not report DT data
Truss W, Welden C, Edwards AL, Pamboukian SV, Peter S. Clinical predictors for repeat hospitalizations in LVAD patients with gastrointestinal bleeding. *Gastroenterology* 2016;(1):S238–9.	Do not report DT data
Tsay J, Lampert B, Whitson B, Hasson R, Emani R, Hasan A, *et al.* Worsening renal function in patients with low output decompensated heart failure is associated with 1-year mortality. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S216.	Do not report DT data
Tsiouris A, Brewer RJ, Borgi J, Hodari A, Nemeh HW, Cogan CM, *et al.* Is resternotomy a risk for continuous-flow left ventricular assist device outcomes? *J Card Surg* 2013;**28**:82–7.	< 50 DT patients
Tsiouris A, Brewer RJ, Borgi J, Nemeh H, Paone G, Morgan JA. Continuous-flow left ventricular assist device implantation as a bridge to transplantation or destination therapy: racial disparities in outcomes. *J Heart Lung Transplant* 2013;**32**:299–304.	< 50 DT patients

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Tsiouris A, Morgan JA, Nemeh HW, Hodari A, Brewer RJ, Paone G. Sex-specific outcomes in patients receiving continuous-flow left ventricular devices as a bridge to transplantation or destination therapy. *ASAIO J* 2014;**60**:199–206.	Do not report DT data
Tsiouris A, Paone G, Nemeh HW, Brewer RJ, Morgan JA. Factors determining post-operative readmissions after left ventricular assist device implantation. *J Heart Lung Transplant* 2014;**33**:1041–7.	Do not report DT data
Tsui SSL. Updates on cardiac transplant and LVAD implants across the UK and Europe. *Heart Asia* 2019;**11**(Suppl. 1):A2.	Do not report DT data
Tsyganenko D, Gromann TW, Schoenrath F, Mueller M, Mulzer J, Starck C, *et al.* Predictors of mid-term outcomes in patients undergoing implantation of a ventricular assist device directly after extracorporeal life support. *Eur J Cardio-Thorac Surg* 2019;**55**:773–9.	Do not report DT data
Tsyganenko D, Hennig F, Kaufmann F, Starck C, Schonrath F, Falk V, *et al.* Predictors for early and midterm outcome after bridge to left ventricular assist device by extracorporeal life support. Thoracic and Cardiovascular Surgeon Conference: 47th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery, DGTHG. 2018;66.	Do not report DT data
Ullah W, Sattar Y, Darmoch F, Al-Khadra Y, Mir T, Ajmal R, *et al.* The impact of peripheral arterial disease on patients with mechanical circulatory support. *Int J Cardiol Heart Vasc* 2020;**28**:100509.	Do not report DT data
Unlu O, Alemany HS, Pabon M, Sobol I, Krishnan U, Goyal P, *et al.* Renal outcomes following left ventricular assist device placement: a single center experience. *J Card Fail* 2020;**26**(10 Suppl.):S160–1.	Do not report DT data
Uribarri A, Rojas SV, Hanke JS, Avsar M, Dogan G, Deniz E, *et al.* Is ICD implantation necessary in patients with left ventricular assist device therapy? *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S14–5.	Do not report DT data
Uriel N, Colombo PC, Cleveland J, Long J, Salerno CT, Goldstein D, *et al.* Hemocompatibility-related outcomes in the multicenter study of maglev technology in patients undergoing mechanical circulatory support therapy with HeartMate 3 (MOMENTUM 3) pivotal trial. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S65.	Do not report DT data
Uriel N, Mehra M. Long-term burden of hemocompatibility related adverse events in the MOMENTUM 3 trial: final analysis of the 1028 patient cohort. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S67.	Do not report DT data
Usoh C, Sherazi S, Szepietowska B, Kutyifa V, McNitt S, Papernov A, *et al.* Diabetes increases risk of mortality in heart failure patients who undergo left ventricular assist device implantation. Endocrine Reviews Conference: 99th Annual Meeting of the Endocrine Society, ENDO. 2017;38.	Do not report DT data
Usoh CO, Sherazi S, Szepietowska B, Kutyifa V, McNitt S, Papernov A, *et al.* Influence of diabetes mellitus on outcomes in patients after left ventricular assist device implantation. *Ann Thorac Surg* 2018;**106**:555–60.	Do not report DT data
van den Bergh WM, Lansink-Hartgring AO, van Duijn AL, Engstrom AE, Lahpor JR, Slooter AJ. Thromboembolic stroke in patients with a HeartMate-II left ventricular assist device – the role of anticoagulation. *J Cardiothorac Surg* 2015;**10**:128.	Do not report DT data
VanderPluym CJ, Cedars A, Eghtesady P, Maxwell BG, Gelow JM, Burchill LJ, *et al.* Outcomes following implantation of mechanical circulatory support in adults with congenital heart disease: an analysis of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). *J Heart Lung Transplant* 2018;**37**:89–99.	Wrong outcomes
VanderPluym CJ, Eghtesady P, Maxwell BG, Gelow JM, Burchill LJ, Maltais S, *et al.* Utilization and outcomes of ventricular assist device support in adult congenital heart disease: an analysis of the interagency registry for mechanically assisted circulatory support (INTERMACS). *J Heart Lung Transplant* 2016;(1):S151–2.	Do not report DT data
Veasey TM, Floroff CK, Strout SE, McElray KL, Brisco-Bacik MA, Cook JL, *et al.* Evaluation of anticoagulation and nonsurgical major bleeding in recipients of continuous-flow left ventricular assist devices. *Artif Organs* 2019;**43**:736–44.	Wrong outcomes

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TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Veen KM, Muslem R, Soliman OI, Caliskan K, Kolff MEA, Dousma D, *et al.* Left ventricular assist device implantation with and without concomitant tricuspid valve surgery: a systematic review and meta-analysis. *Eur J Cardio-Thorac Surg* 2018;**54**:644–51.	Wrong outcomes
Vellanki NS, Kennedy K, Grandin EW, Garan AR, Motiwala SR, Quintero P, *et al.* Women have more early right heart failure but no increase in later right heart failure after LVAD implantation: an INTERMACS analysis. *J Card Fail* 2020;**26** 10 Suppl.):S145.	Do not report DT data
Vellipuram AR, Chaudary Chaudary MR, Maud A, Rodriguez Rodriguez G, Piriyawat P, Cruz-Flores S, *et al.* Cerebrovascular events as complication of left ventricular assist device: analysis of nationwide inpatient sample (NIS) database (2005-2014). *Eur Stroke J* 2019;**4**(Suppl. 1):715.	Do not report DT data
Verma S, Bassily E, Leighton S, Mhaskar R, Sunjic I, Martin A, *et al.* Renal function and outcomes with use of left ventricular assist device implantation and inotropes in end-stage heart failure: a retrospective single center study. *J Clin Med Res* 2017;**9**:596–604.	Do not report DT data
Vest AR, Kennel PJ, Maldonado D, Young JB, Mountis MM, Naka Y, *et al.* Recovery of serum cholesterol predicts survival after left ventricular assist device implantation. *Circ Heart Fail* 2016;**9**:09.	Do not report DT data
Vidula H, Chen A, Tankut S, Yoruk A, Alexis J, Gosev I, *et al.* Arrhythmia burden from implantable device interrogation during long-term follow-up in LVAD patients. *J Heart Lung Transplant* 2021;**40**(4 Suppl.):S395.	Do not report DT data
Vidula H, Kutyifa V, Johnson BA, Strawderman RL, Harrington D, Polonsky B, *et al.* Readmission patterns during long-term follow-up after left ventricular assist device implantation. *Am J Cardiol* 2018;**122**:1021–7.	Wrong outcomes
Vidula H, McNitt S, Papernov A, Wang M, Kutyifa V, Alexis JD. Clinical relevance of late and very late right heart failure after LVAD implantation. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S423.	Do not report DT data
Vidula H, McNitt S, Wang M, Polonsky B, Sherazi S, Ayers B, *et al.* Long-term survival of patients requiring early temporary RVAD support following LVAD implantation. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S358.	Do not report DT data
Vidula H, McNitt S, Wang M, Polonsky S, Sherazi S, Gosev I, *et al.* Time-dependent association of renal function with long-term survival following LVAD implantation. *J Heart Lung Transplant* 2019;**38**(4 Suppl.):S233–4.	Do not report DT data
Vidula H, Wang M, Antaki J, Polonsky B, Sherazi S, Alexis J, *et al.* Risk score for mortality prediction after one-year on left ventricular assist device support. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S181.	Do not report DT data
Vierecke J, Gahl B, de By T, Antretter H, Beyersdorf F, Caliskan K, *et al.* Results of primary biventricular support: an analysis of data from the EUROMACS registry. *Eur J Cardio-Thorac Surg* 2019;**56**:1037–45.	Do not report DT data
Vierecke J, Gahl B, De By TM, Loforte A, Mohacsi P. The purpose of this study was to analyze pre-and postoperative bvad euromacs-registry patient data. *Artif Organs* 2020;**44**(3):E75–6.	Do not report DT data
Vinholo TF, Mullan CW, Mori M, Caraballo C, Ravindra NG, Miller E, *et al.* Outcomes of left ventricular assist device implantation with mitral regurgitation with and without concomitant mitral operation. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S441–2.	Do not report DT data
Volkovicher N, Kurihara C, Critsinelis A, Kawabori M, Sugiura T, Manon M, 2nd, *et al.* Outcomes in patients with advanced heart failure and small body size undergoing continuous-flow left ventricular assist device implantation. *J Artif Organs* 2018;**21**:31–8.	Duplicate record
Vora TA, Afari-Armah N, Hofmeyer M, Sheikh FH, Rodrigo M, Molina E, *et al.* Heart failure hospitalizations in a contemporary LVAD population. *J Card Fail* 2017;**23**(8 Suppl. 1):S59–60.	Do not report DT data
Vrtovec B, Radovancevic R, Delgado RM, Radovancevic B, Bracey AW, Gregoric ID, *et al.* Significance of anaemia in patients with advanced heart failure receiving long-term mechanical circulatory support. *Eur J Heart Fail* 2009;**11**:1000–4.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Wagner T, Schrage B, Bernhardt A, Reichenspurner H, Blankenberg S, Grahn H. Right heart failure before predicts right heart failure after LVAD implantation. *Eur Heart J* 2018;**39**(Suppl. 1):385.	Do not report DT data
Ward ST, Liang Q, Pagani FD, Zhang M, Kormos RL, Aaronson KD, *et al.* A roadmap for evaluating the use and value of durable ventricular assist device therapy. *J Heart Lung Transplant* 2018;**37**:146–50.	Wrong study design
Warraich HJ, Allen LA, Blue LJ, Chaussee EL, Thompson JS, McIlvennan CK, *et al.* Comorbidities and the decision to undergo or forego destination therapy left ventricular assist device implantation: an analysis from the Trial of a Shared Decision Support Intervention for Patients and their Caregivers Offered Destination Therapy for End-Stage Heart Failure (DECIDE-LVAD) study. *Am Heart J* 2019;**213**:91–6.	Wrong intervention
Wasson LT, Yuzefpolskaya M, Wakabayashi M, Takayama H, Naka Y, Uriel N, *et al.* Hypertension: an unstudied potential risk factor for adverse outcomes during continuous flow ventricular assist device support. *Heart Fail Rev.* 2014;05.	Wrong study design
Waters SB, Sheridan BC, Watkins R, Duva M, Chang PP, Katz JN. Survival and thrombotic events in left ventricular assist device patients are not influenced by socioeconomic status. *J Heart Lung Transplant* 2016;(1):S166.	Do not report DT data
Wavell C, Sokolowski A, Klingel ML, Yin C, Nagpal AD. Clinical effectiveness of therapy with continuous-flow left ventricular assist devices in nonischemic versus ischemic cardiomyopathy: a systematic review and meta-analysis. *Can J Surg* 2021;**64**:E39–47.	Do not report DT data
Welp H, Dell'Aquila A, Hoffmeier A, Scherer M. Medical and financial considerations regarding long-term mechanical left ventricular support. Thoracic and Cardiovascular Surgeon Conference: 49th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery Germany. 2020;68.	Duplicate record
Welp HA, Dell'Aquila AM, Hoffmeier A, Martens S, Scherer M. Medical and economic consideration regarding long term mechanical left ventricular support. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S366.	Do not report DT data
Westaby S, Siegenthaler M, Beyersdorf F, Massetti M, Pepper J, Khayat A, *et al.* Destination therapy with a rotary blood pump and novel power delivery. *Eur J Cardio-Thorac Surg* 2010;**37**:350–6.	< 50 DT patients
Westhofen S, Bernhardt A, Reichenspurner H, Barten M. Gender differences in cardiac reverse remodeling in mechanically unloaded hearts. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S385.	Do not report DT data
Westhofen S, Bernhardt A, Reichenspurner H, Barten M. Gender differences in cardiac reverse remodeling in mechanically unloaded hearts. Thoracic and Cardiovascular Surgeon Conference: 48th Annual Meeting German Society for Thoracic, Cardiac, and Vascular Surgery Germany. 2019;67.	Do not report DT data
Westhofen S, Bernhardt A, Sadeq A, Reichenspurner H, Barten M. Cardiac reverse remodeling in mechanically unloaded hearts: analysis of gender-specific differences. Thoracic and Cardiovascular Surgeon Conference: 49th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery Germany. 2020;68.	Do not report DT data
Wever Pinzon JR, Wang W, Hu N, Larsen R, Yu T, Yin L, *et al.* Outcomes of Asian-Americans undergoing left ventricular assist device implantations as a bridge to transplant or destination therapy: an intermacs analysis. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S253–4.	Do not report DT data
White-Williams C, Fazeli-Wheeler P, Myers S, Kirklin J, Pamboukian S, Naftel D, *et al.* HRQOL improves from before to 2 years after MCS, regardless of implant strategy: analyses from INTERMACS. *J Heart Lung Transplant* 2016;(1):S25.	Do not report DT data
Whitson BA, Eckman P, Kamdar F, Lacey A, Shumway SJ, Liao KK, *et al.* Hemolysis, pump thrombus, and neurologic events in continuous-flow left ventricular assist device recipients. *Ann Thorac Surg* 2014;**97**:2097–103.	Do not report DT data

continued

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Wilcox J, Kao AC, Hsich E, Dew MA, Kormos R, Andrei AC, *et al.* Change in caregiver health-related quality of life from before to early after surgery: findings from the Sustaining Quality of Life of the Aged: Transplant or Mechanical Support (SUSTAIN-IT) study. *J Card Fail* 2019;**25**(8 Suppl.):S15–6.	Do not report DT data
Wilhelms LA, Blumenthal-Barby JS, Kostick KM, Estep JD, Bruce CR. Patients' perspectives on transplantation while undergoing left ventricular assist device support. *ASAIO J* 2017;**63**:740–4.	< 50 DT patients
Witman MA, Garten RS, Gifford JR, Groot HJ, Trinity JD, Stehlik J, *et al.* Further peripheral vascular dysfunction in heart failure patients with a continuous-flow left ventricular assist device: the role of pulsatility. *JACC Heart Fail* 2015;**3**:703–11.	Do not report DT data
Wong JK, Forrest A, Sherazi S, Chen L, Alexis J, Friedman SM, *et al.* Recurrent falls in patients with CF-LVAD's are associated with major morbidity and mortality. *J Heart Lung Transplant* 2017;**36**(4 Suppl. 1):S100–1.	Do not report DT data
Wood CT, O'Malley TJ, Maynes EJ, Vishnevsky A, Morris RJ, Samuels LE, *et al.* Survival outcomes of stenting outflow graft stenosis in continuous-flow left ventricular assist devices: a systematic review. *Heart Fail Rev.* 2019.	< 50 DT patients
Worku B, Gambardella I, Rahouma M, Demetres M, Gaudino M, Girardi L. Thoracotomy versus sternotomy? The effect of surgical approach on outcomes after left ventricular assist device implantation: a review of the literature and meta-analysis. *J Card Surg* 2021.	Wrong intervention
Wu L, Weng YG, Dong NG, Krabatsch T, Stepanenko A, Hennig E, *et al.* Outcomes of HeartWare ventricular assist system support in 141 patients: a single-centre experience. *Eur J Cardio-Thorac Surg* 2013;**44**:139–45.	< 50 DT patients
Wu S, Xu P, Lee A, Fong M. Coronary artery disease and right ventricular function predict outcomes after ventricular assist device placement. Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC. 2018;71.	Do not report DT data
Xu PZ, Wu S, Tun H, Adenuga G, Fong M. Impact of contemporary ventricular assist device therapy on renal outcomes in end stage heart failure. *J Heart Lung Transplant* 2018;**37** (4 Suppl. 1):S473–4.	Do not report DT data
Xuereb L, Go PH, Kaur B, Akrawe S, Nemeh HW, Borgi J, *et al.* Impact of preoperative atrial fibrillation on postoperative thromboembolic events after left ventricular assist device implantation. *Ann Thorac Surg* 2016;**102**:1543–9.	Do not report DT data
Xuereb L, Kaur B, Akrawe S, Rashty J, Nemeh HW, Borgi J, *et al.* Reoperation for bleeding does not adversely impact long-term outcomes in LVAD recipients. *J Heart Lung Transplant* 2016;(1):S249.	Do not report DT data
Yager JE, Felker GM. Left ventricular assist devices as destination therapy for end-stage heart failure. *Am Heart J* 2004;**148**:252–3.	Wrong study design
Yalcin YC, Rasheed M, Muslem R, Brugts JJ, Constantinescu AA, Manintveld OC, *et al.* Outcomes over one and a half decade following HeartMate II versus HeartMate 3 left ventricular assist device therapy: the Rotterdam experience. *J Heart Lung Transplant* 2021;**40**(4 Suppl.):S422–3.	Do not report DT data
Yang JA, Kato TS, Shulman BP, Takayama H, Farr M, Jorde UP, *et al.* Liver dysfunction as a predictor of outcomes in patients with advanced heart failure requiring ventricular assist device support: use of the Model of End-stage Liver Disease (MELD) and MELD eXcluding INR (MELD-XI) scoring system. *J Heart Lung Transplant* 2012;**31**:601–10.	< 50 DT patients
Yap S, Muslem R, Ramjankhan F, De Jonge N, Constantinescu AA, Manintveld OC, *et al.* Incidence and impact of sustained ventricular arrhythmias after continuous-flow left ventricular assist device implantation. *J Heart Lung Transplant* 2016;(1):S10–1.	Do not report DT data
Yassin AS, Subahi A, Adegbala O, Abubakar H, Akintoye E, Ahmed A, *et al.* Clinical impact of diabetes mellitus on short-term outcomes and in-hospital mortality of cardiac mechanical support with Left Ventricular Assist Device (LVAD): a retrospective study from a National Database. *Cardiovasc Revasc Med* 2019;**20**:883–6.	Do not report DT data

TABLE 29 Full text excluded studies with reasons (*continued*)

Study ID	Reason for exclusion
Yin C, Wavell C, Sokolowski A, Klingel M, Nagpal D. Clinical effectiveness of continuous-flow LVAD therapy in non-ischemic versus ischemic cardiomyopathy: a systematic review and meta-analysis. *Can J Cardiol* 2020;**36**(10 Suppl.):S61–2.	Do not report DT data
Yin C, Wavell C, Sokolowski A, Klingel M, Nagpal D. Clinical effectiveness of continuous-flow LVAD therapy in non-ischemic versus ischemic cardiomyopathy: a systematic review and meta-analysis. *Can J Cardiol* 2020;**36**:S61–2.	Do not report DT data
Yoshioka D, Takayama H, Colombo PC, Yuzefpolskaya M, Garan AR, Topkara VK, *et al.* Changes in end-organ function in patients with prolonged continuous-flow left ventricular assist device support. *Ann Thorac Surg* 2017;**103**:717–24.	< 50 DT patients
Yost G, Coyle L, Gallagher C, Graney N, Siemeck R, Tatooles A, *et al.* The impact of extreme obesity on outcomes after left ventricular assist device implantation. *J Thorac Dis* 2017;**9**:4441–6.	< 50 DT patients
Yousefzai R, Baykaner T, Rappelt M, Ghashghaei R, Baeza C, Al Khayyat A, *et al.* Neurohormonal therapy in patients with left ventricular assist devices. *J Card Fail* 2016;**22**(Suppl. 8):S63–4.	Do not report DT data
Yuan N, Arnaoutakis GJ, George TJ, Allen JG, Ju DG, Schaffer JM, *et al.* The spectrum of complications following left ventricular assist device placement. *J Card Surg* 2012;**27**:630–8.	< 50 DT patients
Yuzefpolskaya M, Nasiri M, Onat D, Royzman EA, Nwokocha J, Pinsino A, *et al.* Gut microbiome-generated metabolite trimethylamine-n-oxide is reduced after heart transplantation and continuous flow left ventricular assist device therapy in advanced heart failure patients. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S235.	Do not report DT data
Zalawadiya S, Shah A, Keebler M, John R, Gregoric I, Kilic A, *et al.* Impact of anemia on survival among patients with durable ventricular assist device: an analysis of the prevent study. *J Heart Lung Transplant* 2018;**37**(4 Suppl. 1):S161.	Do not report DT data
Zhalbinova MR, Rakhimova SE, Bekbosynova MS, Andosova SA, Abdirova BU, Akilzhanova AR. The cause of the bleeding and thrombosis in patients with implanted left ventricular assist devices. *J Heart Lung Transplant* 2020;**39**(4 Suppl.):S399.	Do not report DT data
Zhang L, Purohit M, Hassett C, Cho S, Buletko A. Neurologic complications of heartware and heartmate II. Neurology Conference: 71st Annual Meeting of the American Academy of Neurology, AAN. 2019;92.	Do not report DT data
Zhigalov K, Sa MPBO, Arjomandi Rad A, Vardanyan R, Goerdt L, Chrosch T, *et al.* The impact of obesity on left ventricular assist device outcomes. *Medicina.* 2020;56.	Do not report DT data
Zimpfer D, Gustafsson F, Potapov E, Pya Y, Schmitto J, Berchtold-Herz M, *et al.* Two-year outcome after implantation of a full magnetically levitated left ventricular assist device: results from the ELEVATE Registry. *Eur Heart J* 2020;**41**:3801–9.	Do not report DT data
Zimpfer D, Netuka I, Schmitto JD, Pya Y, Garbade J, Morshuis M, *et al.* Multicentre clinical trial experience with the HeartMate 3 left ventricular assist device: 30-day outcomes. *Eur J Cardiothorac Surg* 2016;**50**:548–54.	< 50 DT patients
Ziv O, Dizon J, Thosani A, Naka Y, Magnano AR, Garan H. Effects of left ventricular assist device therapy on ventricular arrhythmias. *J Am Coll Cardiol* 2005;**45**:1428–34.	Do not report DT data
Zubarevich A, Szczechowicz M, Osswald A, Arjomandi Rad A, Vardanyan R, Pompeu BOSM, *et al.* Impact of gender in patients with continuous-flow left ventricular assist device therapy in end-stage heart failure. *Int J Artif Organs.* 2021.	Do not report DT data

Appendix 4 Risk of bias for clinical effectiveness review

TABLE 30 Detailed risk-of-bias assessment for intervention trials

Study name	Outcome	Domain 1 (randomisation process)	Domain 2 (deviations from intended interventions)	Domain 3 (missing outcome data)	Domain 4 (measurement of the outcome)	Domain 5 (selection of reported result)	Overall risk of bias
ROADMAP (2015)	Survival	N/A	Low	Low	Low	Low	Low
			No deviations from intended intervention due to trial context, both ITT and as treated analyses carried out	*No missing data*	*Survival appropriate outcome, survival outcome objective*	*Protocol available, analyses implemented as planned*	
	QoL	N/A	Low	High	Some concerns	Low	High
			Blinding cannot be avoided, investigators aware of treatments, no deviations arose due to trial context, as treated analysis but only similar small number of patients missing from each arm	*Both intervention and control group had < 95% patient data at 12 months, no methods to correct for bias, ability to carry out QoL questionnaire may have been impeded by QoL*	*Valid appropriate QoL tool, self-report, outcome assessors likely aware of treatments*	*Protocol available and analyses align with this, QoL measured at 0, 6, 12, 24 months Reported at 0, 12, 24 – not reported at 6 months but change from baseline analysis was conducted*	
REMATCH (2001)	Survival	Some concerns	Low	Low	Low	Low	Low
		No information given on allocation concealment or full randomisation process though groups were similar	*Blinding cannot be avoided. Investigators except statisticians were unaware of outcome data, ITT analysis*	*Data were available for all participants*	*Survival appropriate outcome, study personnel except statisticians blind to treatment*	*Protocol available though some outcomes not mentioned Multiple results reported for each outcome, not selected*	
	QoL	Some concerns	Low	High	Low	Some concerns	High
		No information given on allocation concealment or full randomisation process though groups were similar	*Blinding cannot be avoided Investigators except statisticians were unaware of outcome data, ITT analysis*	*Only 50% of patients had QoL data in MM group, ability to carry out QoL questionnaire may have been impeded by QoL*	*Valid appropriate QoL tool, study personnel except statisticians blind to treatment*	*Not all outcomes in protocol reported in results*	

TABLE 30 Detailed risk of bias assessment for intervention trials (*continued*)

Study name	Outcome	Domain 1 (randomisation process)	Domain 2 (deviations from intended interventions)	Domain 3 (missing outcome data)	Domain 4 (measurement of the outcome)	Domain 5 (selection of reported result)	Overall risk of bias
MOMENTUM 3 (2019)	Survival	Low	Some concerns	Low	Low	Low	Some concerns
		Randomisation permuted blocks and with stratification according to trial centre and was implemented through an electronic data-capture system, similar groups	*Blinding cannot be avoided, event adjudicators blinded to treatments, per protocol analysis, eight patients did not receive LVAD but unlikely to impact results and reflective of real life*	*No missing participant data*	*Survival appropriate outcome, adjudicators unlikely to be blinded to survival outcome but survival is objective*	*Protocol available, analyses implemented as planned*	
	QoL	Low	Some concerns	Low	Some concerns	Low	Some concerns
		Randomisation permuted blocks and with stratification according to trial centre and was implemented through an electronic data-capture system, similar groups	*Blinding cannot be avoided, event adjudicators blinded to treatments, per protocol analysis, eight patients did not receive LVAD but unlikely to impact results and reflective of real life*	*Missing data at each timepoint, sensitivity analysis carried out suggesting this did not affect QoL outcome*	*QoL tools valid and appropriate, patients aware of treatment which, could influence self-report of QoL, but unlikely strong beliefs in any beneficial effects*	*Protocol available, analyses implemented as planned*	
HMII DT (2009)	Survival	Some concerns	High	Low	Low	Some concerns	High
		Randomisation was stratified according to study centre and with the use of permuted blocks, no information on allocation concealment	*Blinding cannot be avoided; carers and clinicians likely knew allocation* *As treated – up to 17% not analysed in intervention group and > 50% in the control, which could have a significant effect*	*Some participants swapped device after randomisation due to insurance coverage, not included in analysis* *However missingness in outcome unlikely to depend on true value*	*Survival appropriate outcome, objective*	*No protocol available though outcomes defined in trial registry page* *However no clear analysis plan described*	

continued

TABLE 30 Detailed risk of bias assessment for intervention trials (*continued*)

Study name	Outcome	Domain 1 (randomisation process)	Domain 2 (deviations from intended interventions)	Domain 3 (missing outcome data)	Domain 4 (measurement of the outcome)	Domain 5 (selection of reported result)	Overall risk of bias
	QoL	Some concerns	High	High	Some concerns	Some concerns	High
		Randomisation was stratified according to study centre and with the use of permuted blocks, no information on allocation concealment	*Blinding cannot be avoided; carers and clinicians likely knew allocation* *As treated analysis* *Some drop out, crossover and some transplanted, which could have impacted results*	*Greater than half of patients did not report QoL at 24 months and at other time points (after considering those still alive)* *No reasons for missing data, ability to carry out QoL questionnaire may have been impeded by QoL*	*QoL tools valid and appropriate, patients aware of treatment, which could influence self-report of QoL, but unlikely strong beliefs in any beneficial effects*	*No protocol so difficult to tell if any other analyses were intended that are not described in the results paper*	
ENDURANCE DT (2017)	Survival	Low	Low	Low	Low	Low	Low
		Randomisation was performed with the use of a permuted block, central randomisation scheme and was implemented with a web-based interactive response system *Groups were similar*	*Blinding cannot be avoided, no deviations from intended intervention due to trial context, ITT and as treated analyses carried out*	*Only two participants randomised dropped out at the start of the study (1 from each group) and f/up was 99.7% and 99.3% for each group*	*Survival appropriate outcome, objective, all safety data were adjudicated by blinded assessors*	*Protocol and full statistical plan given, all results reported as per the analysis plan*	
	QoL	Low	Some concerns	High	Some concerns	Low	High
		Randomisation was performed with the use of a permuted block, central randomisation scheme and was implemented with a web-based interactive response system *Groups were similar*	*Blinding cannot be avoided, some participants switched after randomisation due to insurance coverage (though very small number)* *As treated analysis*	*Around 90% of available pts completed the outcome at 24 months in both groups, unclear why QoL was not measured for 10% of patients at 24 months f/up, ability to carry out QoL questionnaire may have been impeded by QoL*	*QoL tools valid and appropriate, patients aware of treatment, which could influence self-report of QoL, but unlikely strong beliefs in any beneficial effects*	*Protocol and full statistical plan given, all results reported as per the analysis plan*	

TABLE 30 Detailed risk of bias assessment for intervention trials (*continued*)

Study name	Outcome	Domain 1 (randomisation process)	Domain 2 (deviations from intended interventions)	Domain 3 (missing outcome data)	Domain 4 (measurement of the outcome)	Domain 5 (selection of reported result)	Overall risk of bias
ENDURANCE DT 2 (2018)	Survival[a]	Low	High	Low	Low	Some concerns	High
		No information given on randomisation and allocation concealment; groups similar	*Blinding cannot be avoided, modified ITT analysis that excluded 10 participants from the analysis implying more like an as treated analysis*	*Only 10 missing from analyses in total from both arms, unlikely to have an effect*	*Survival objective, definition of disabling stroke more subjective but based on established criteria, outcome unlikely to be influenced by knowledge of intervention*	*No protocol, little information on analysis plan*	
	QoL	Low	Low	Low	Some concerns	High	High
		No information given on randomisation and allocation concealment; groups similar	*Blinding cannot be avoided, no deviations from intended intervention due to trial context, ITT analysis*	*ITT population, no missing data at 12 months*	*QoL tools valid and appropriate, patients aware of treatment, which could influence self-report of QoL, but unlikely strong beliefs in any beneficial effects*	*No protocol, little information on analysis plan, reported EQ-5D VAS only and overall summaries only, unclear if this was intended plan*	

ITT, intention to treat; N/A, not applicable (study was a non-randomised intervention study).
a Survival only reported as part of composite outcome of survival free from death, disabling stroke, or need for device replacement or urgent transplantation.

Appendix 5 Forest plots of results of non-HeartMate3 devices by outcome

Survival

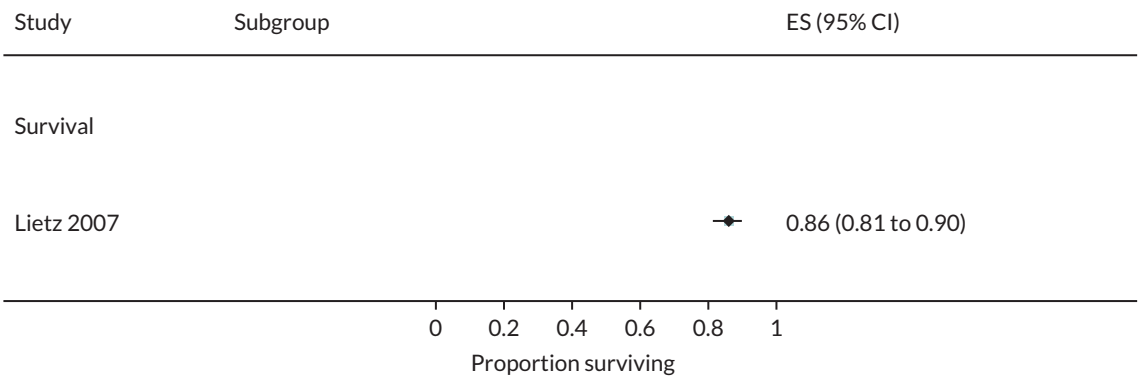

FIGURE 28 Survival data in HeartMate XVE at 1-month follow-up.

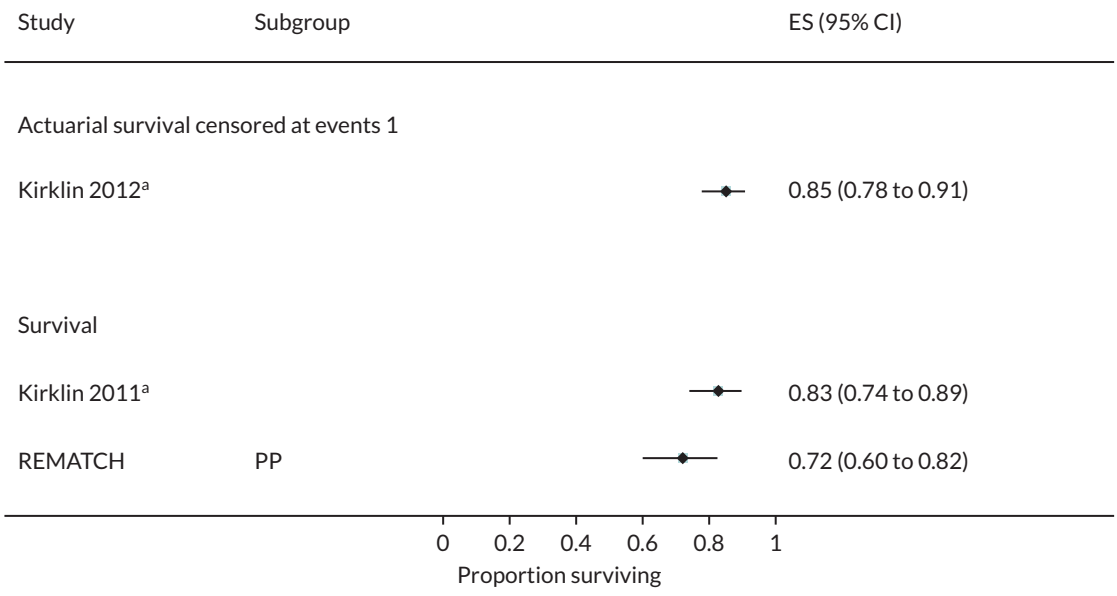

FIGURE 29 Survival data in HeartMate XVE at 3 months follow-up. a, Data from a registry report. Events 1, censored at transplant and recovery; PP, per protocol analysis.

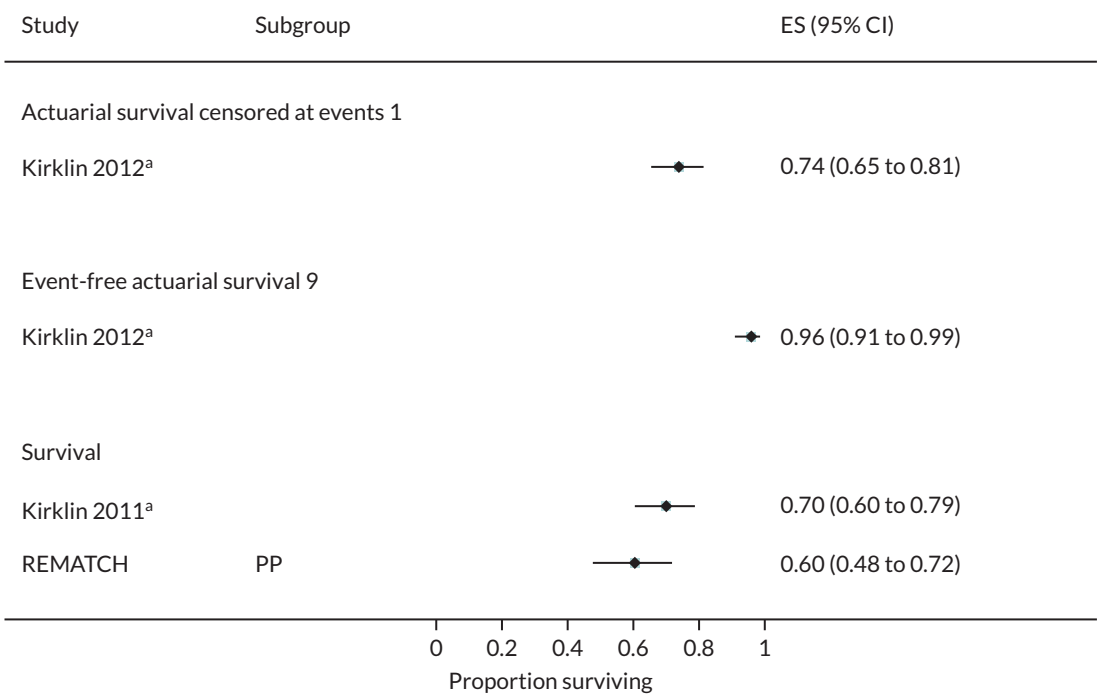

FIGURE 30 Survival data in HeartMate XVE at 6 months follow-up. a, Data from a registry report. Survival censored at events 1, censored at transplant and recovery; event-free actuarial survival 9, free from device exchange or death secondary to device malfunction or device complication; PP, per protocol analysis.

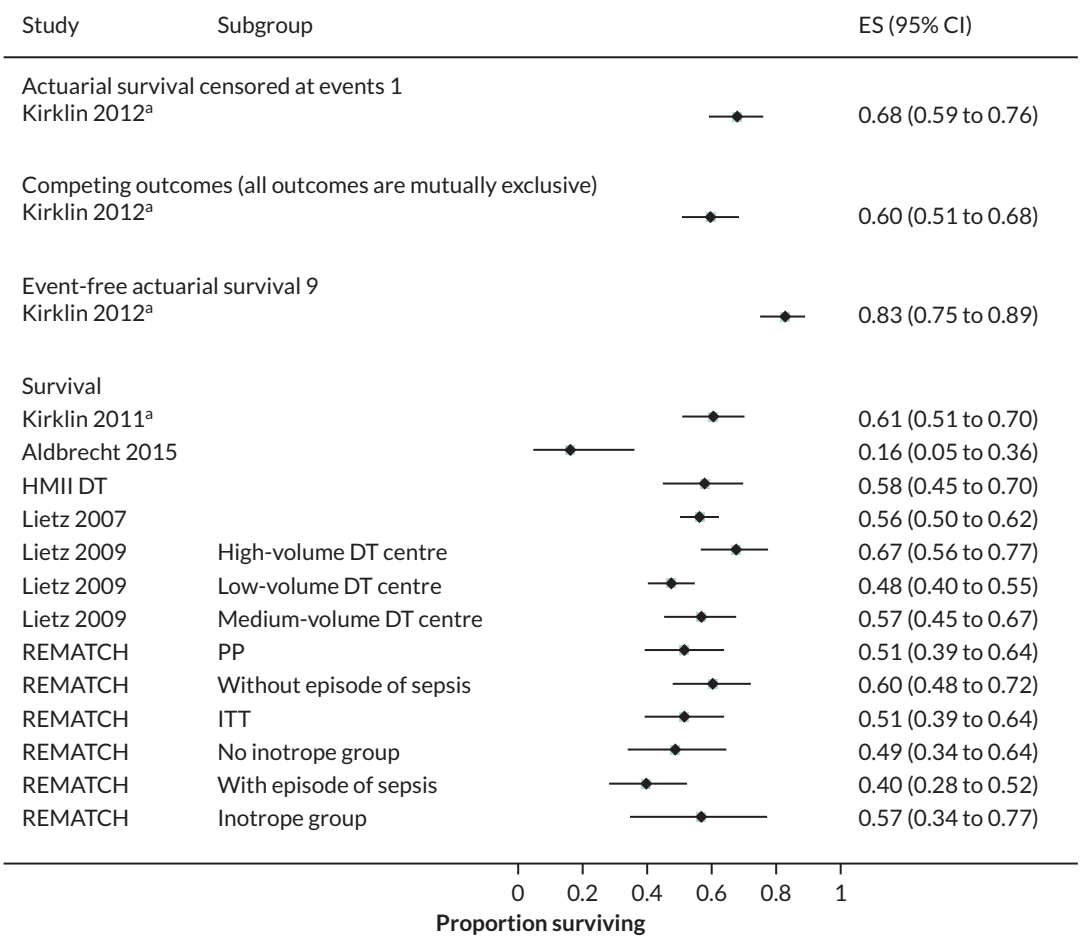

FIGURE 31 Survival data in HeartMate XVE at 12 months follow-up. a, Data from a registry report. Survival censored at events 1, censored at transplant and recovery; event-free actuarial survival 9, free from device exchange or death secondary to device malfunction or device complication.

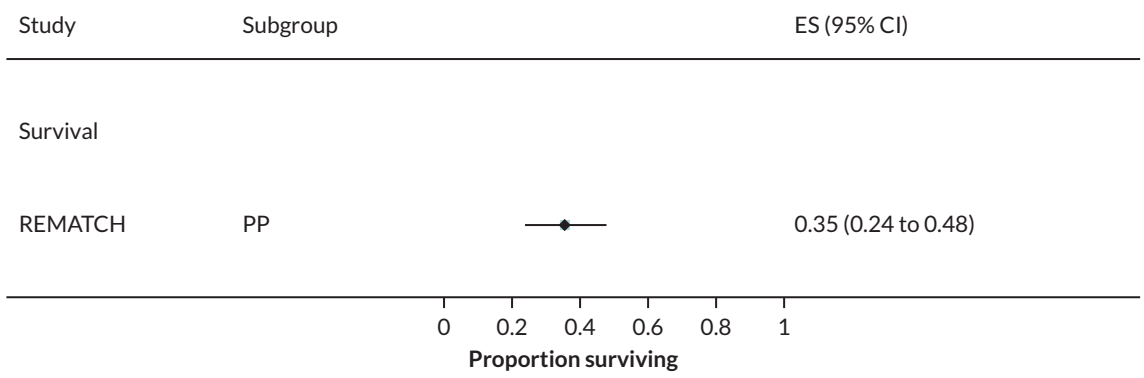

FIGURE 32 Survival in HeartMate XVE at 18 months follow-up. PP, per protocol analysis.

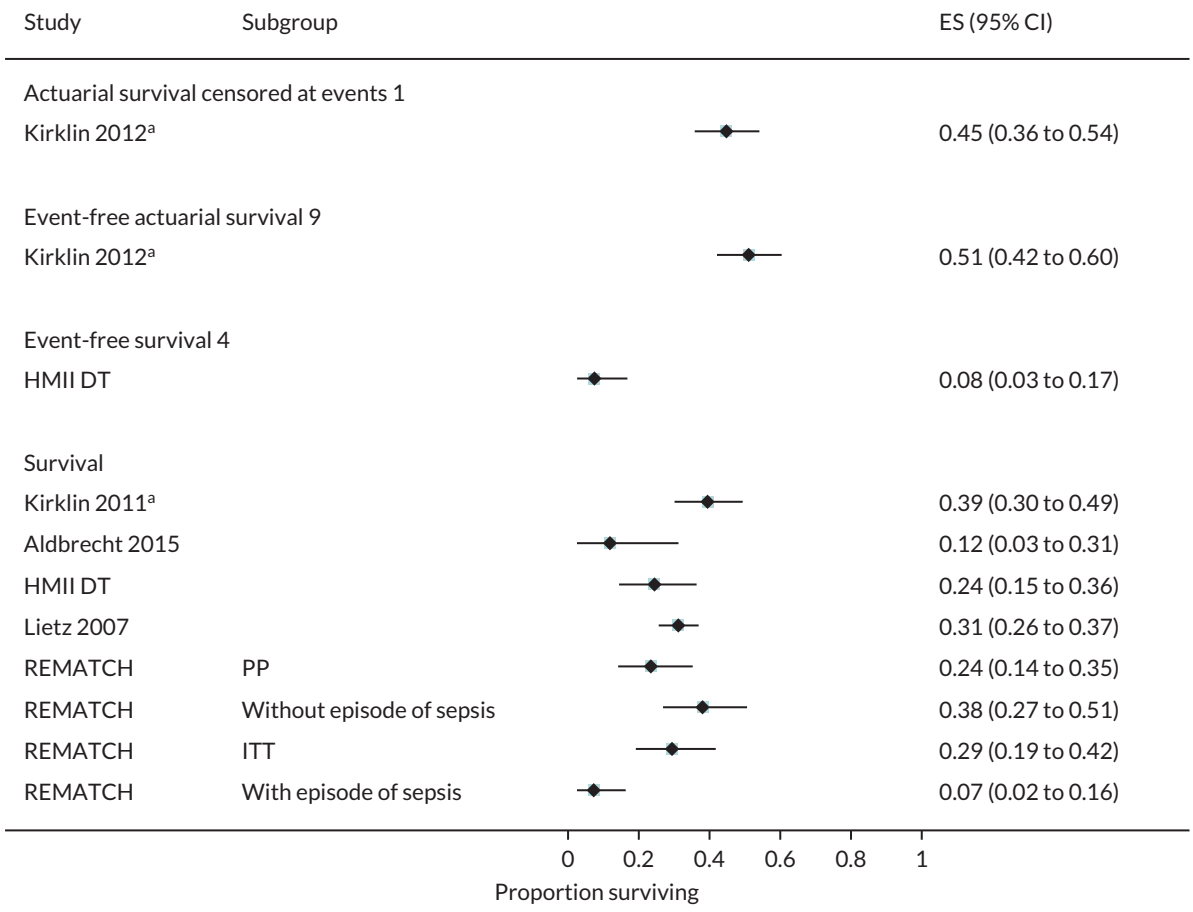

FIGURE 33 Survival in HeartMate XVE at 24 months follow-up. a, Data from a registry report. Survival censored at events 1, censored at transplant and recovery; event-free actuarial survival 9, free from device exchange or death secondary to device malfunction or device complication; event-free survival 4, free from disabling stroke or reoperation to repair or replace LVAD; ITT, intention to treat analysis; PP, per protocol analysis.

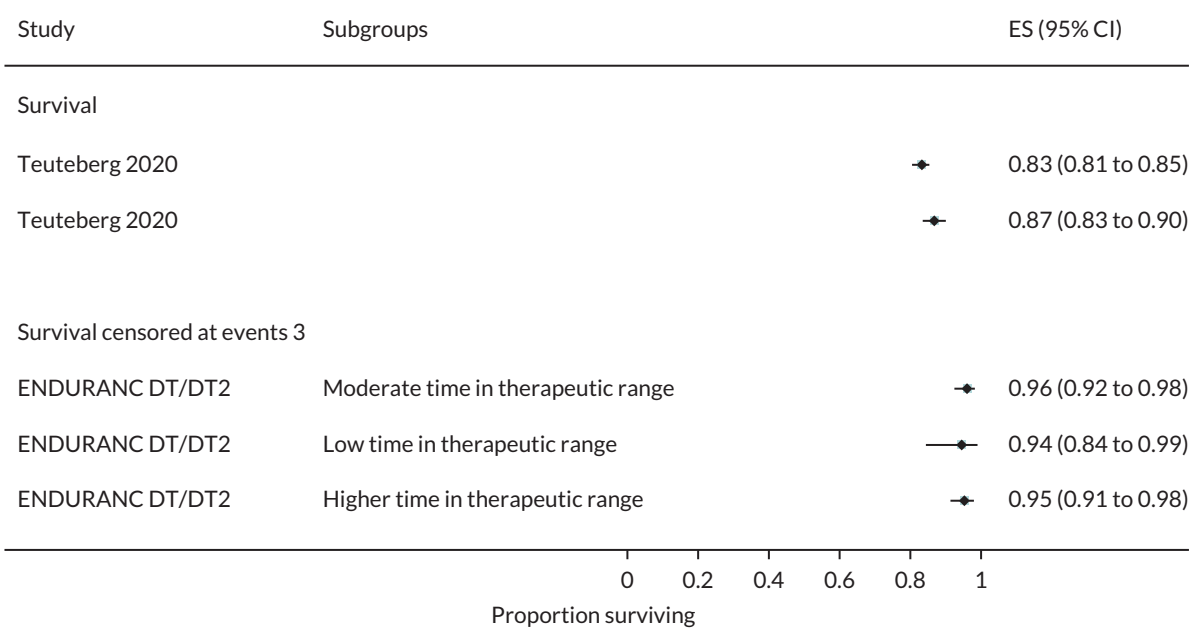

FIGURE 34 Survival in HeartWare HVAD at 6 months follow-up. Survival censored at events 3, free from disabling stroke or need for device replacement.

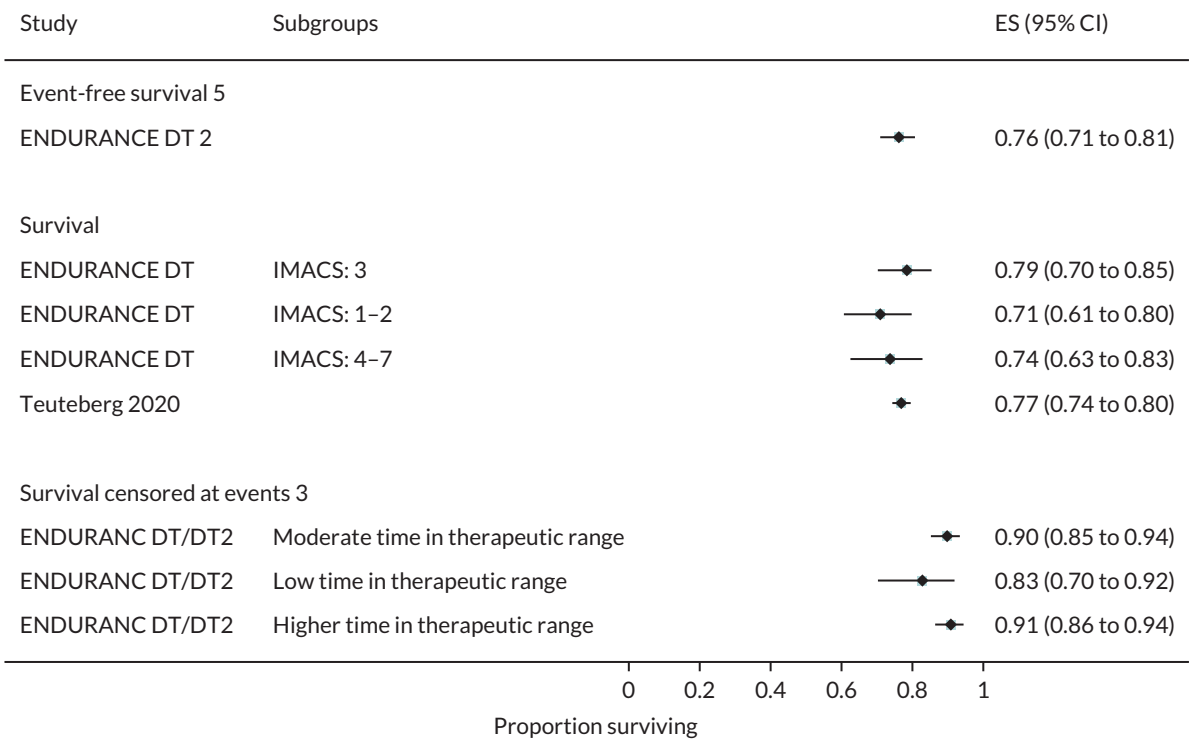

FIGURE 35 Survival in HeartWare HVAD at 12 months follow-up. Event-free survival 5, free from disabling stroke and device malfunction or failure requiring exchange, explantation, or urgent transplantation; survival censored at events 3, censored either at time of device explant due to PE or removal for recovery, heart transplant, or at loss to follow-up 2 years post implant.

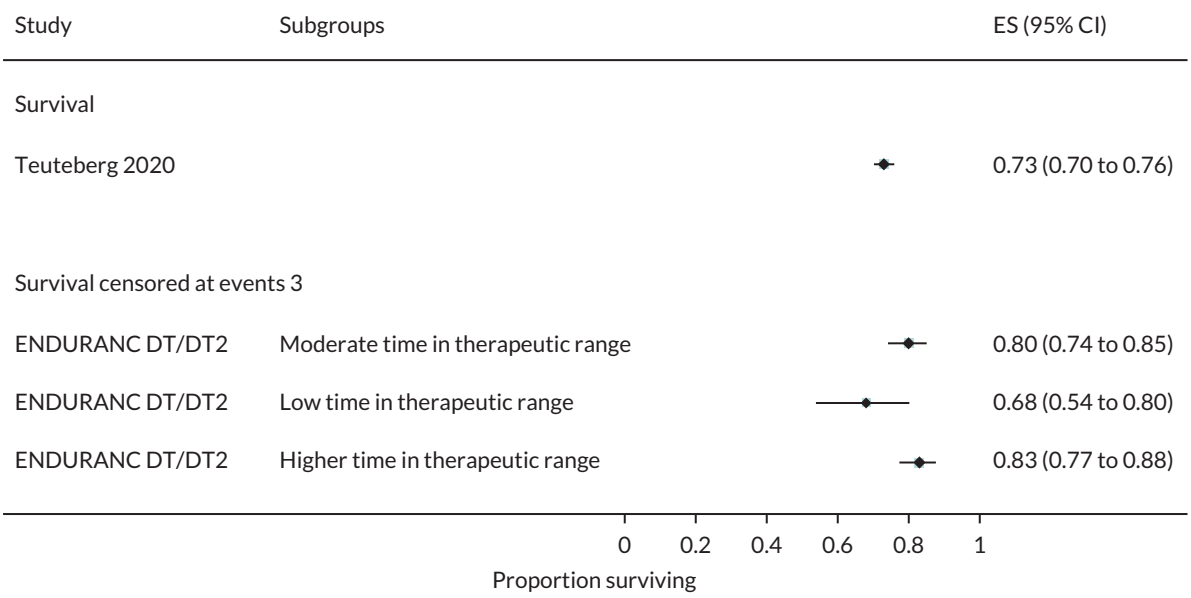

FIGURE 36 Survival in HeartWare HVAD at 18 months follow-up. Survival censored at events 3, censored either at time of device explant due to pump exchange or removal for recovery, heart transplant, or at loss to follow-up 2 years post implant.

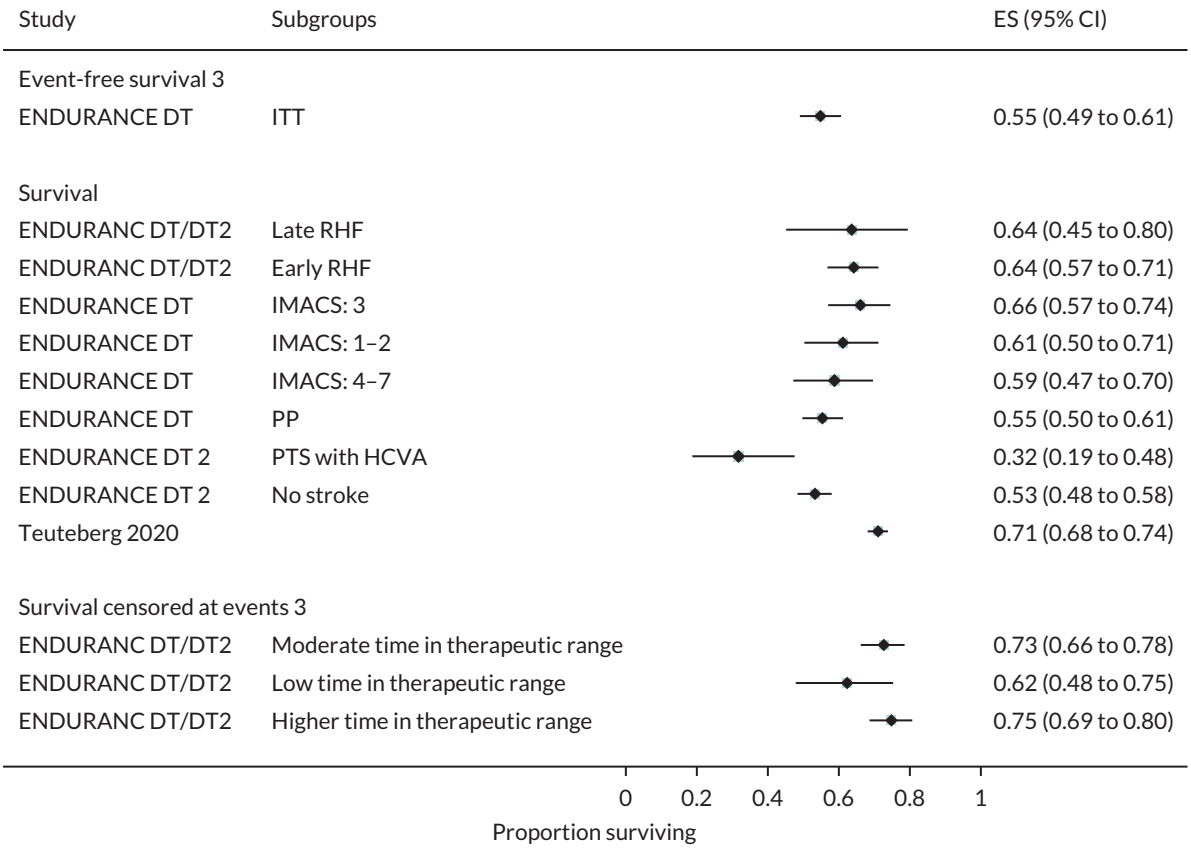

FIGURE 37 Survival in HeartWare HVAD at 24 months follow-up. Event-free survival 3, free from disabling stroke or need for device replacement; ITT, intention to treat analysis; survival censored at events 3, censored either at time of device explant due to PE or removal for recovery, heart transplant, or at loss to follow-up 2 years post implant.

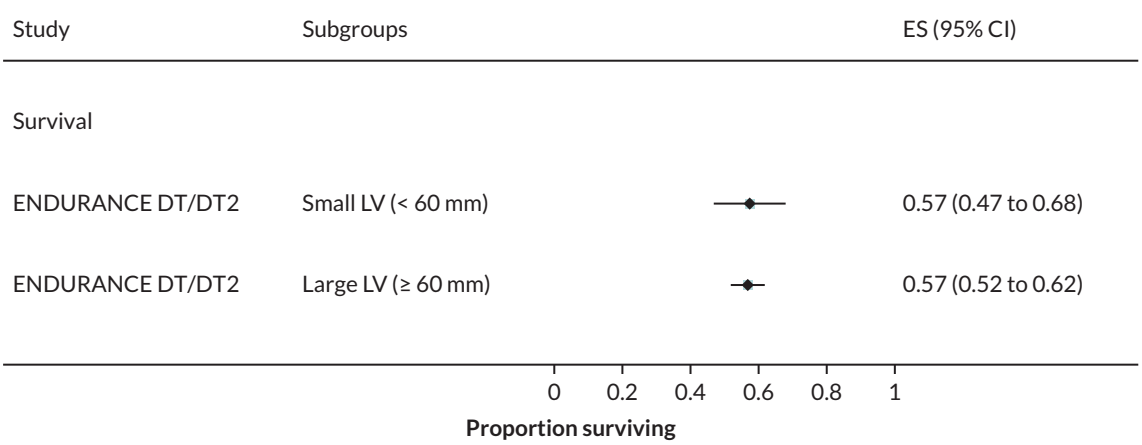

FIGURE 38 Survival in HeartWare HVAD at 36 months follow-up.

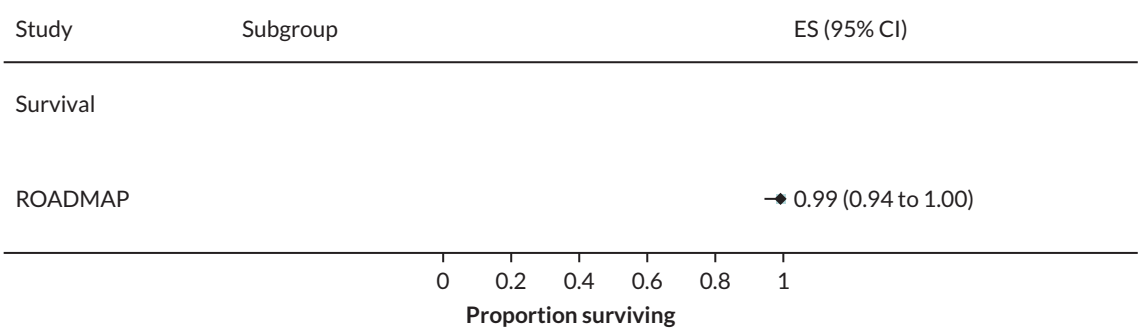

FIGURE 39 Survival in HeartMate II at 1-month follow-up.

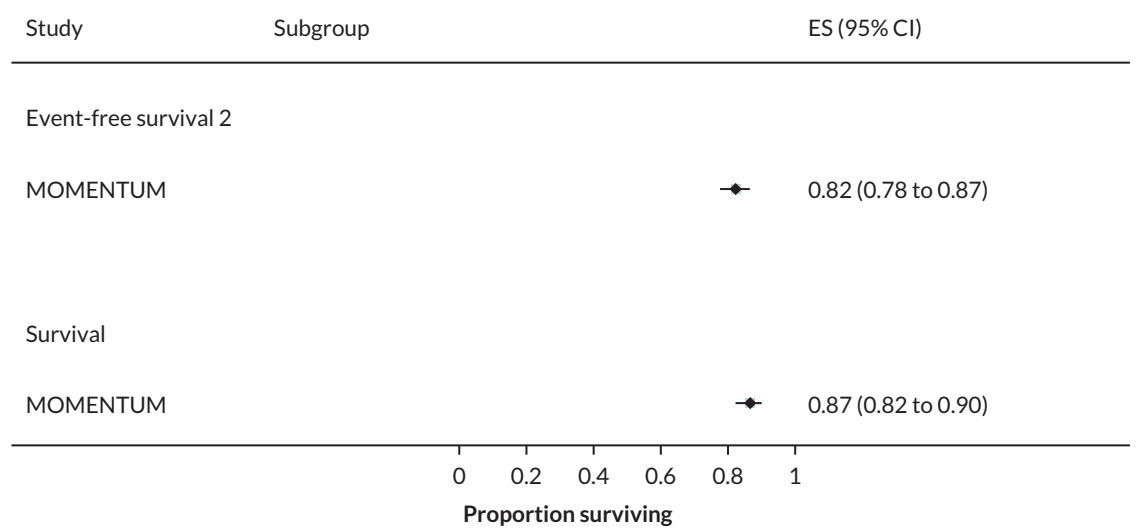

FIGURE 40 Survival in HeartMate II at 6 months follow-up. Event-free survival 2, free from disabling stroke.

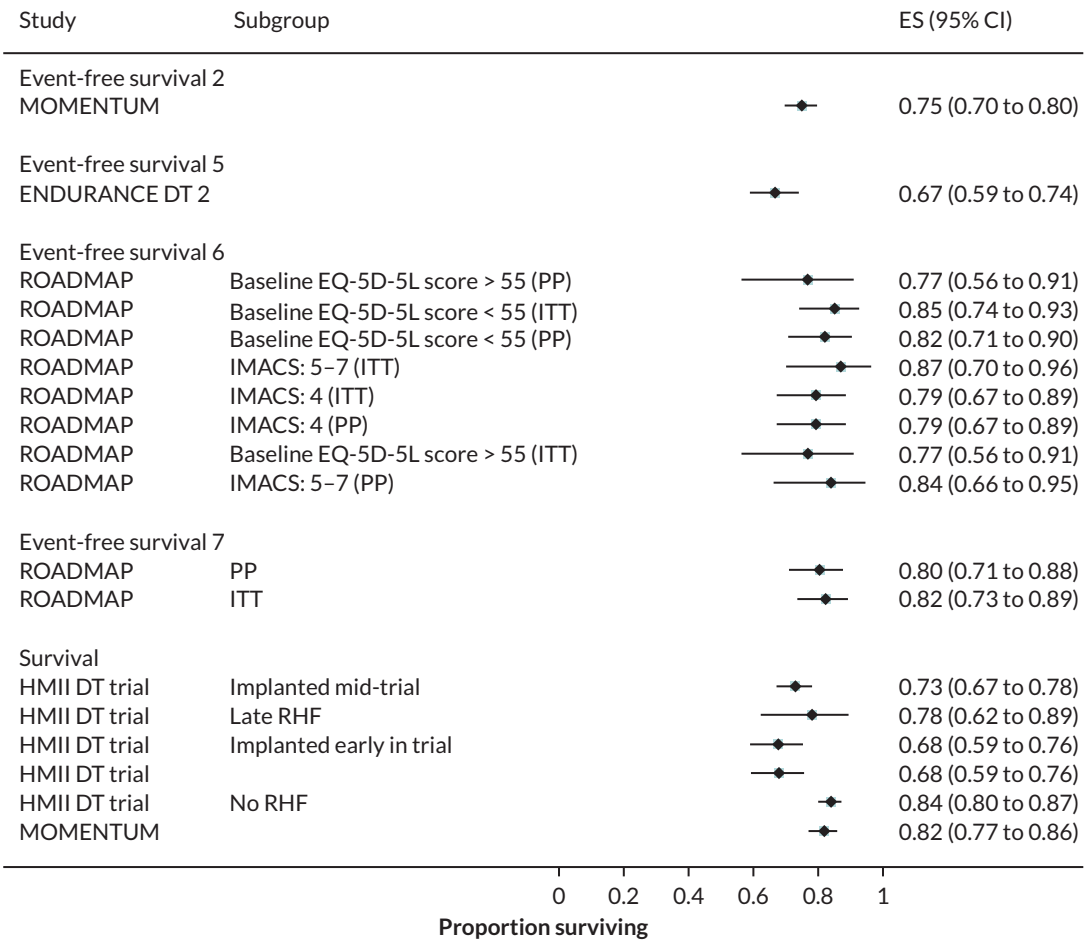

FIGURE 41 Survival in HeartMate II at 12 months follow-up. Event-free survival 2, free from disabling stroke; event-free survival 5, free from disabling stroke, and device malfunction or failure requiring exchange, explantation, or urgent transplantation; event-free survival 7, free from urgent heart transplant or delayed LVAD; ITT, intention to treat analysis; PP, per protocol analysis.

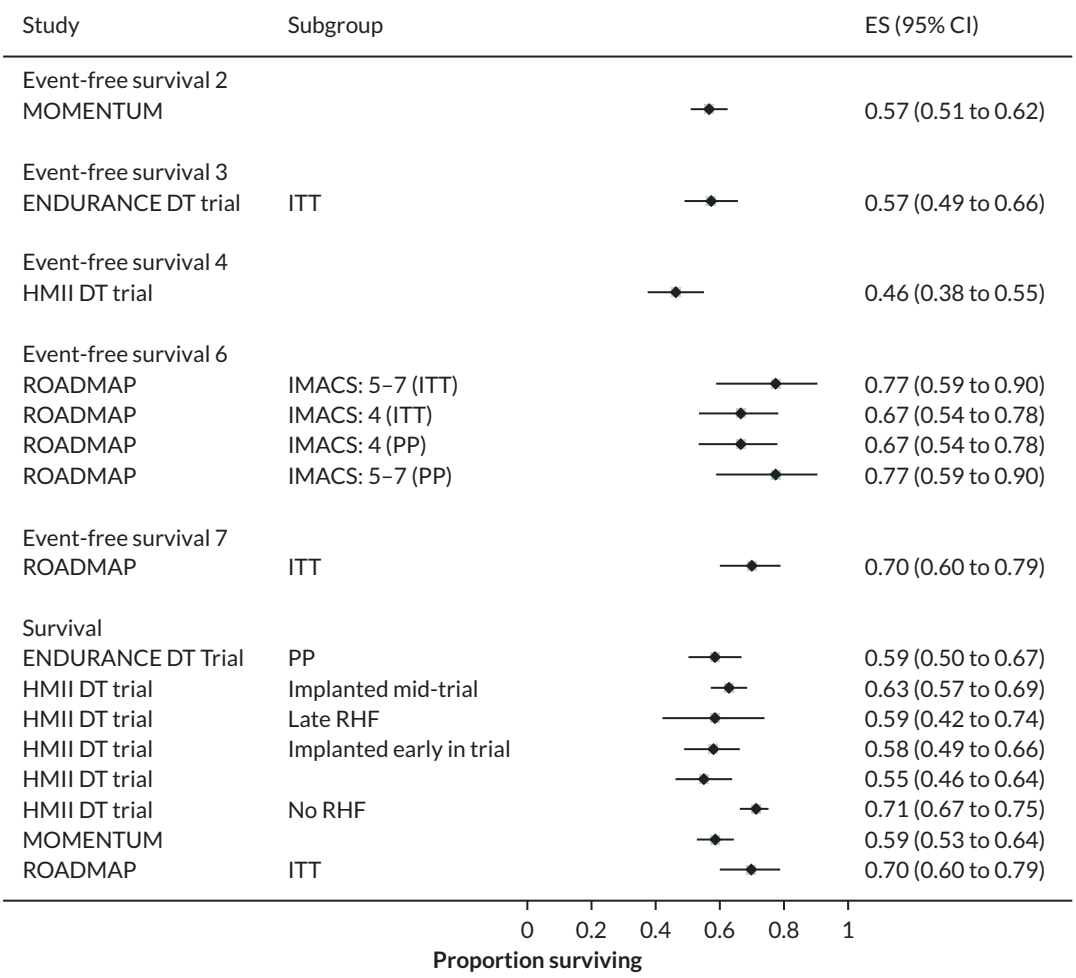

FIGURE 42 Survival in HeartMate II at 24 months follow-up. Event-free survival 2, free from disabling stroke; event-free survival 3, free from disabling stroke or need for device replacement; event-free survival 4, free from disabling stroke or reoperation to repair or replace LVAD; event-free survival 6, free from urgent heart transplant; event-free survival 7, free from urgent heart transplant or delayed LVAD; ITT-intention to treat analysis; PP, per protocol analysis.

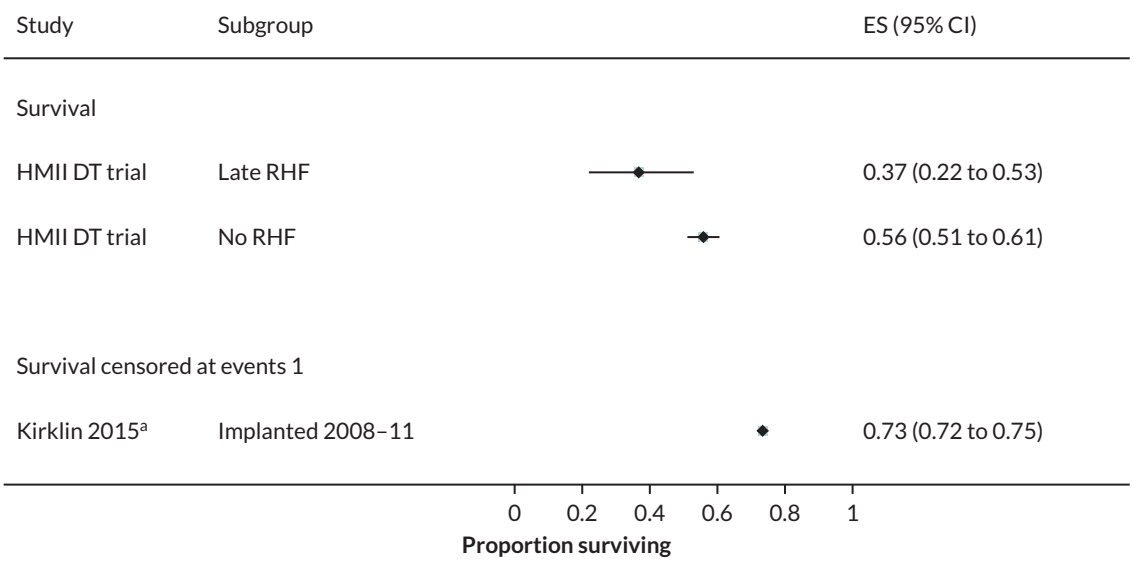

FIGURE 43 Survival in HeartMate II at 36 months follow-up. a, Data from a registry report; survival censored at events 1, censored at transplant and recovery.

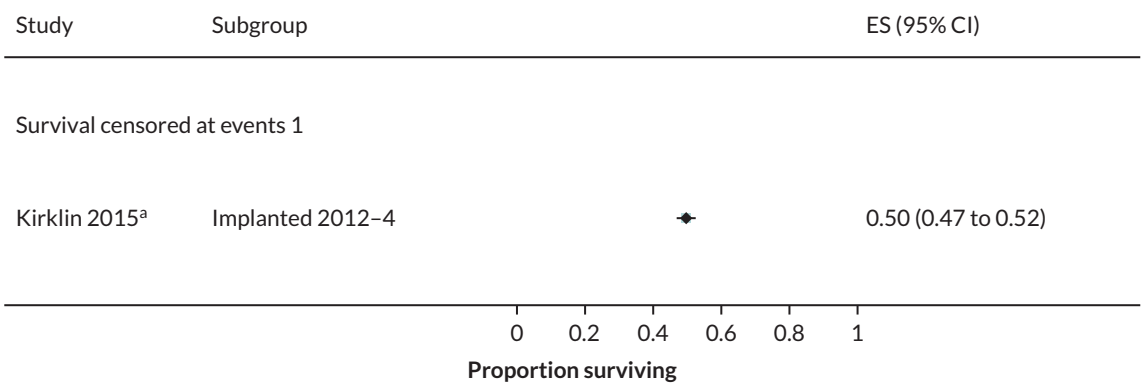

FIGURE 44 Survival in HeartMate II at 48 months follow-up. a, Data from a registry report; survival censored at events 1, censored at transplant and recovery.

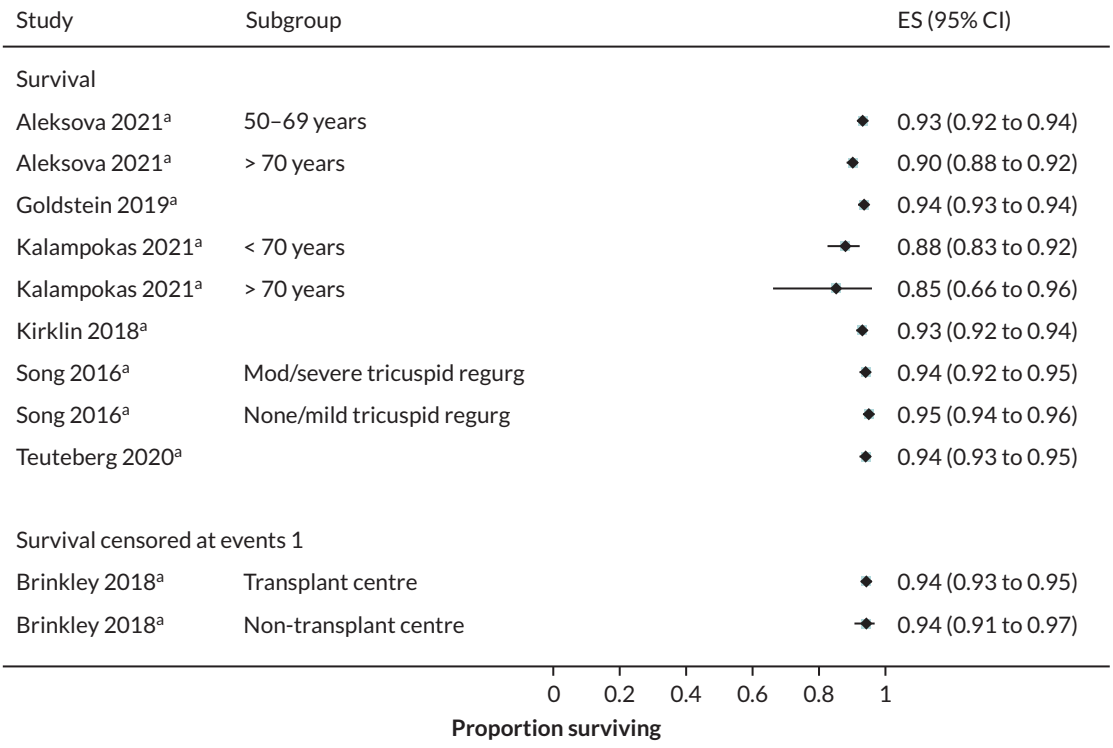

FIGURE 45 Survival in studies with multiple devices at 1-month follow-up. a, Data from a registry report; survival censored at events 1, censored at transplant and recovery.

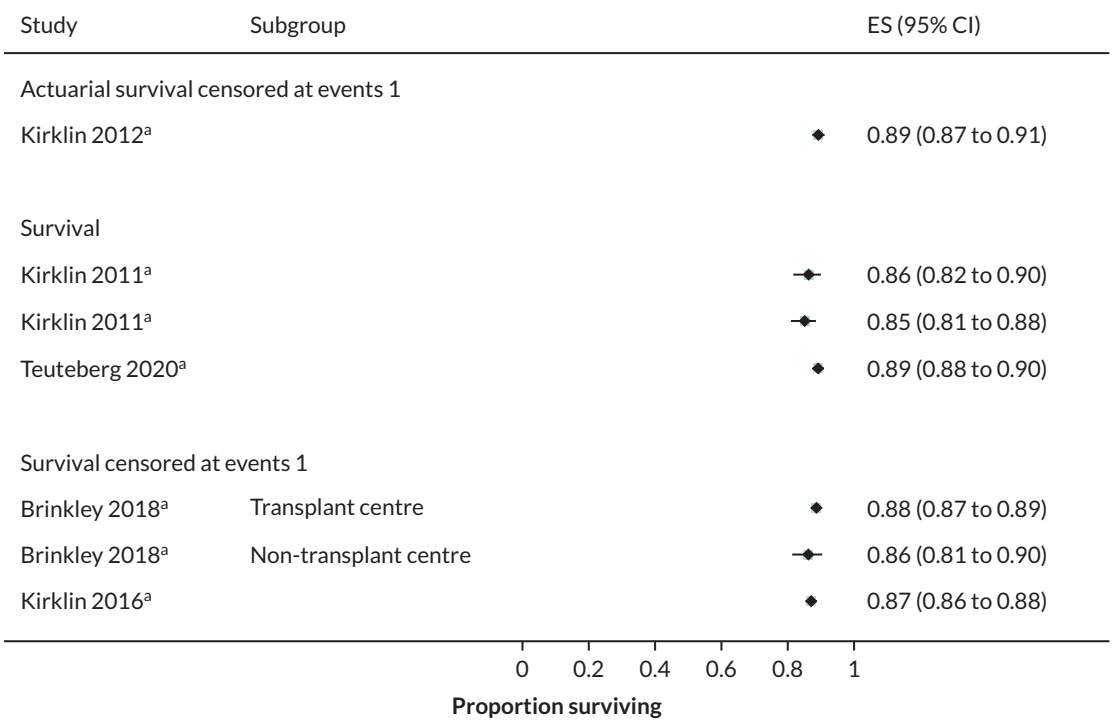

FIGURE 46 Survival in studies with multiple devices at 3 months follow-up. a, Data from a registry report; survival censored at events 1, censored at transplant and recovery.

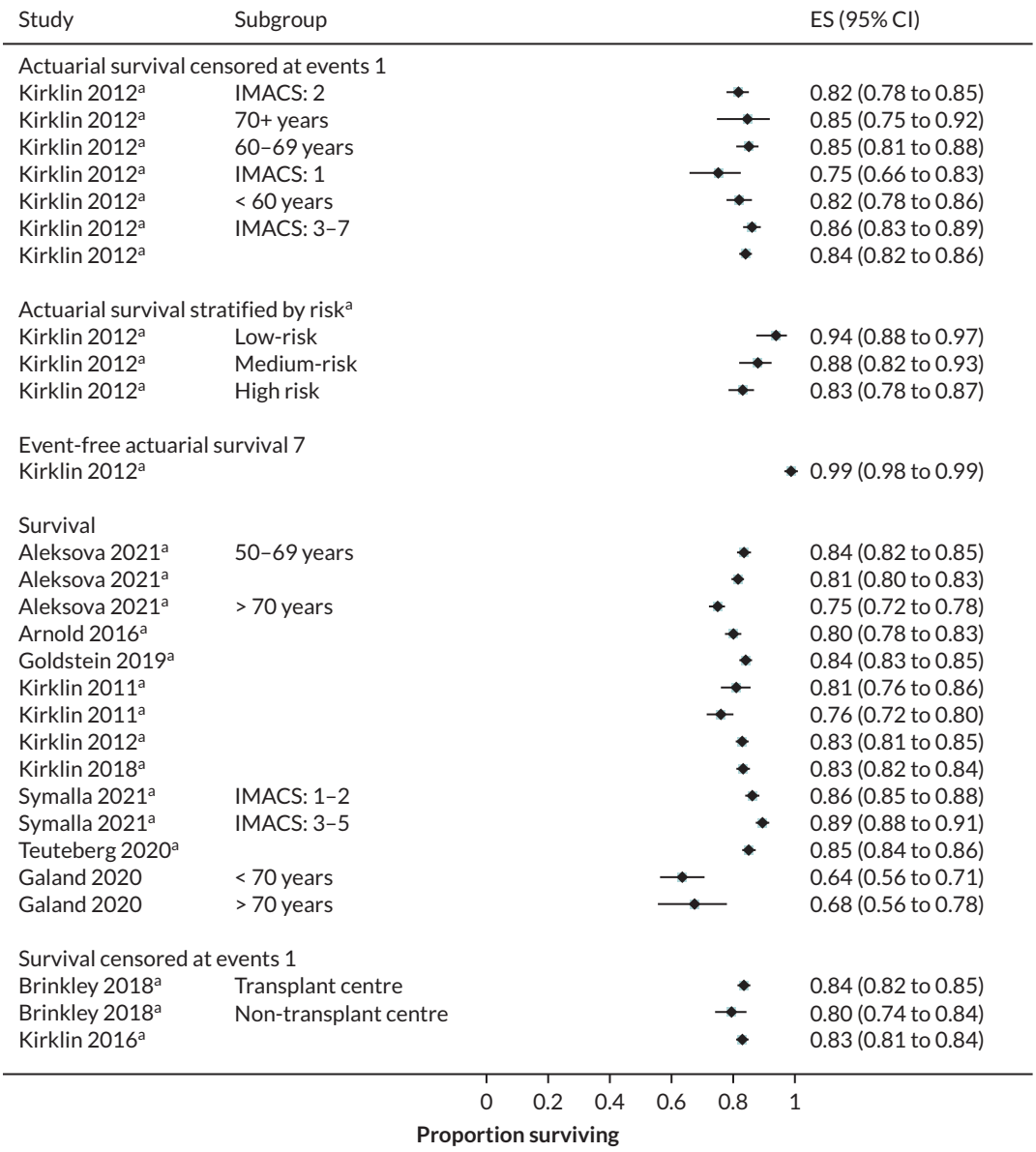

FIGURE 47 Survival in studies with multiple devices at 6 months follow-up. a, Data from a registry report; survival censored at events 1, censored at transplant and recovery; event-free survival 7, free from urgent heart transplant or delayed LVAD.

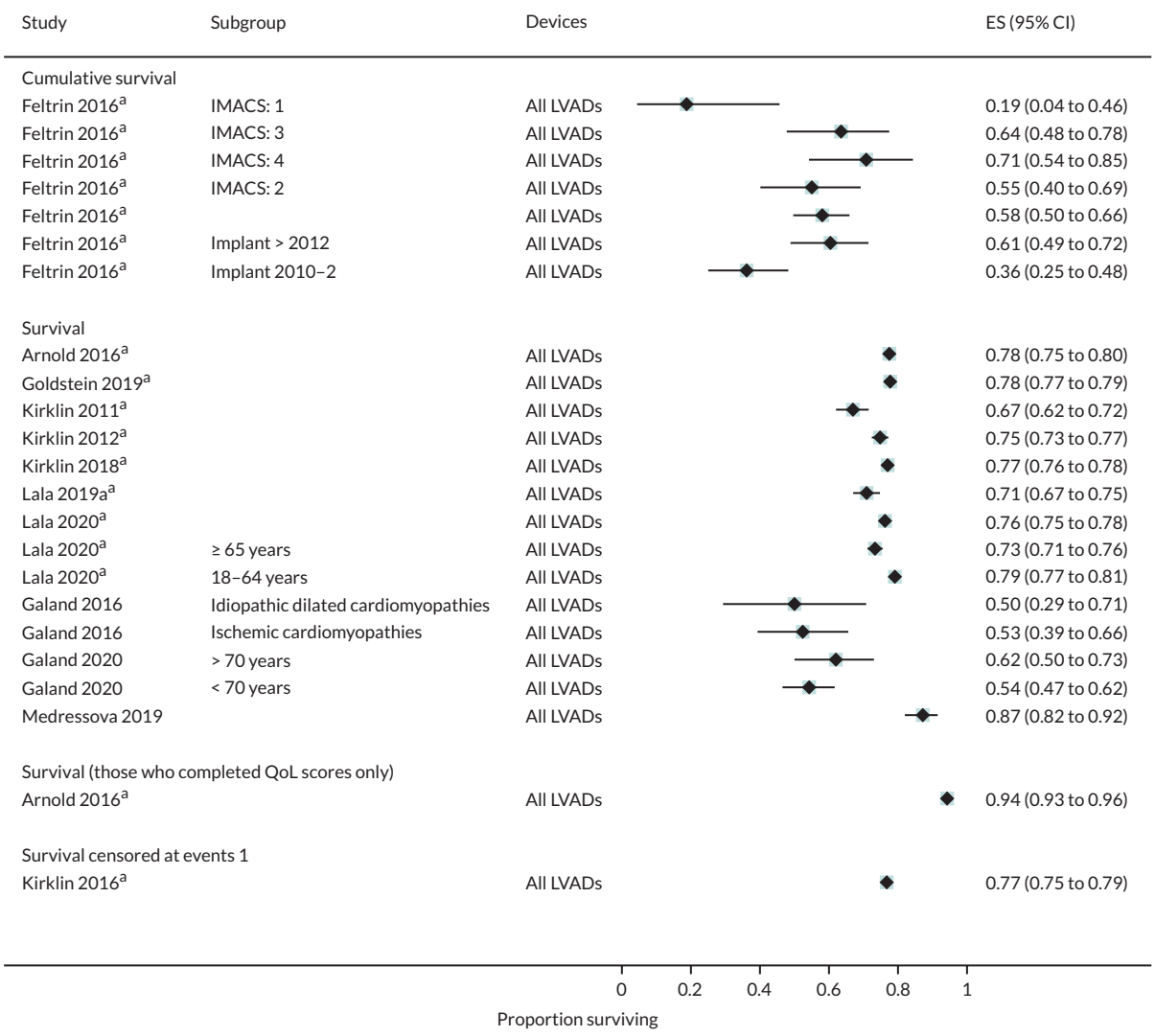

FIGURE 48 Survival in studies with multiple devices at 12 months follow-up. a, Data from a registry report; survival censored at events 1, censored at transplant and recovery; event-free survival 7, free from urgent heart transplant or delayed LVAD; event-free survival 1, free from stroke; survival censored at events 2, censored at transplant or cessation of support.

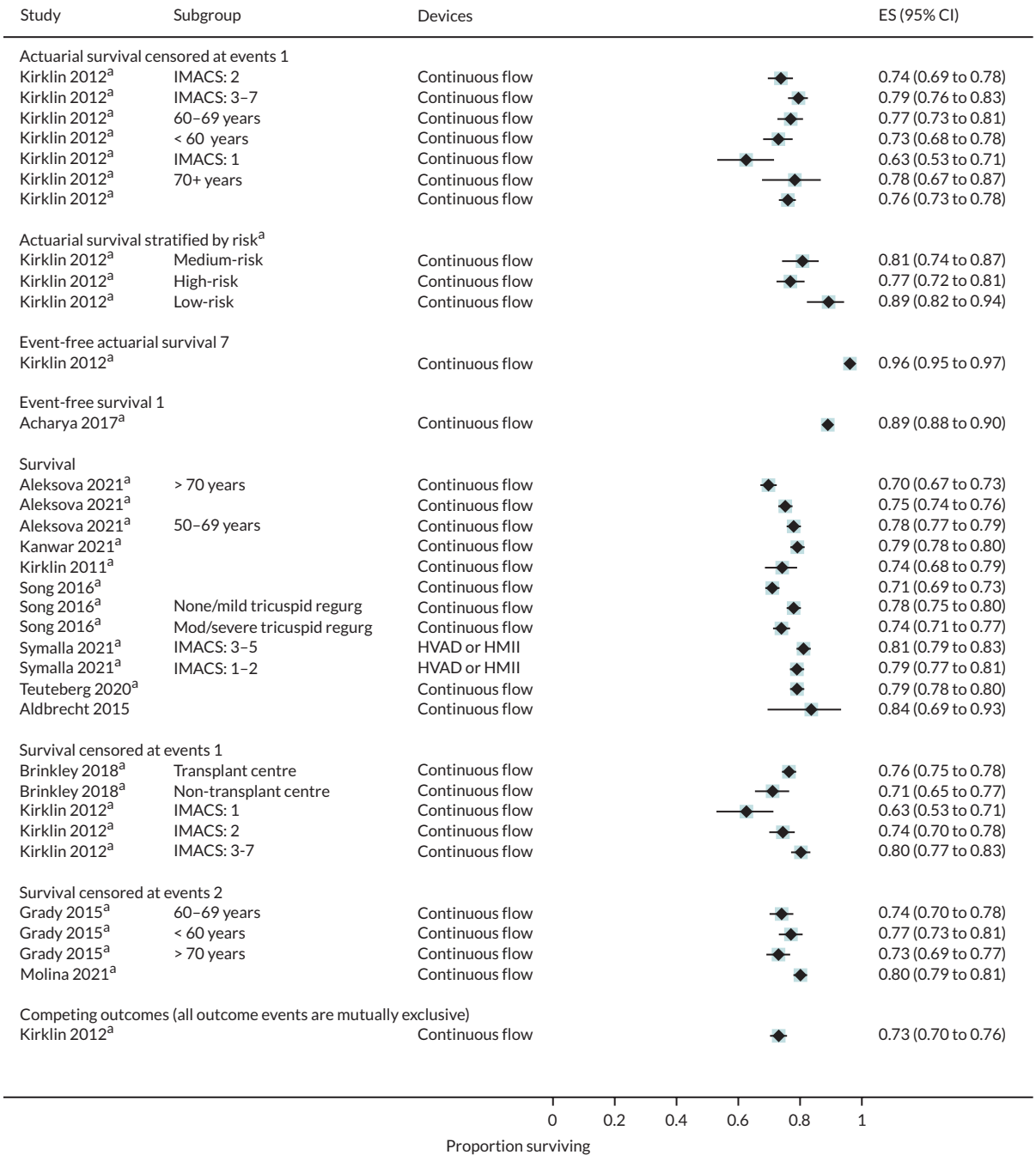

FIGURE 48 Survival in studies with multiple devices at 12 months follow-up. a, Data from a registry report; survival censored at events 1, censored at transplant and recovery; event-free survival 7, free from urgent heart transplant or delayed LVAD; event-free survival 1, free from stroke; survival censored at events 2, censored at transplant or cessation of support. (*continued*)

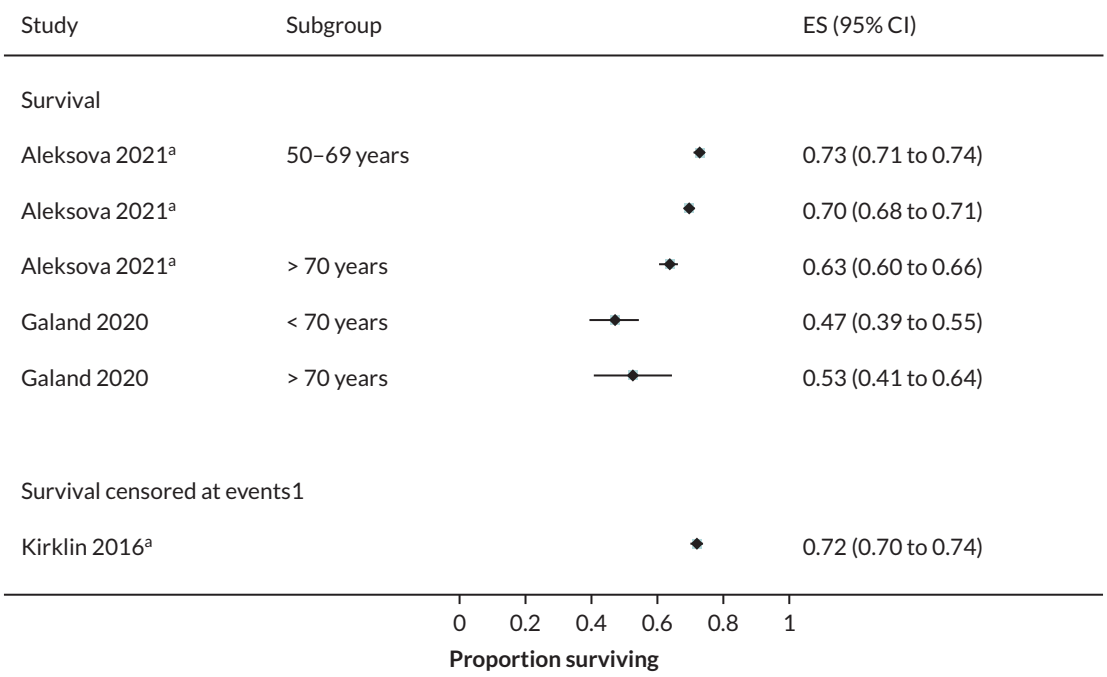

FIGURE 49 Survival in studies with multiple devices at 18 months follow-up. a, Data from a registry report; survival censored at events 1, censored at transplant and recovery.

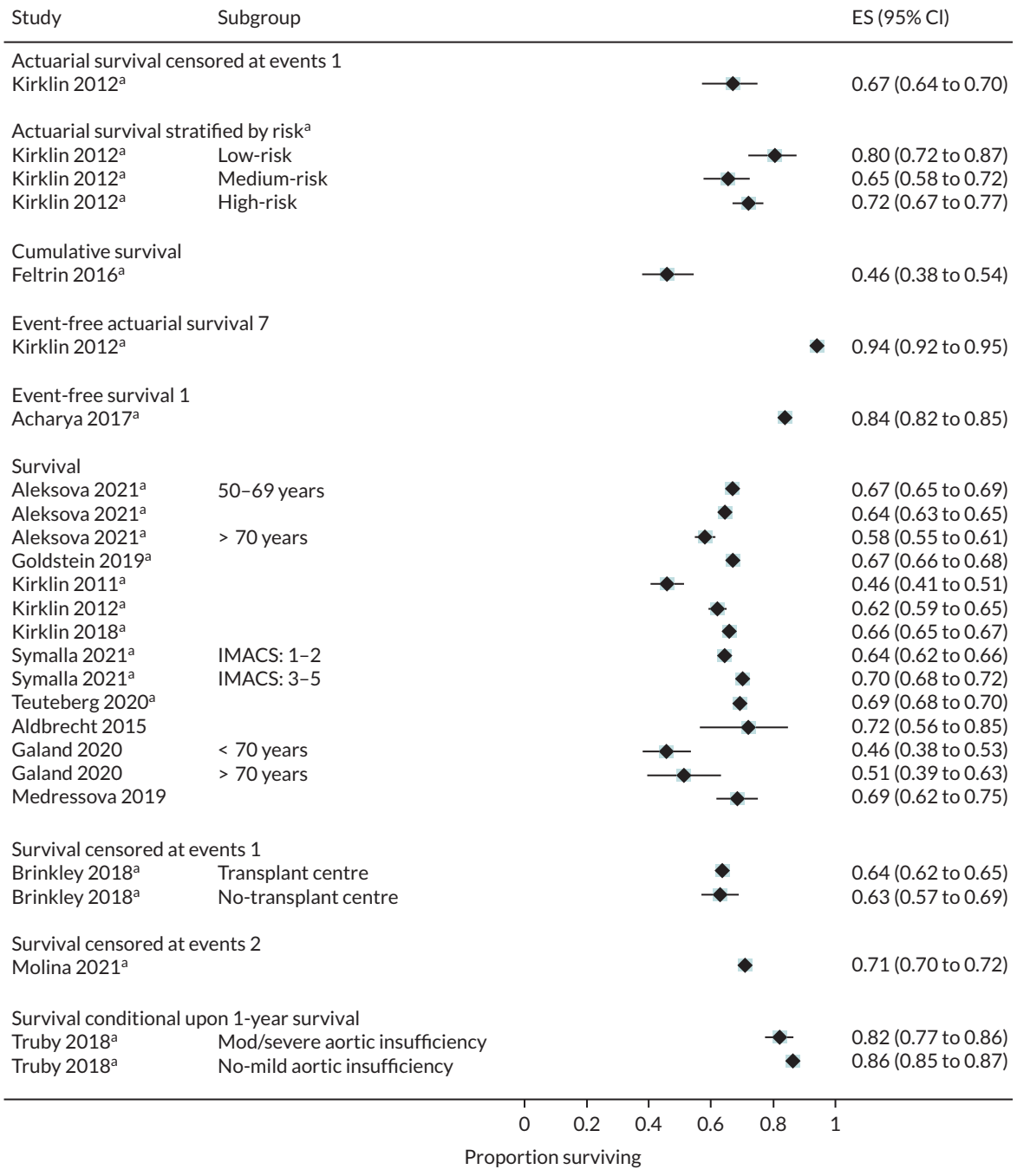

FIGURE 50 Survival in studies with multiple devices at 24 months follow-up. a, Data from a registry report; survival censored at events 1, censored at transplant and recovery; event-free survival 7, free from urgent heart transplant or delayed LVAD; survival censored at events 2, censored at transplant or cessation of support.

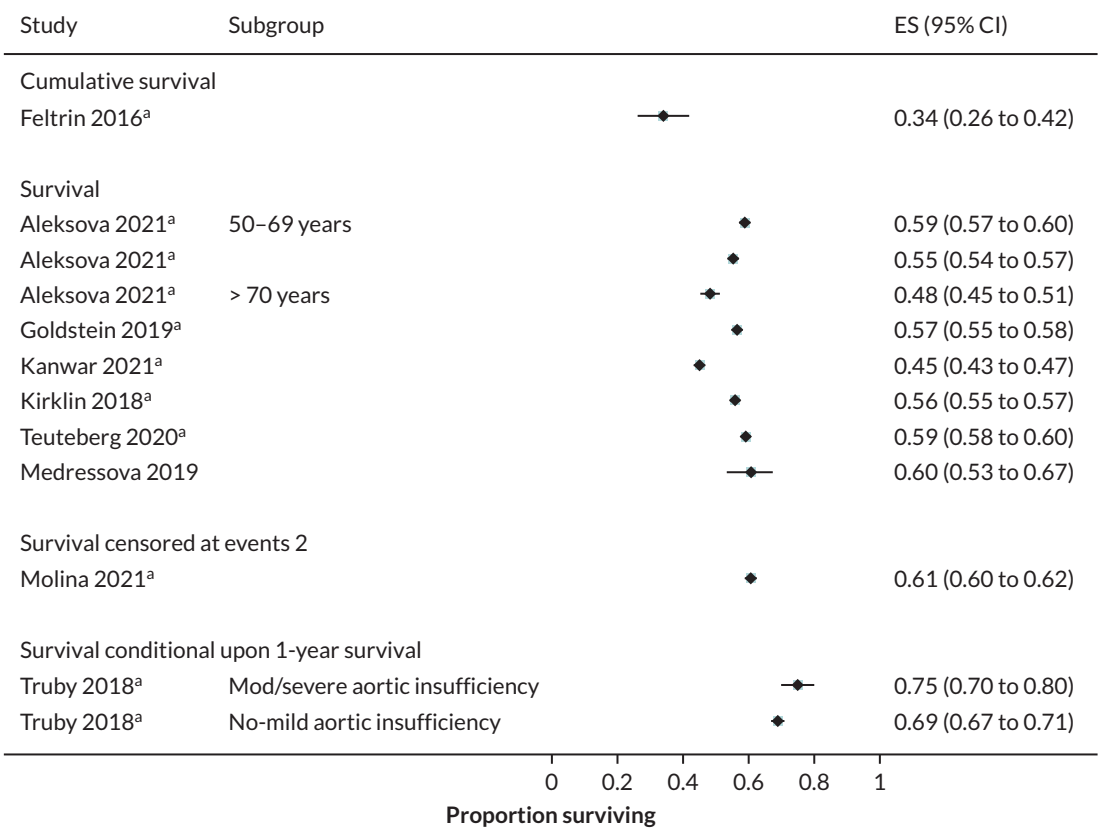

FIGURE 51 Survival in studies with multiple devices at 36 months follow-up. a, Data from a registry report; survival censored at events 2, censored at transplant or cessation of support.

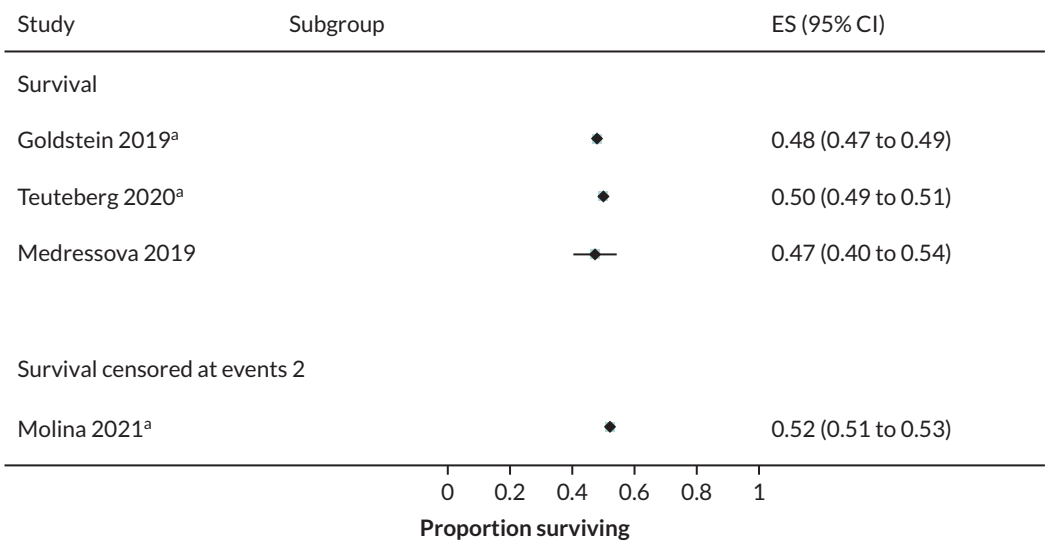

FIGURE 52 Survival in studies with multiple devices at 48 months follow-up. a, Data from a registry report; survival censored at events 2, censored at transplant or cessation of support.

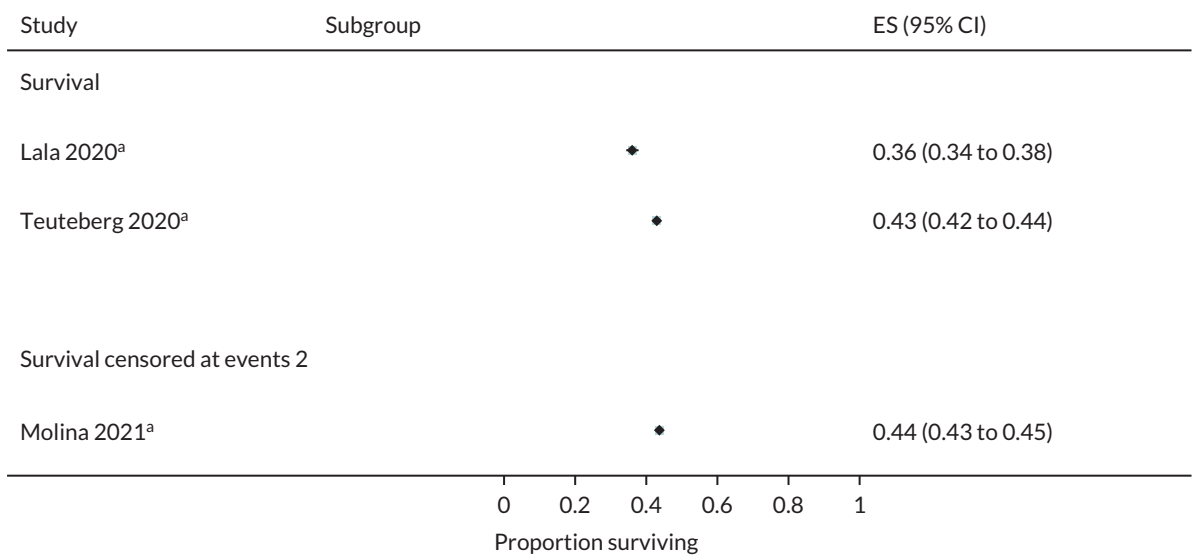

FIGURE 53 Survival in studies with multiple devices at 60 months follow-up. a, Data from a registry report; survival censored at events 2, censored at transplant or cessation of support.

Quality of life

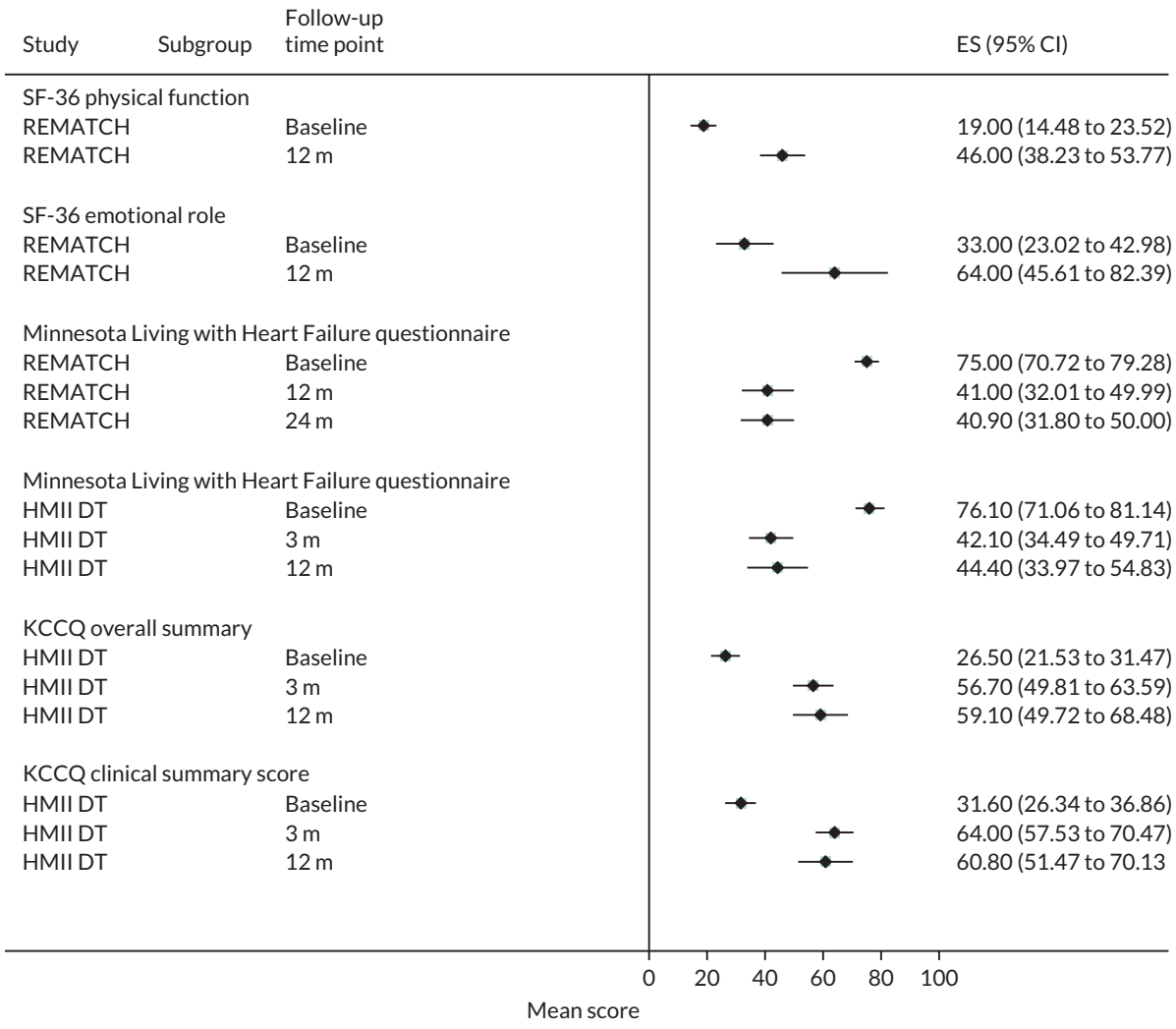

FIGURE 54 Mean QoL scores from different QoL tools in the HeartMate XVE at all reported time points.

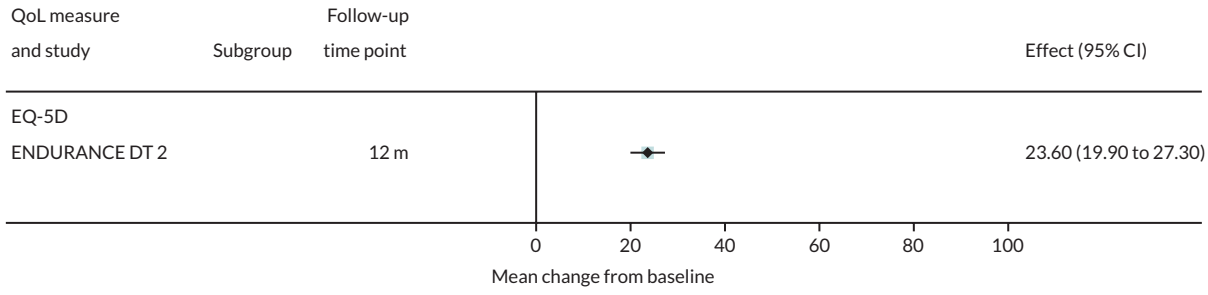

FIGURE 55 Mean change from baseline in QoL score in the HeartWare HVAD at 12 months.

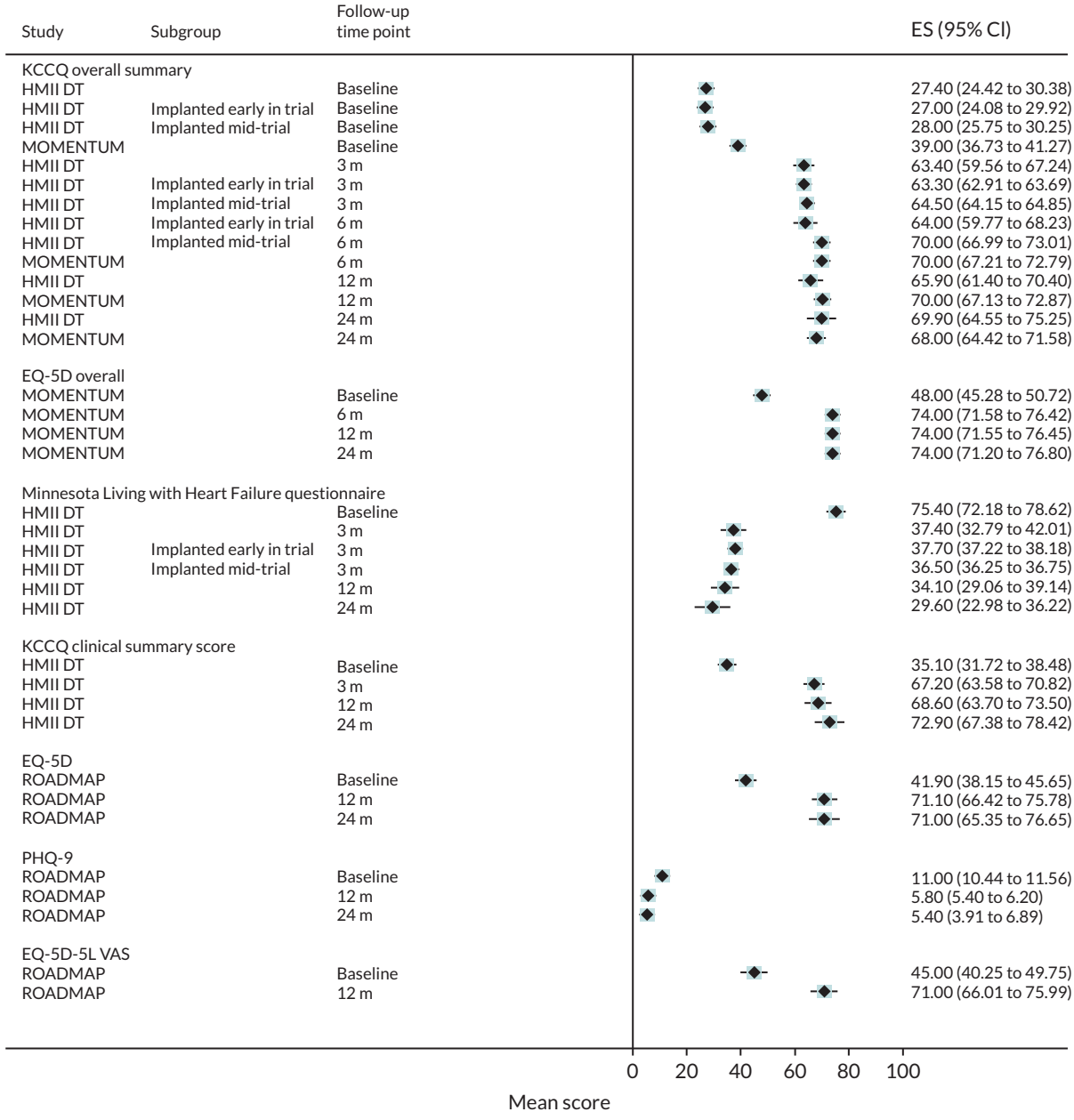

FIGURE 56 Mean QoL scores from different QoL tools in the HeartMate II at all reported time points.

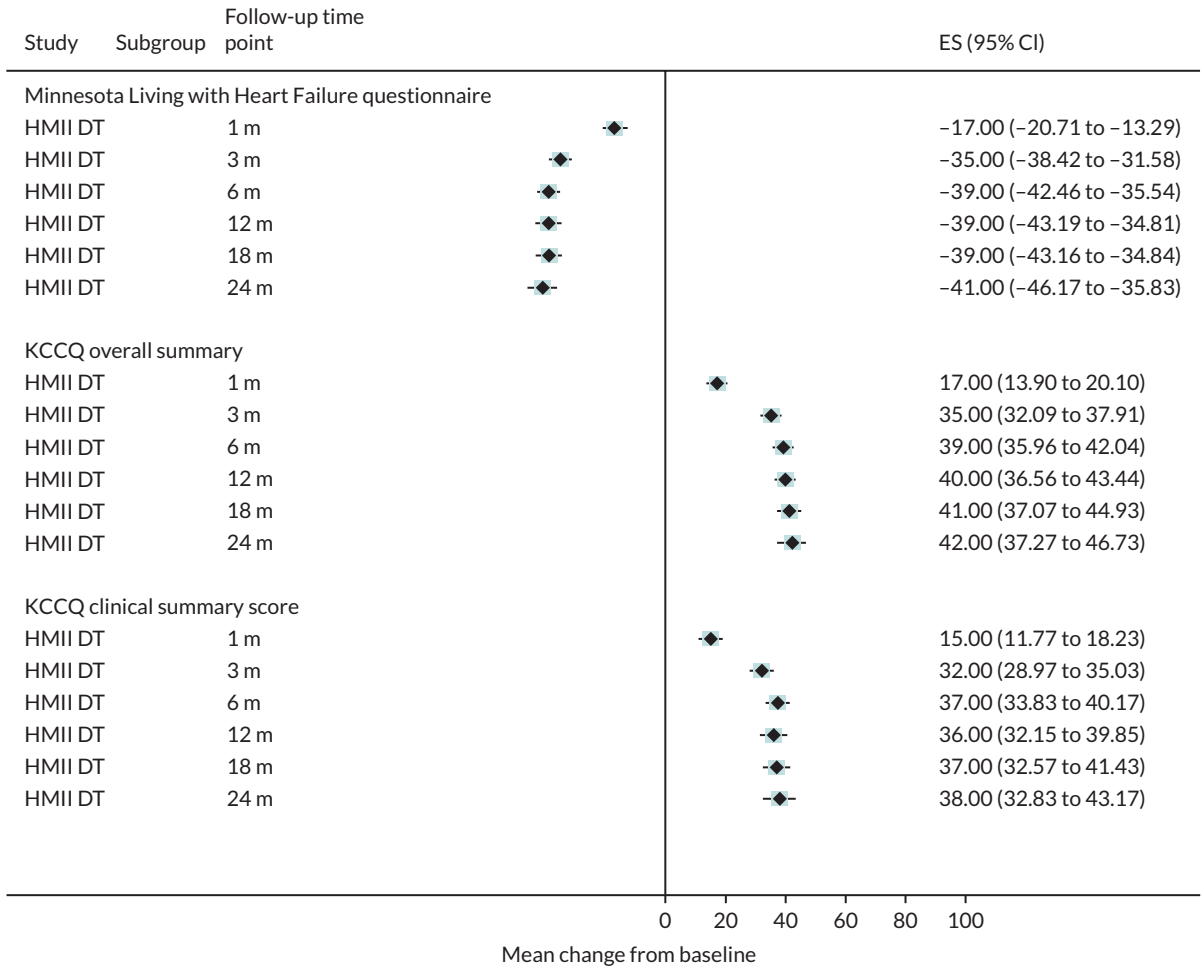

FIGURE 57 Mean change from baseline in QoL score in the HeartMate II at all reported time points.

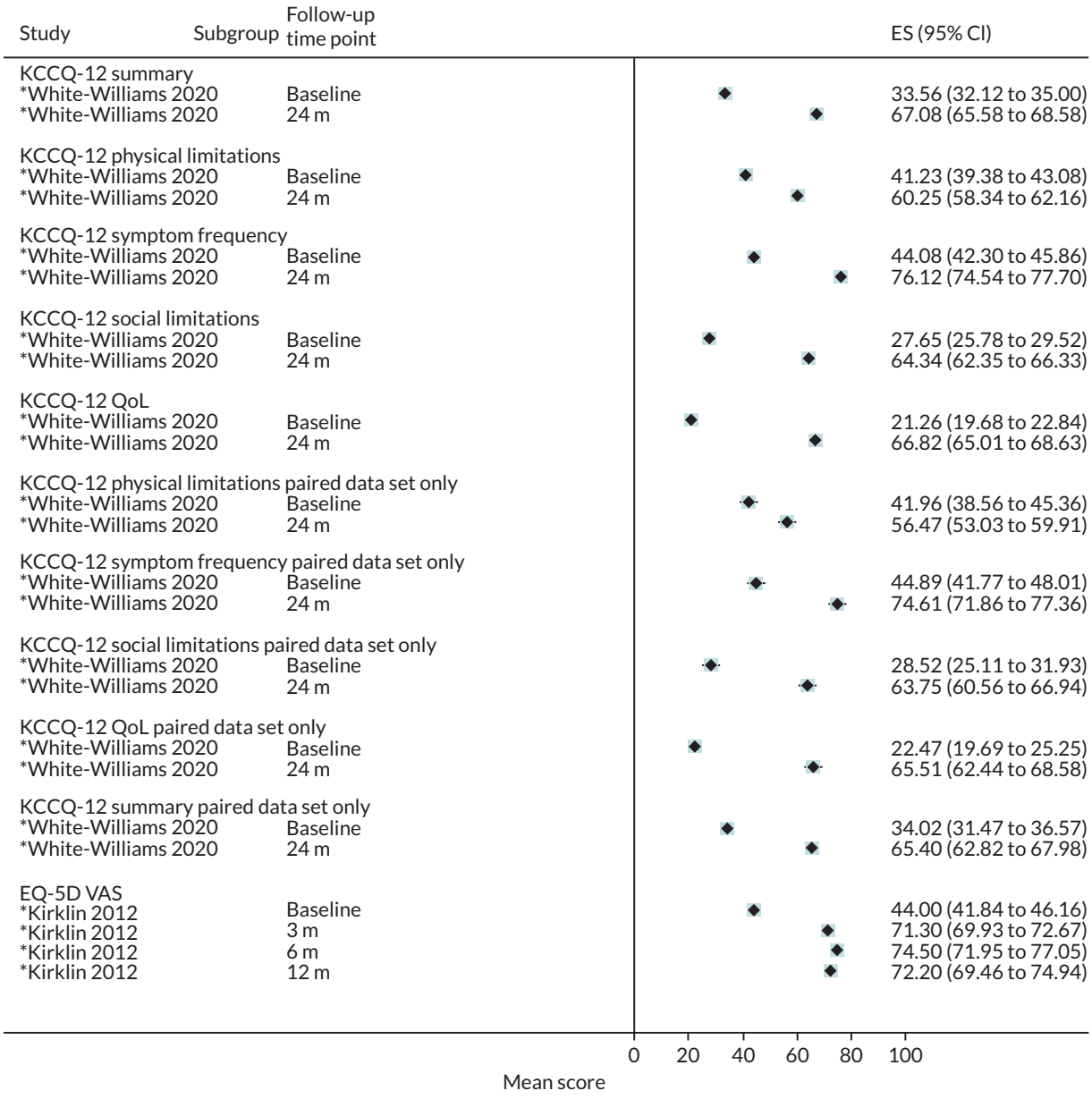

FIGURE 58 Mean QoL scores from different QoL tools in studies with multiple devices at all reported time points. *Report from The National Heart, Lung, and Blood Institute Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).

Hospitalisations

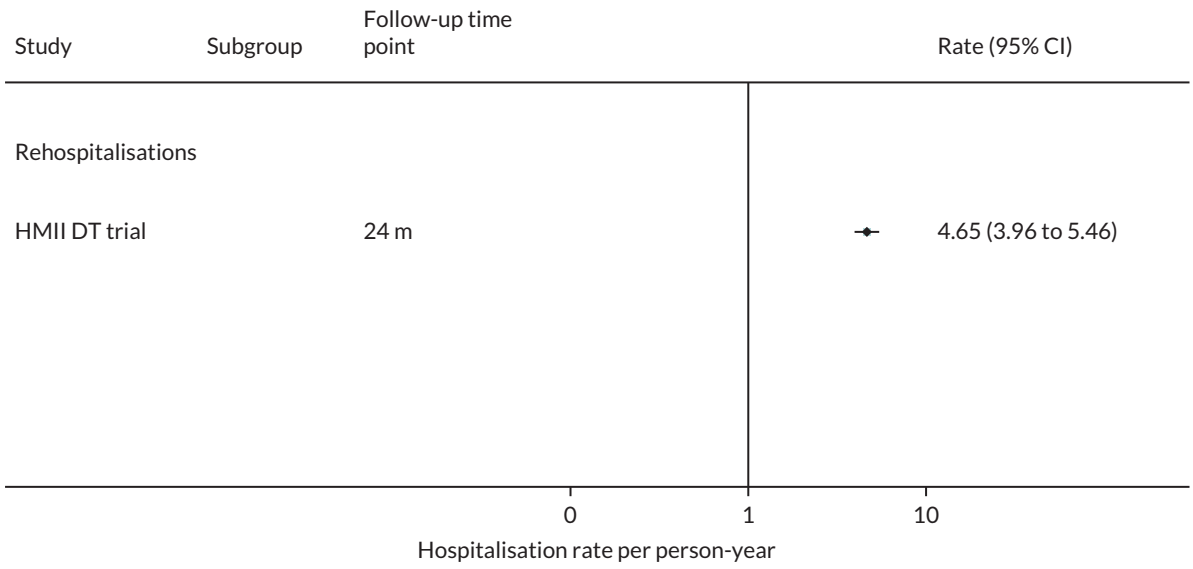

FIGURE 59 Hospitalisation rate per person-years with the HeartMate XVE at all reported time points.

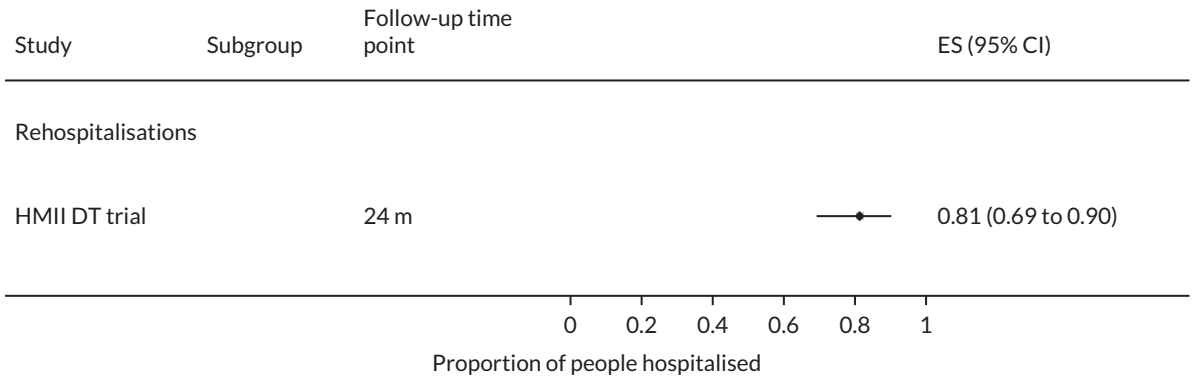

FIGURE 60 Proportion of people hospitalised with the HeartMate XVE at all reported time points.

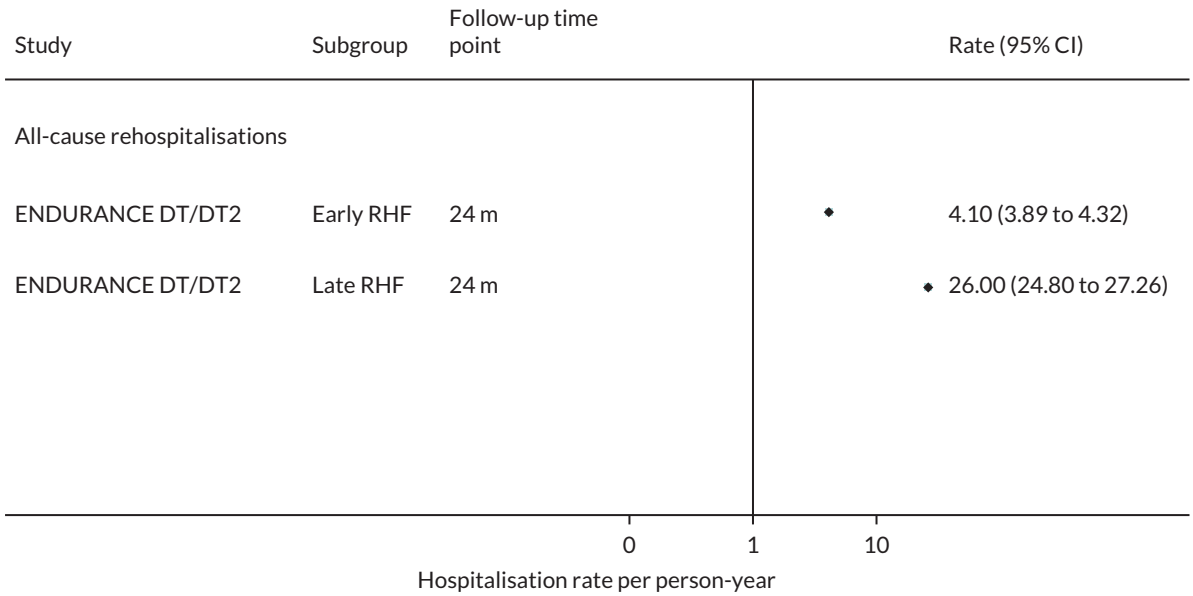

FIGURE 61 Hospitalisation rate per person-years with the HeartWare HVAD at all reported time points.

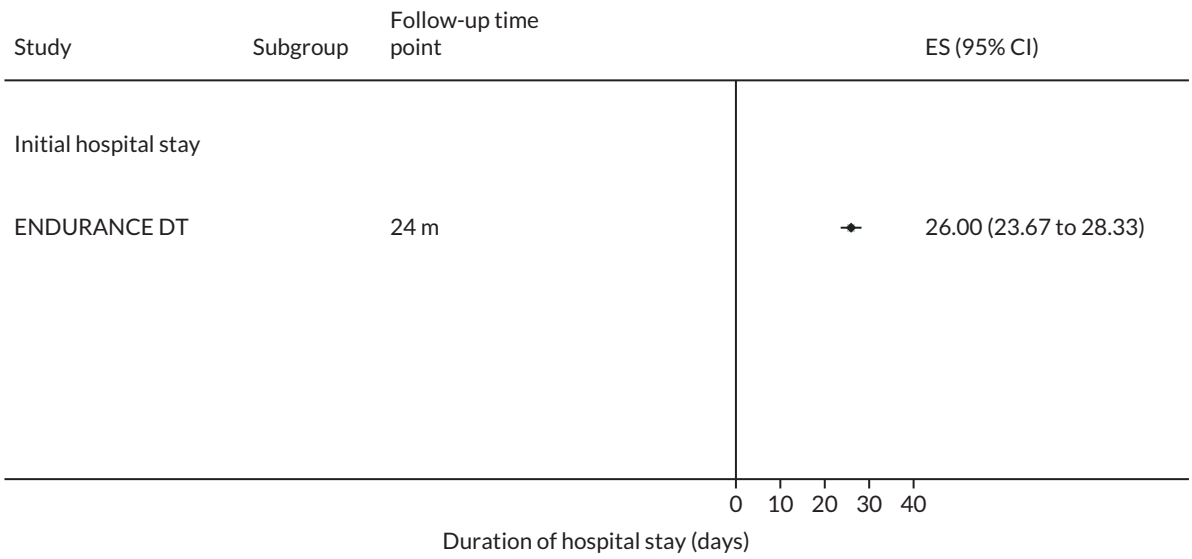

FIGURE 62 Mean duration of hospital stay in days with the HeartWare HVAD at all reported time points.

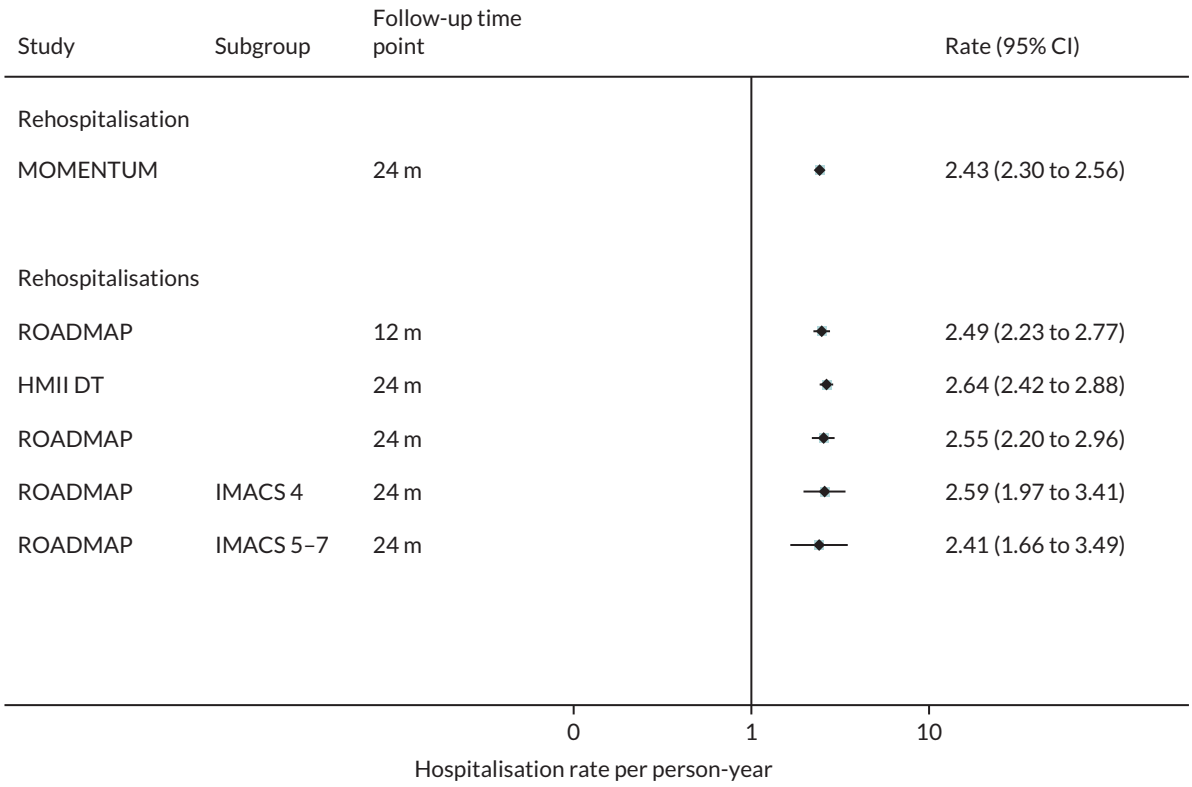

FIGURE 63 Hospitalisation rate per person-years with the HeartMate II at all reported time points.

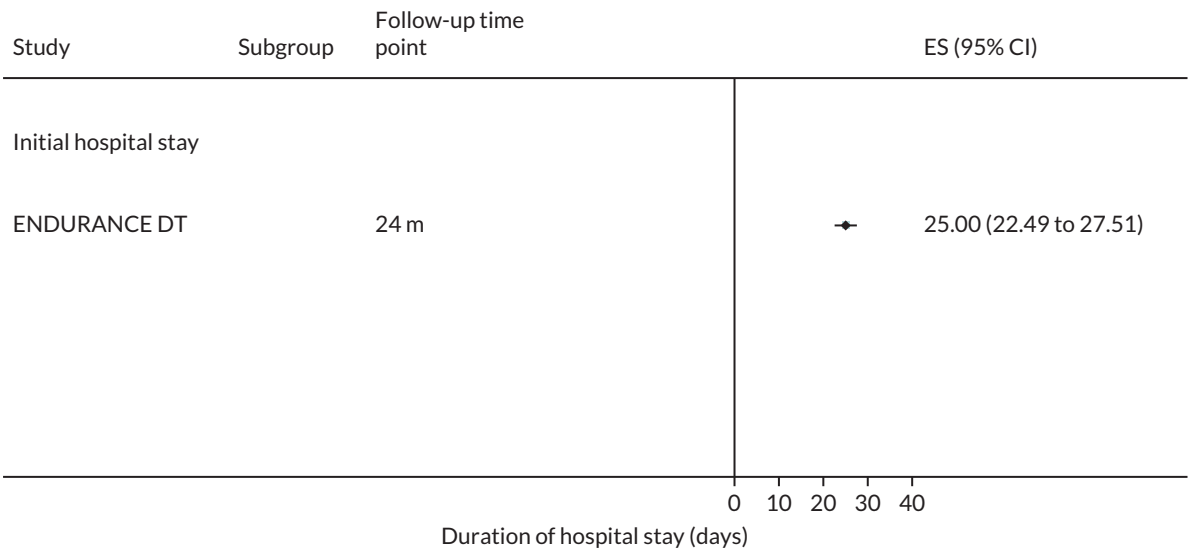

FIGURE 64 Duration of initial hospital stay in days with the HeartMate II.

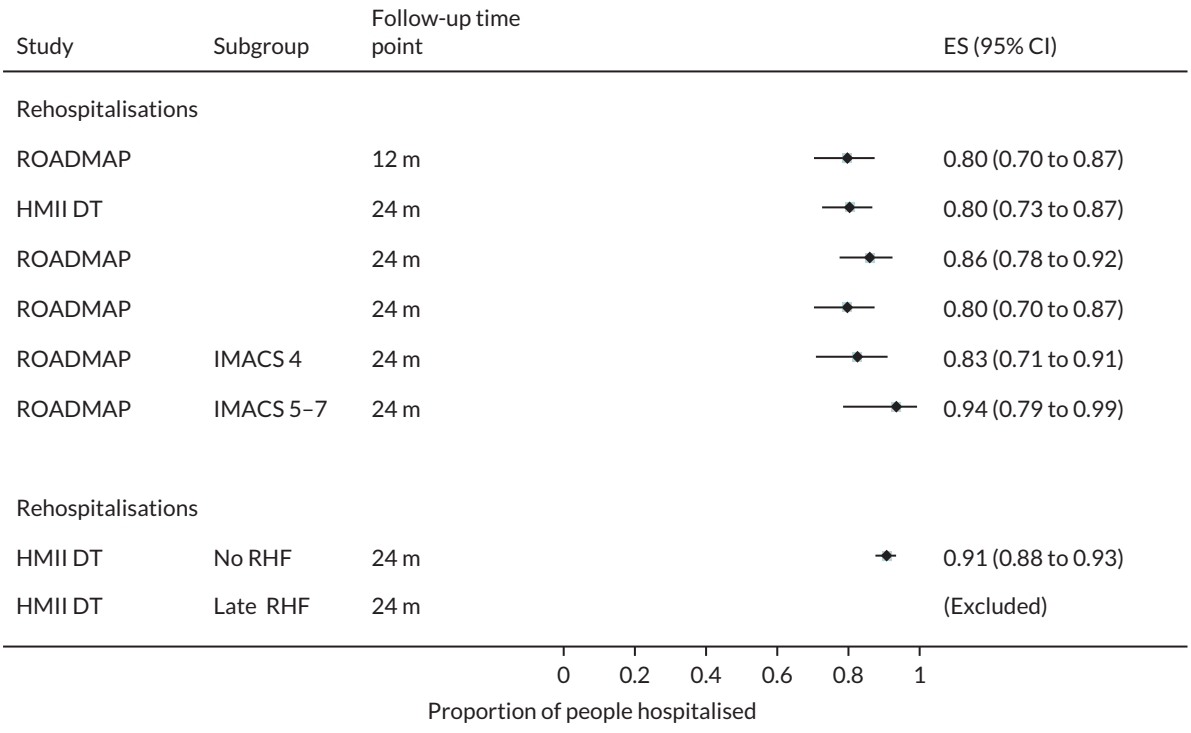

FIGURE 65 Proportion of people hospitalised with the HeartMate II at all reported time points.

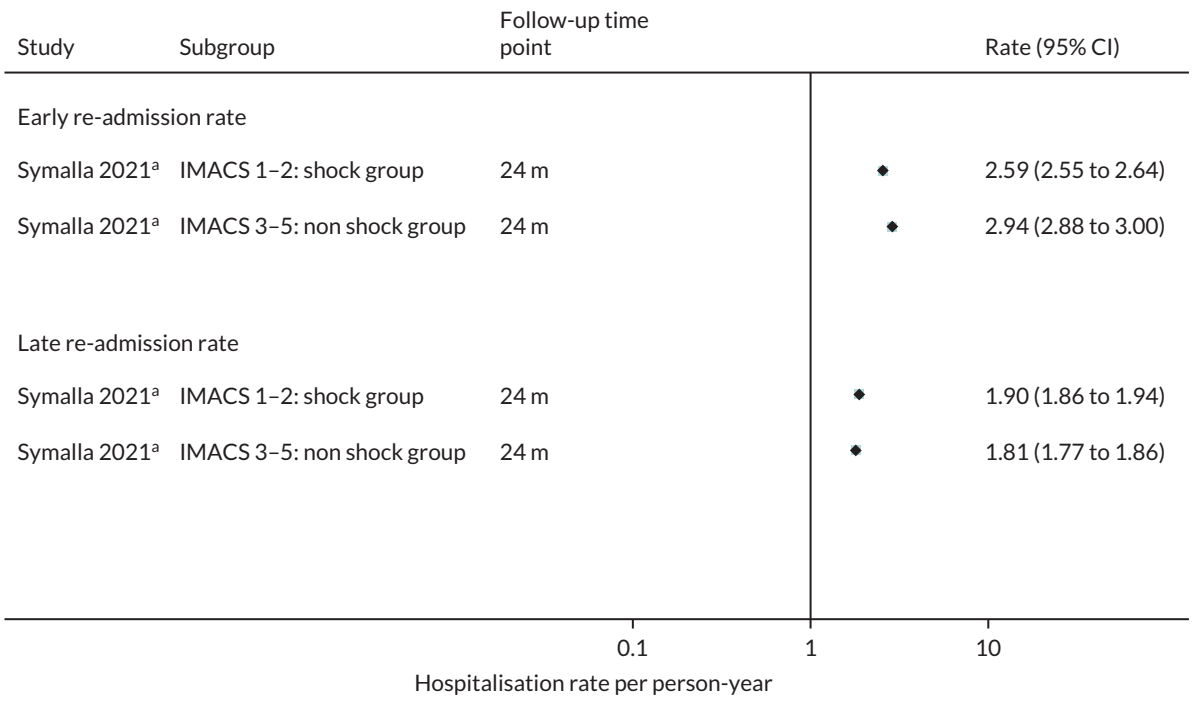

FIGURE 66 Hospitalisation rate per person-years in studies with multiple devices at all reported time points. a, Data are from a registry report.

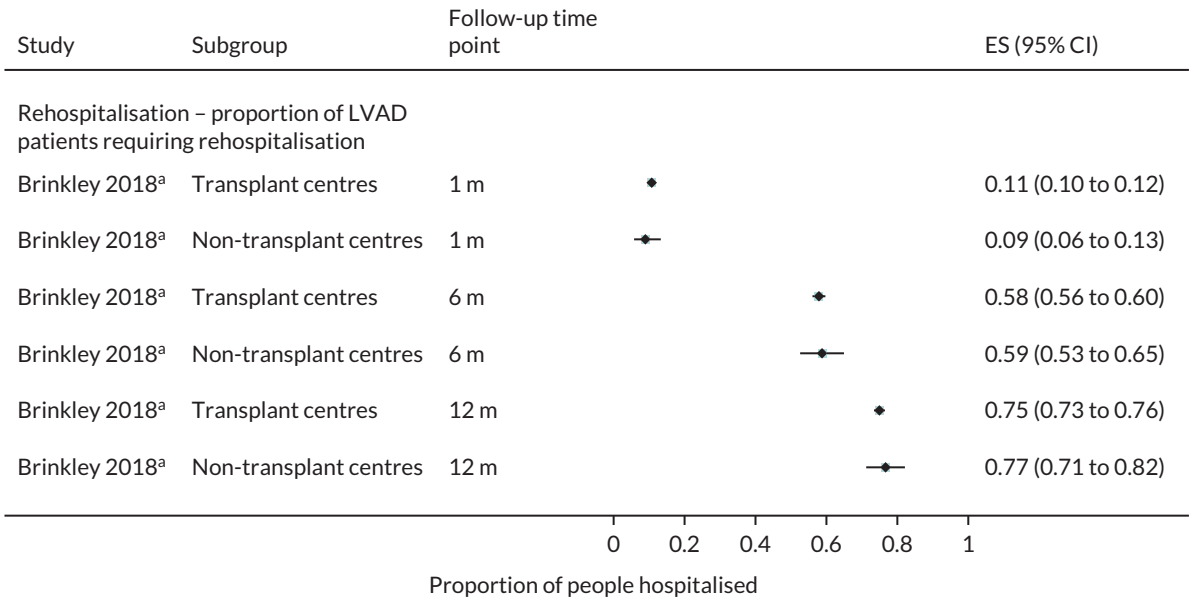

FIGURE 67 Proportion of people hospitalised in studies with multiple devices at all reported time points. a, Data are from a registry report.

Major events

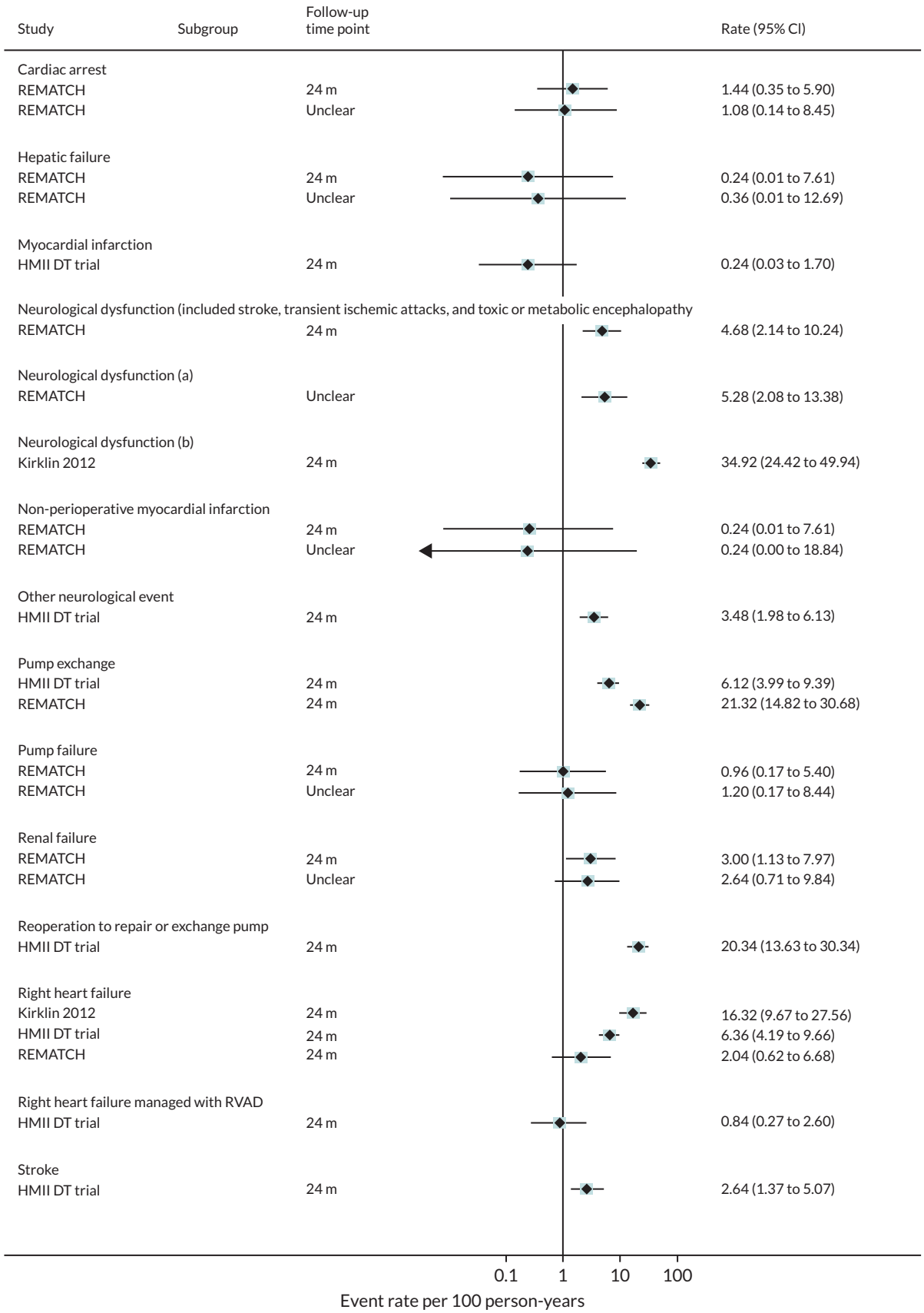

FIGURE 68 Event rate for major events per 100 person-years with the HeartMate XVE at all reported time points.

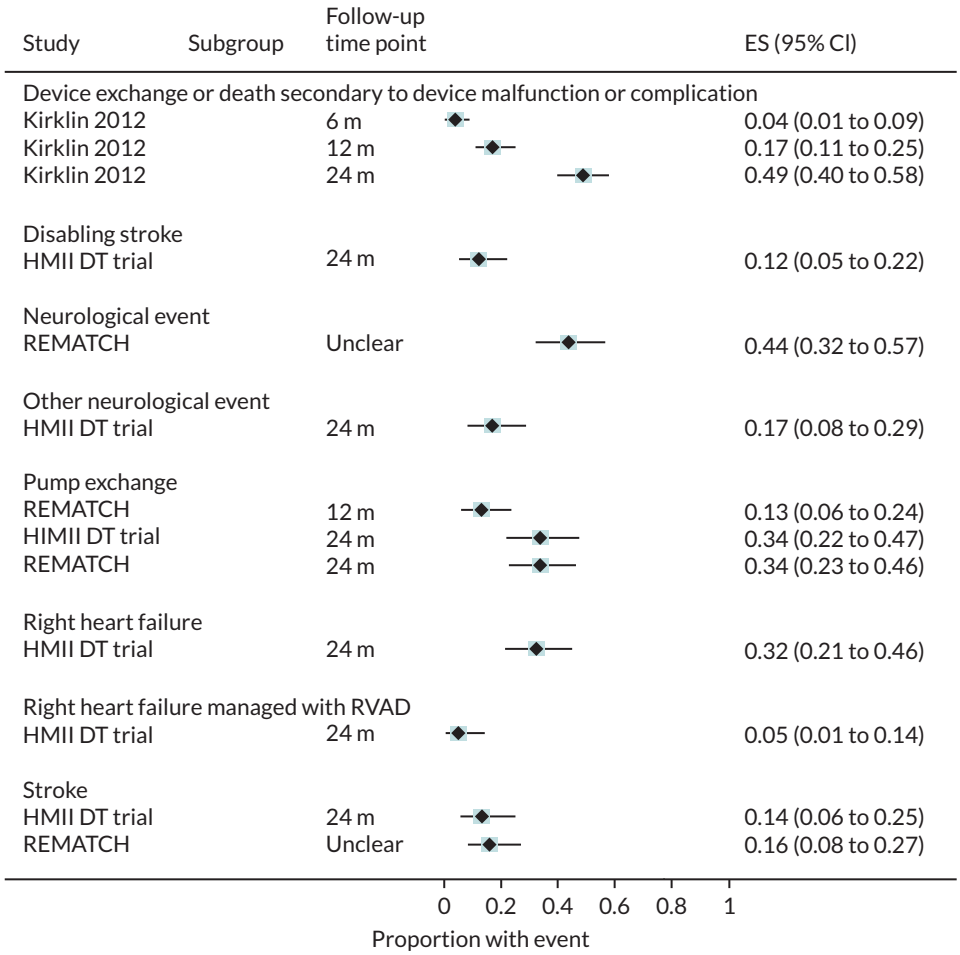

FIGURE 69 Proportion of people with a major event with the HeartMate XVE at all reported time points.

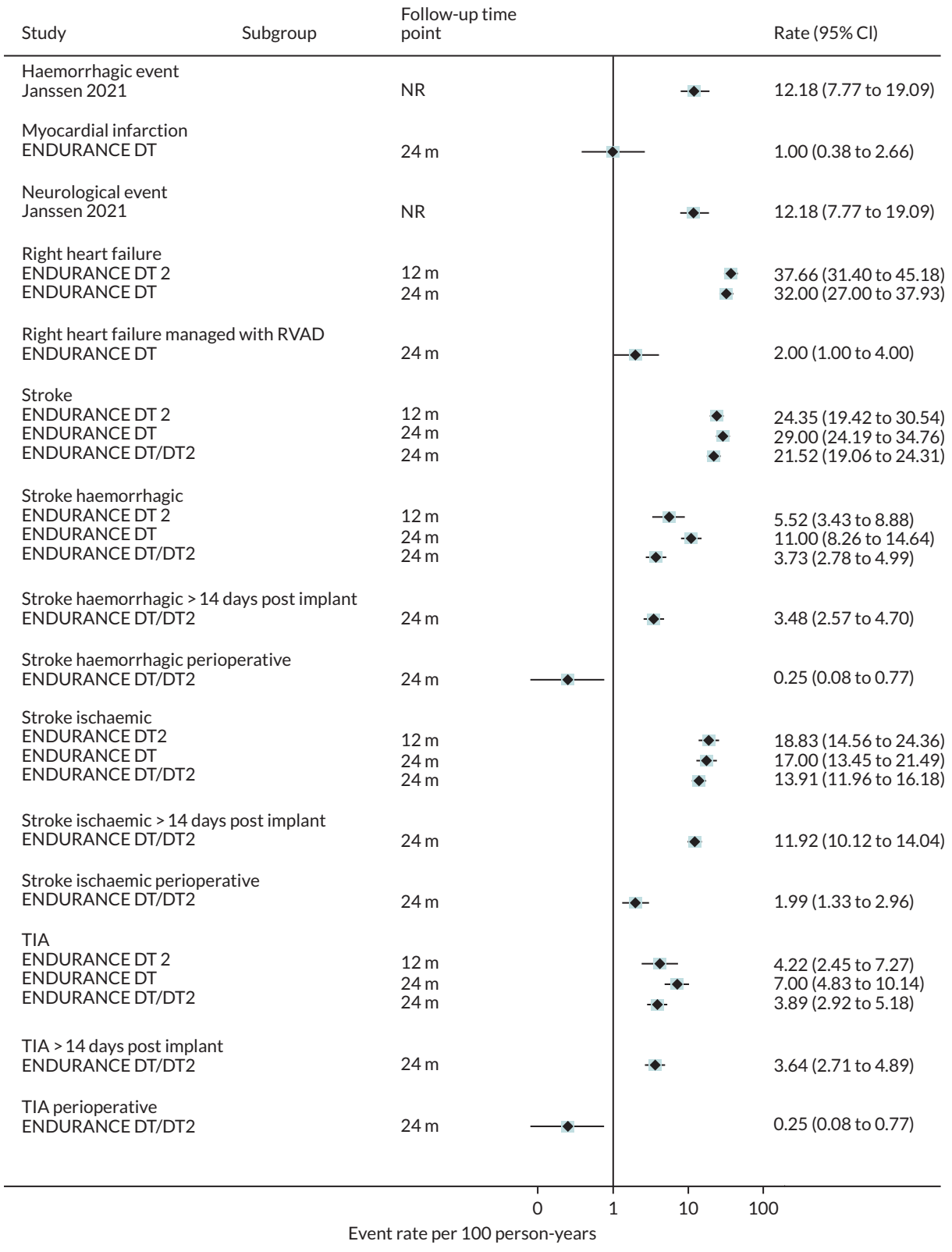

FIGURE 70 Major event rate per 100 person-years with the HeartWare HVAD at all reported time points.

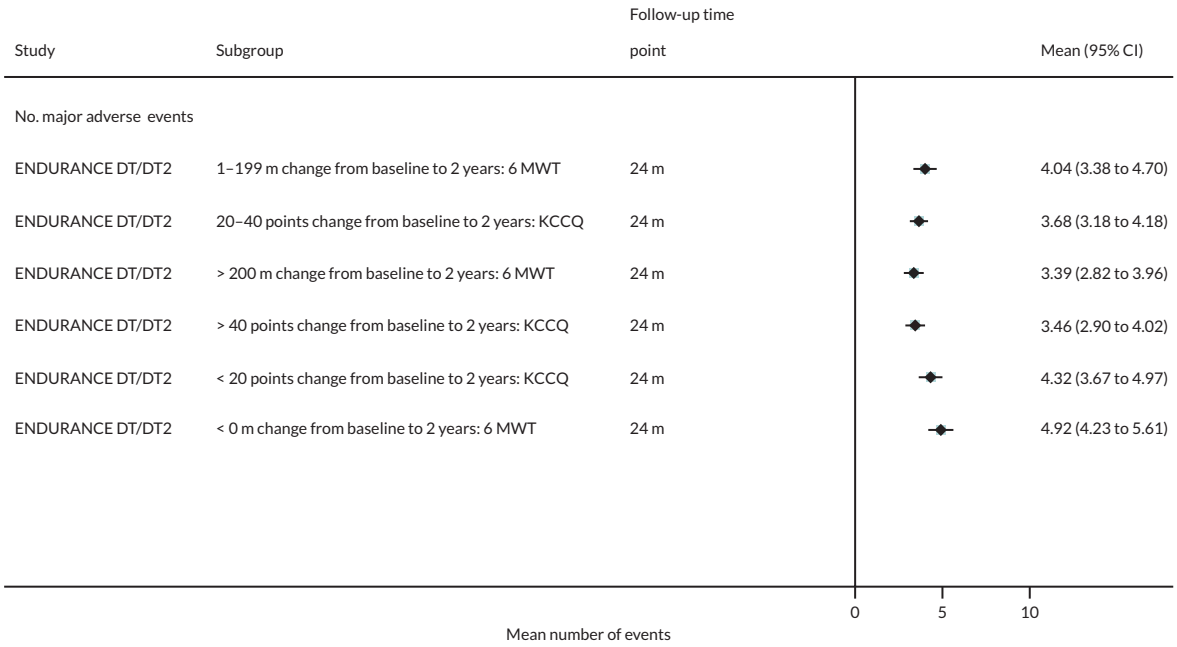

FIGURE 71 Mean number of major events with the HeartWare HVAD at all reported time points.

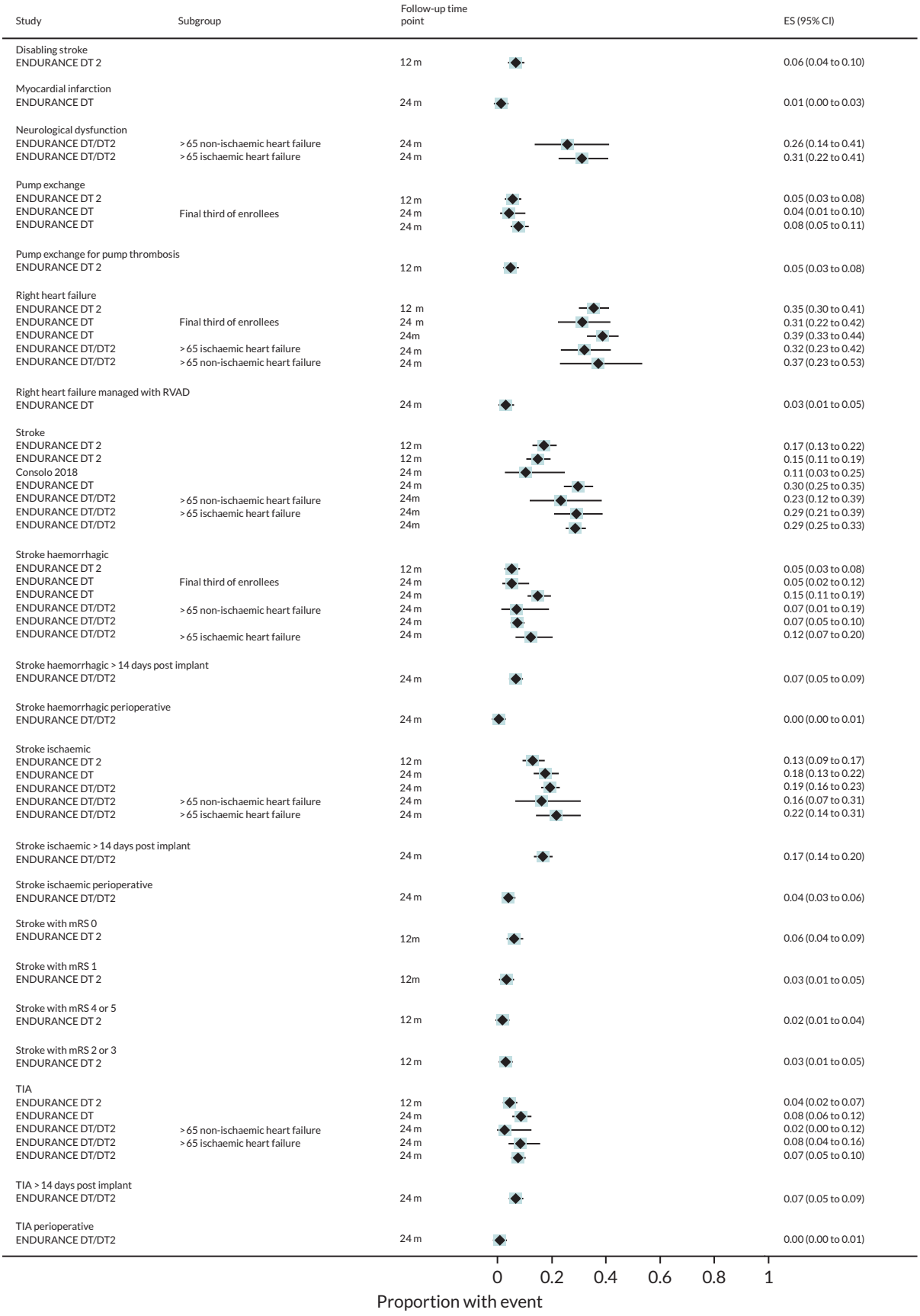

FIGURE 72 Proportion of people with events with the HeartWare HVAD at all reported time points.

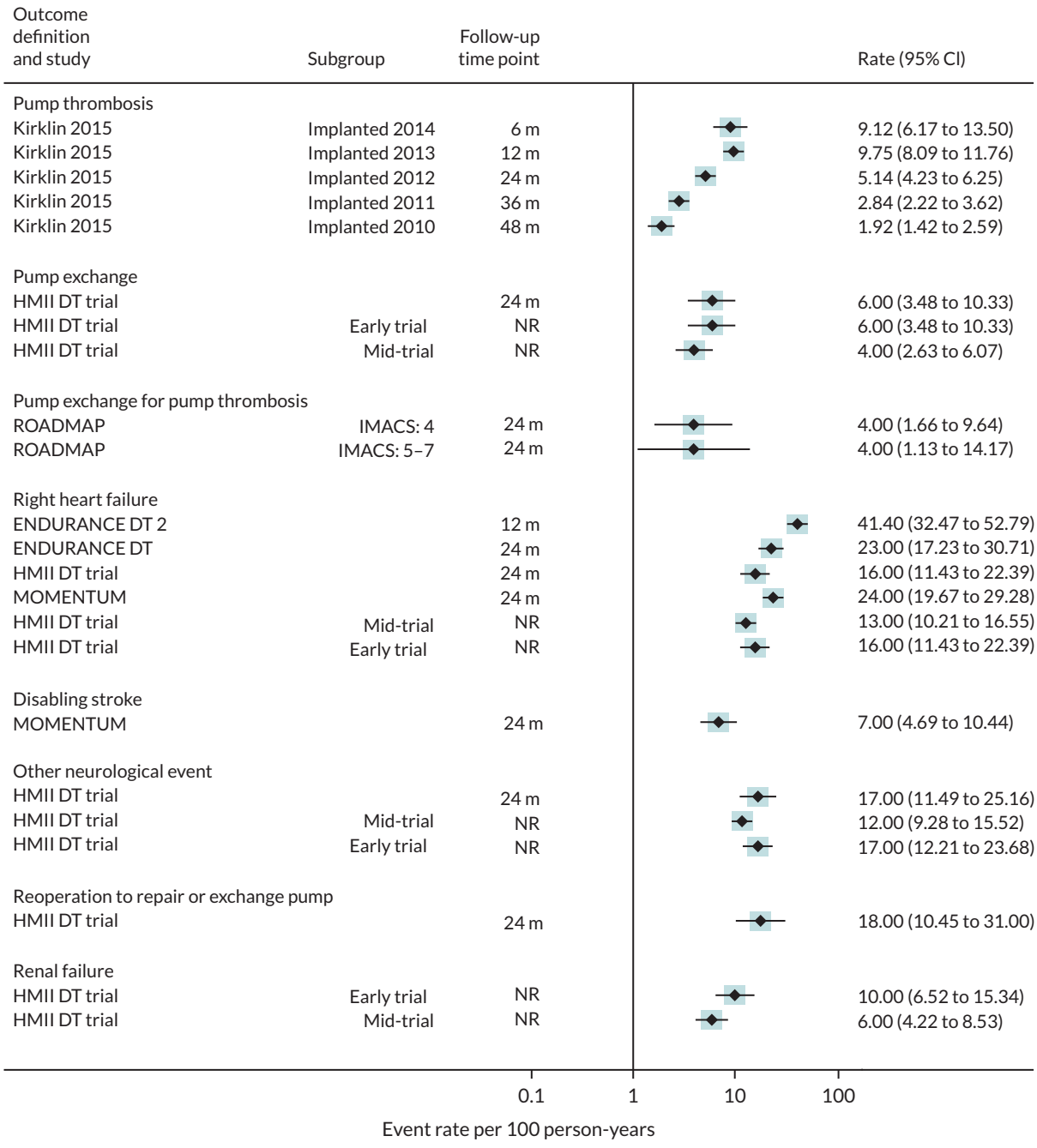

FIGURE 73 A and B major event rate per 100 person-years with the HeartMate II at all reported time points.

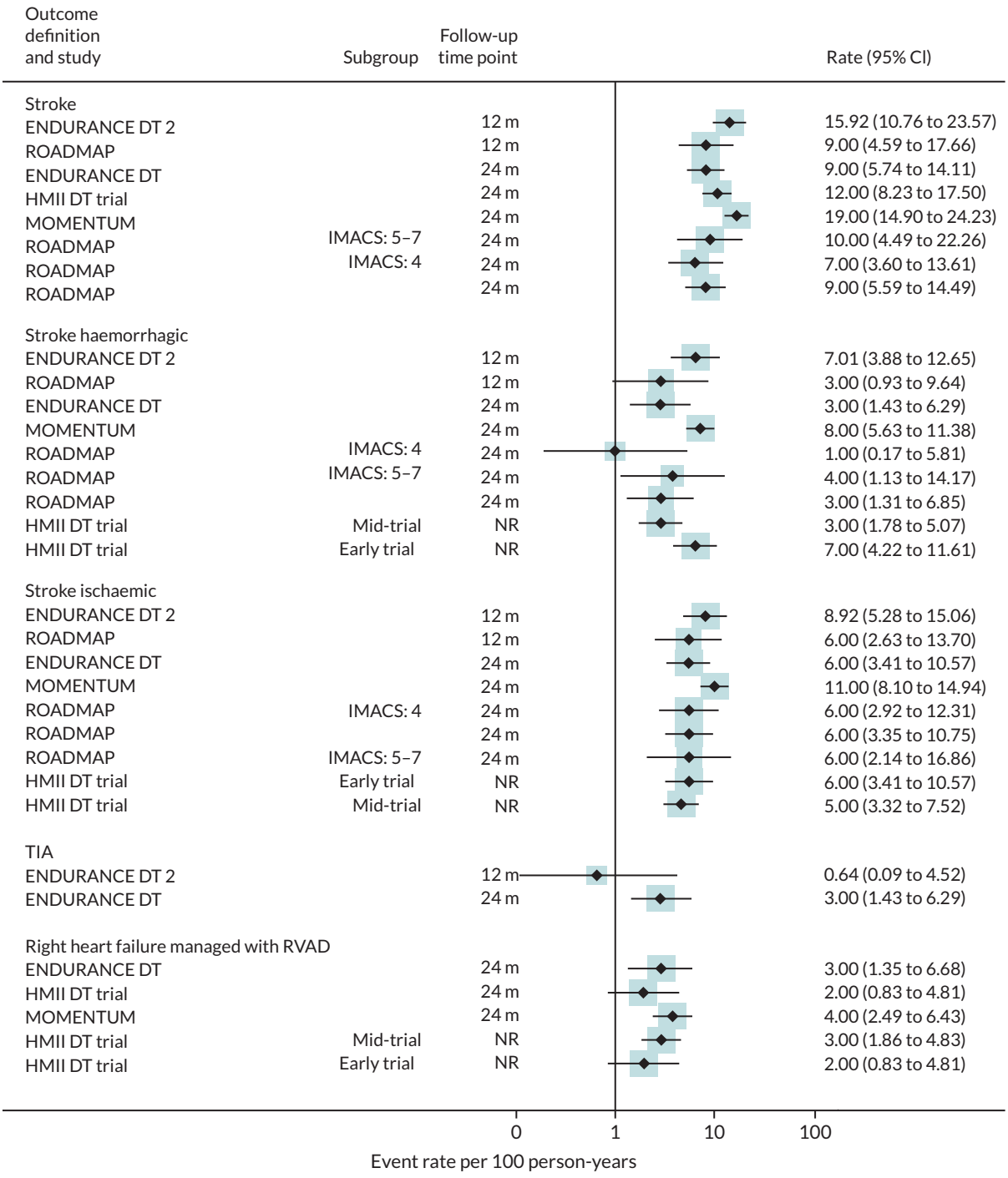

FIGURE 73 A and B major event rate per 100 person-years with the HeartMate II at all reported time points. (*continued*)

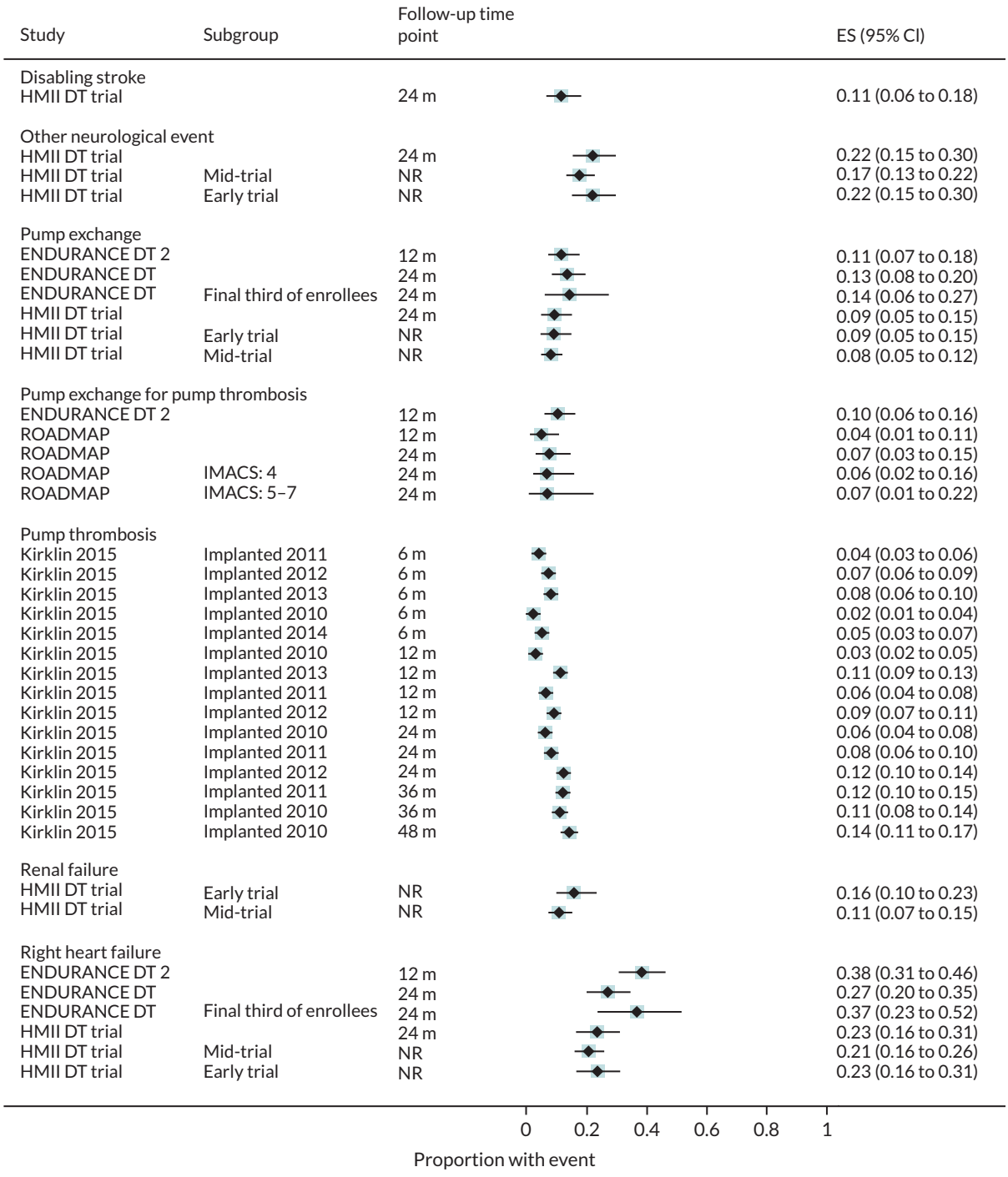

FIGURE 74 A and B proportion of patients with major events with the HeartMate II at all reported time points.

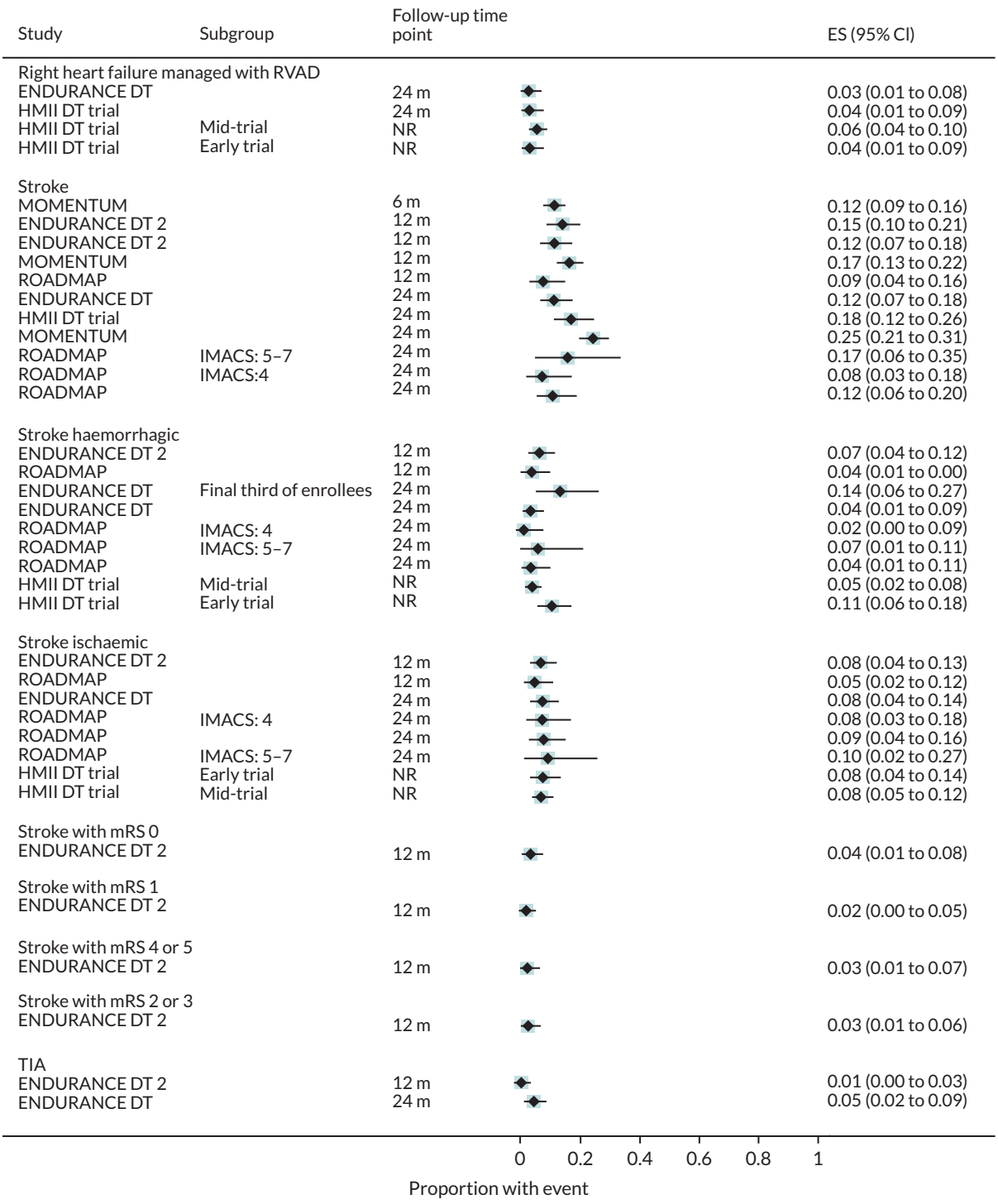

FIGURE 74 A and B proportion of patients with major events with the HeartMate II at all reported time points. (*continued*)

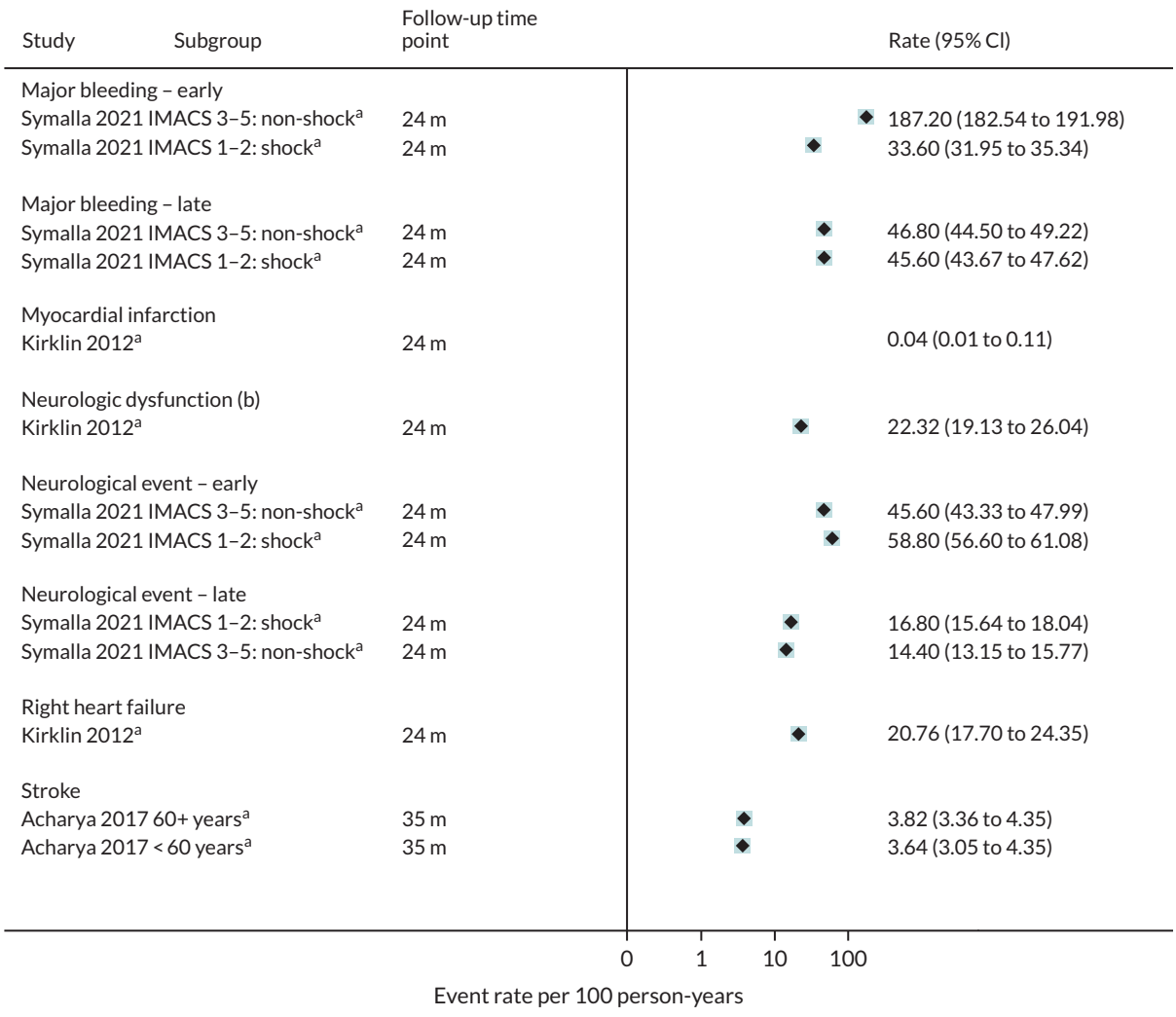

FIGURE 75 Major event rate per 100 person-years in studies with multiple devices at all reported time points. a, Data are from a registry report.

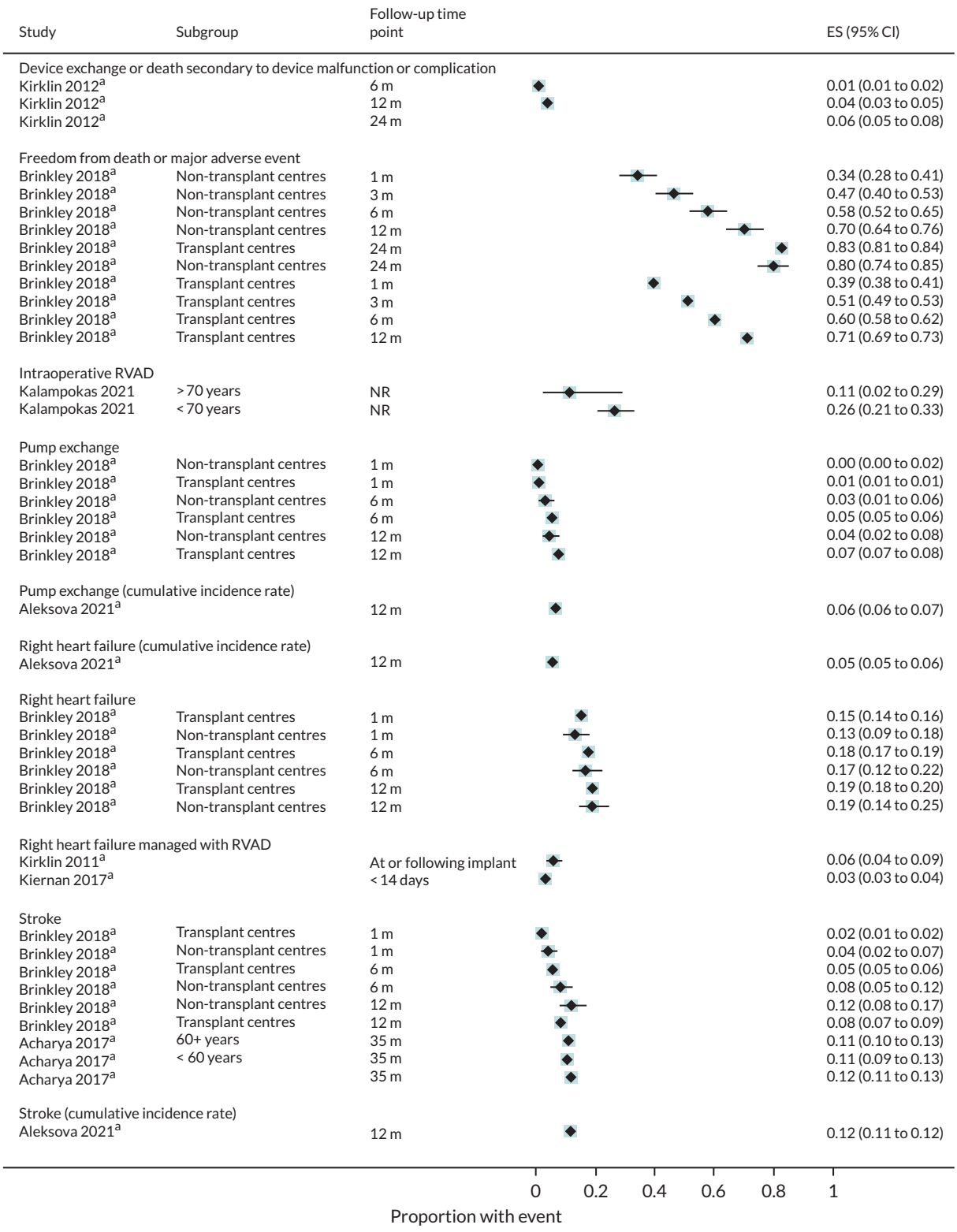

FIGURE 76 Proportion of people with major events in studies with multiple devices at all reported time points. a, Data are from a registry report.

Complications

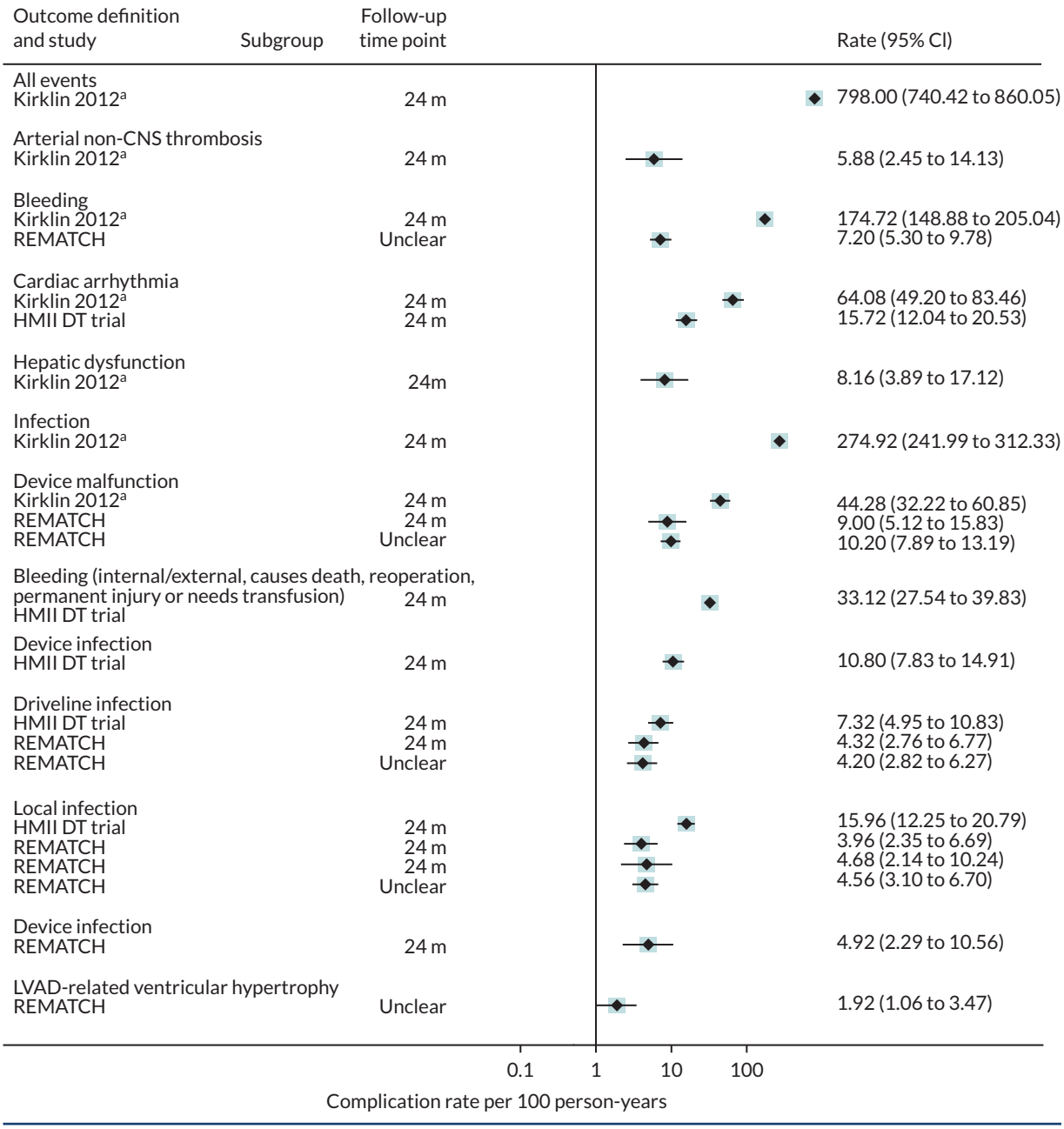

FIGURE 77 A and B rate of complications per 100 person-years in the HeartMate XVE at all reported time points. a, Data are from a registry report.

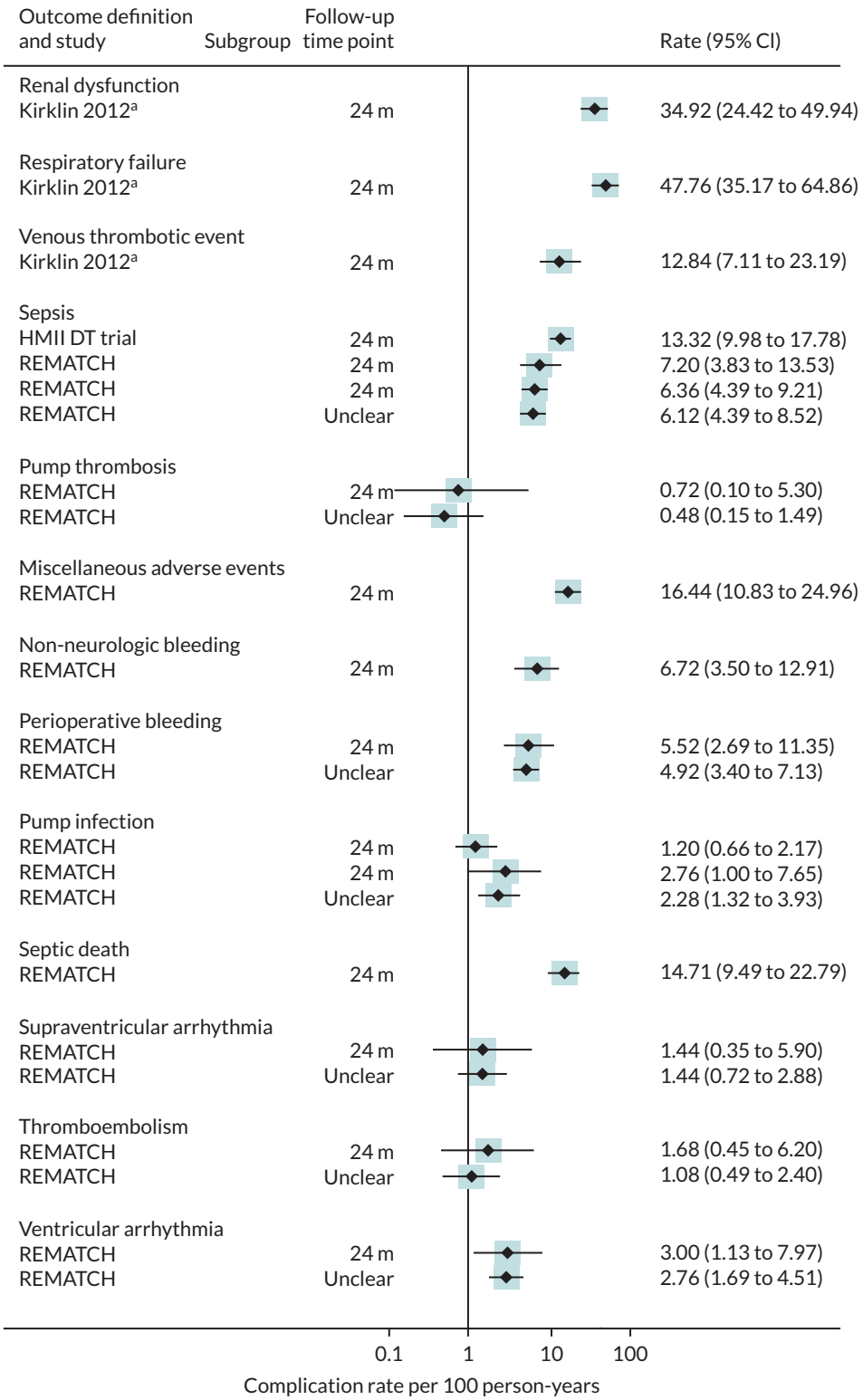

FIGURE 77 A and B rate of complications per 100-person years in the HeartMate XVE at all reported time points. a, Data are from a registry report. (*continued*)

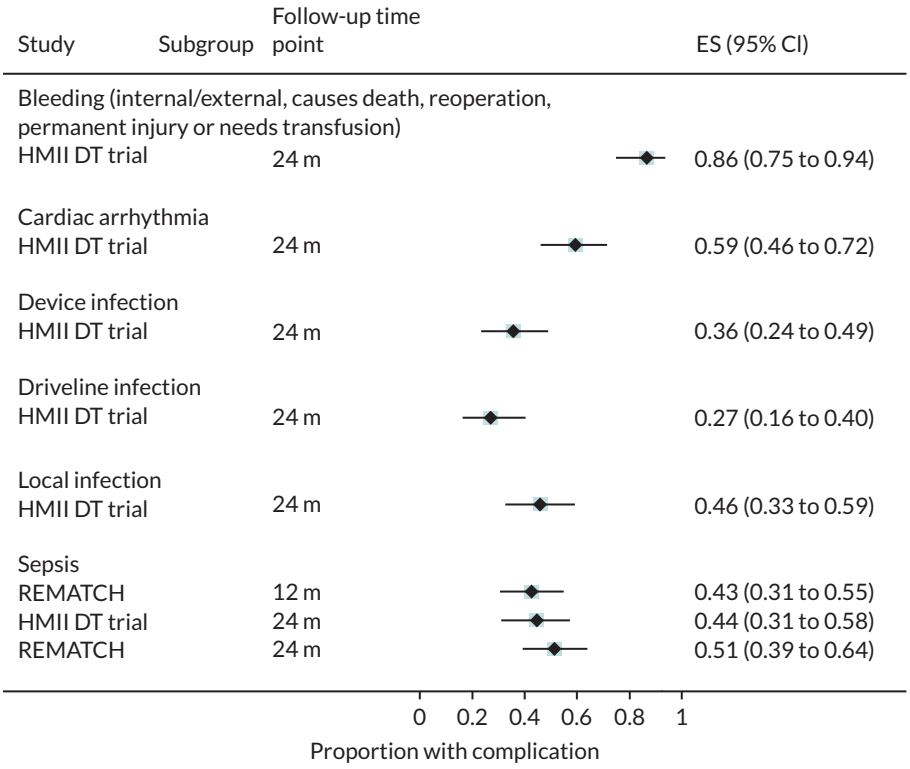

FIGURE 78 Proportion of people with complications in the HeartMate XVE at all reported time points.

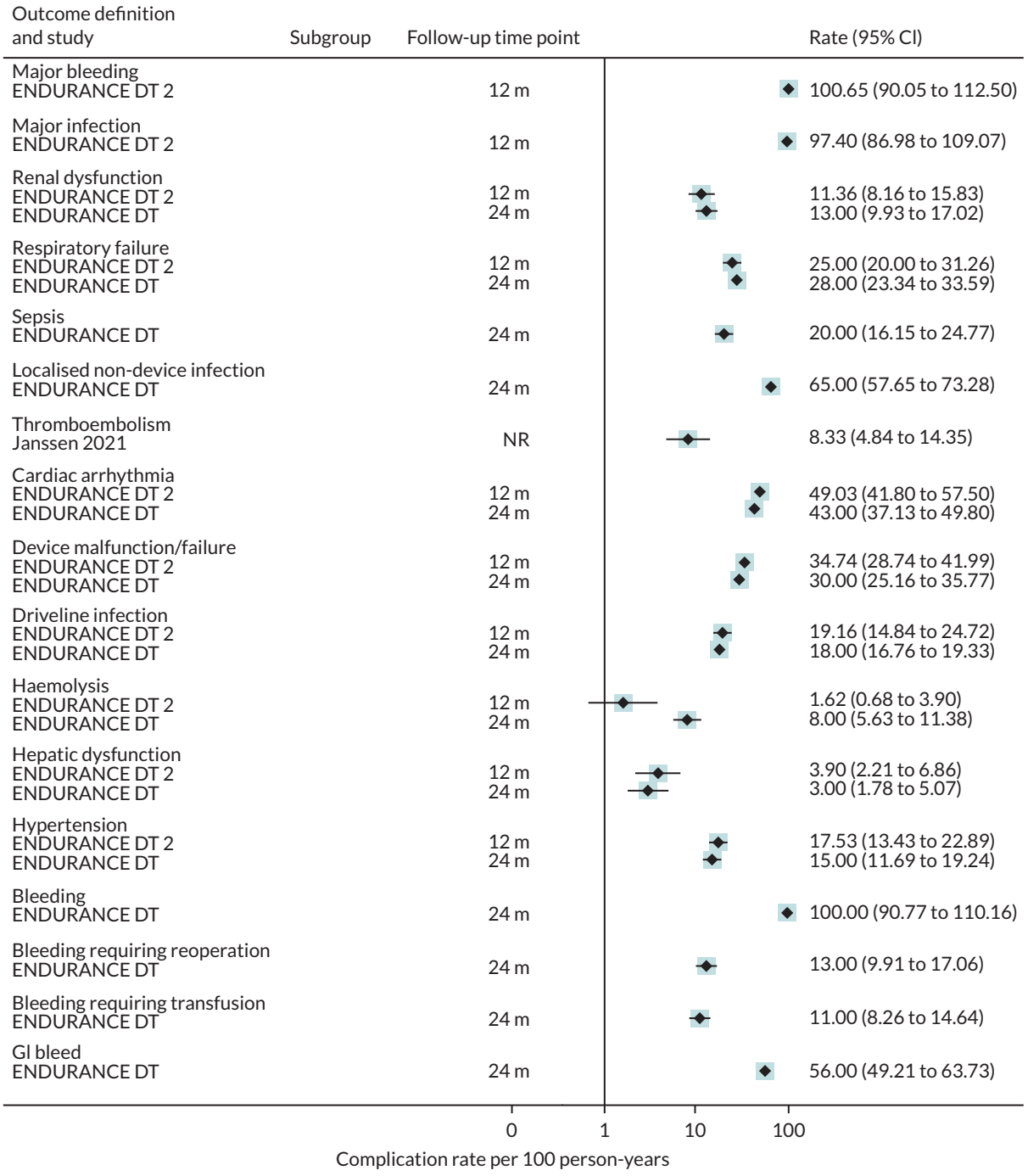

FIGURE 79 Complication rate per 100 person-years in the HeartWare HVAD device at all reported time points.

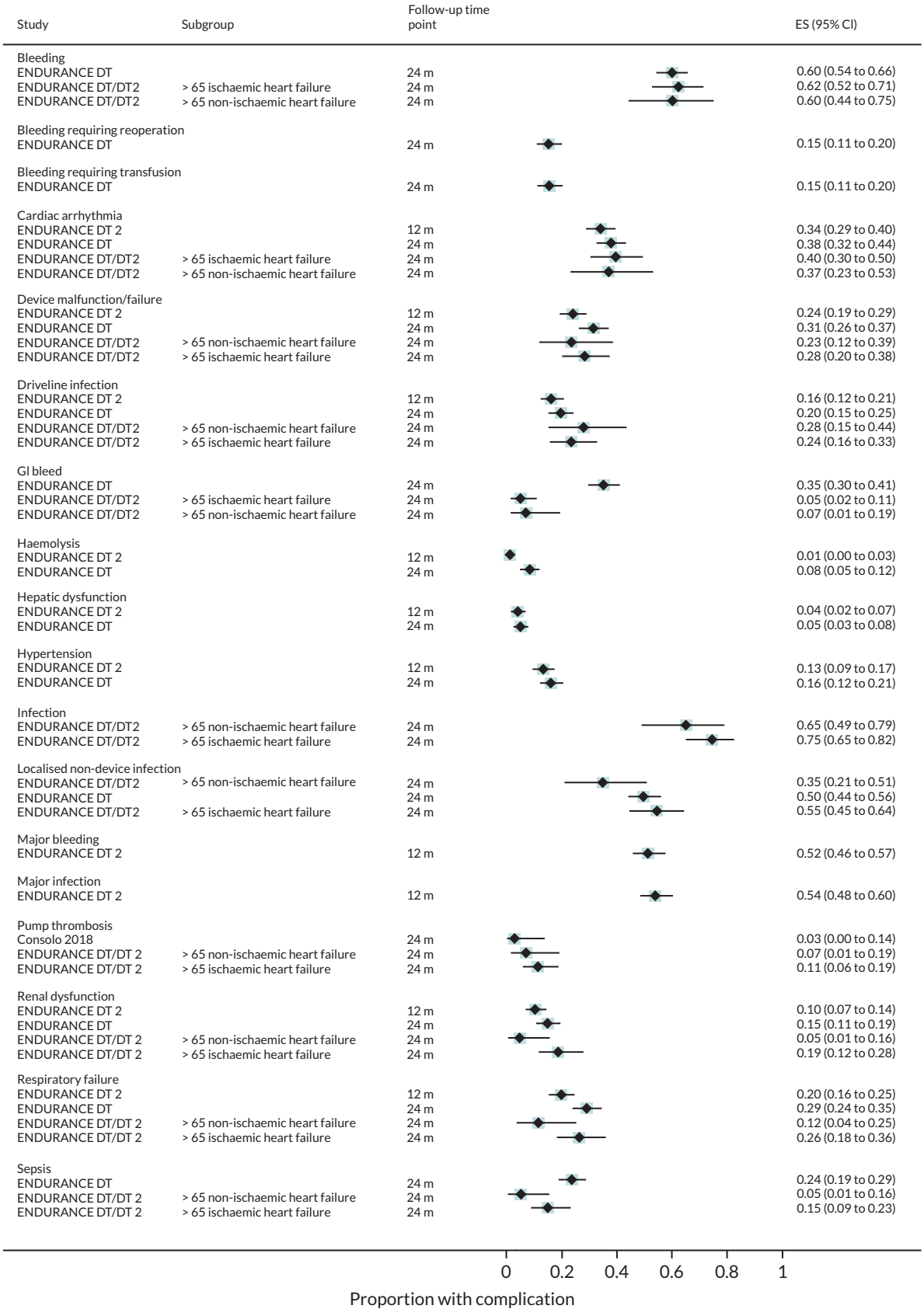

FIGURE 80 Proportion of people with complications in the HeartWare HVAD at all reported time points.

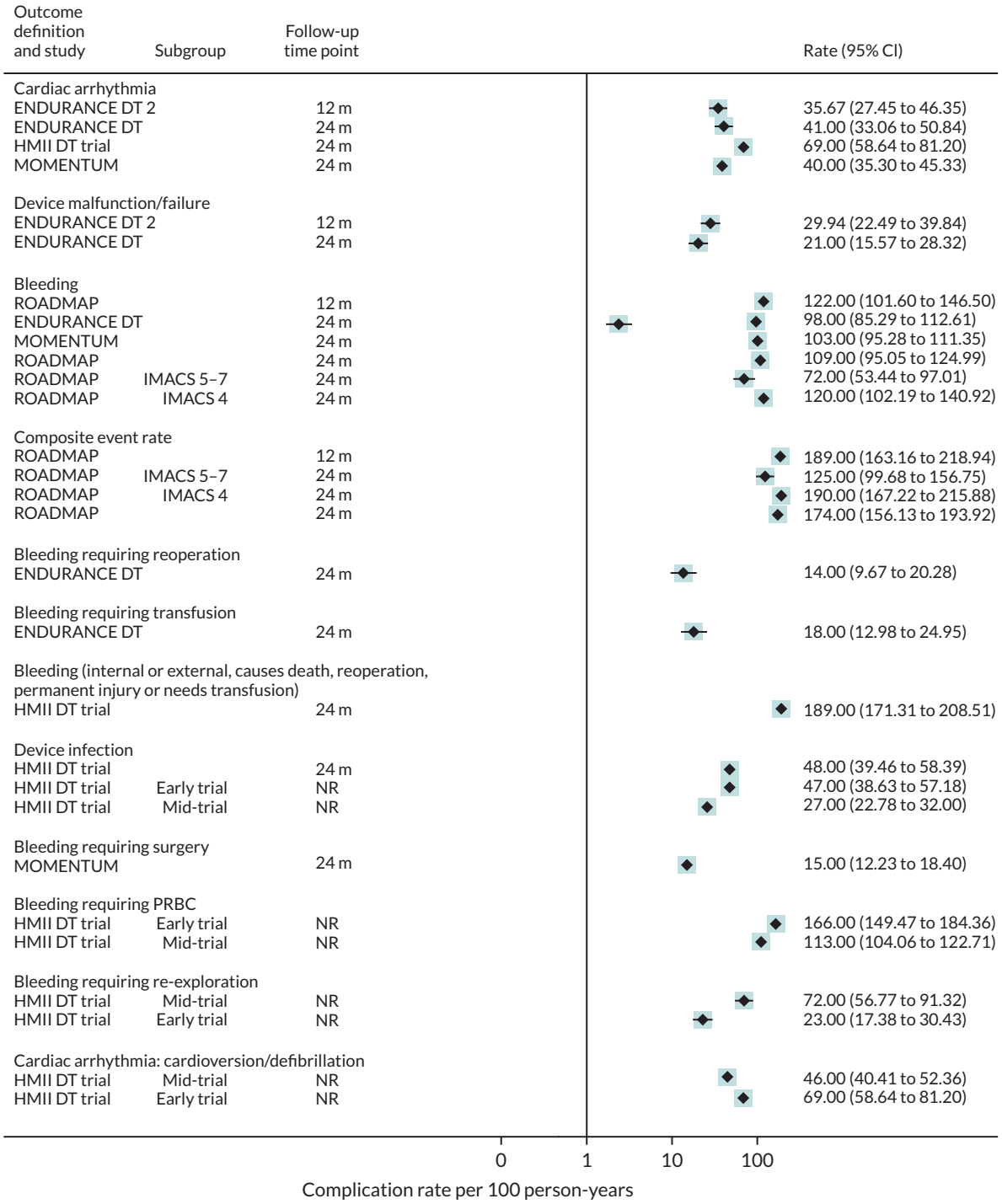

FIGURE 81 A, B and C complication rate per 100 person-years in the HeartMate II at all reported time points.

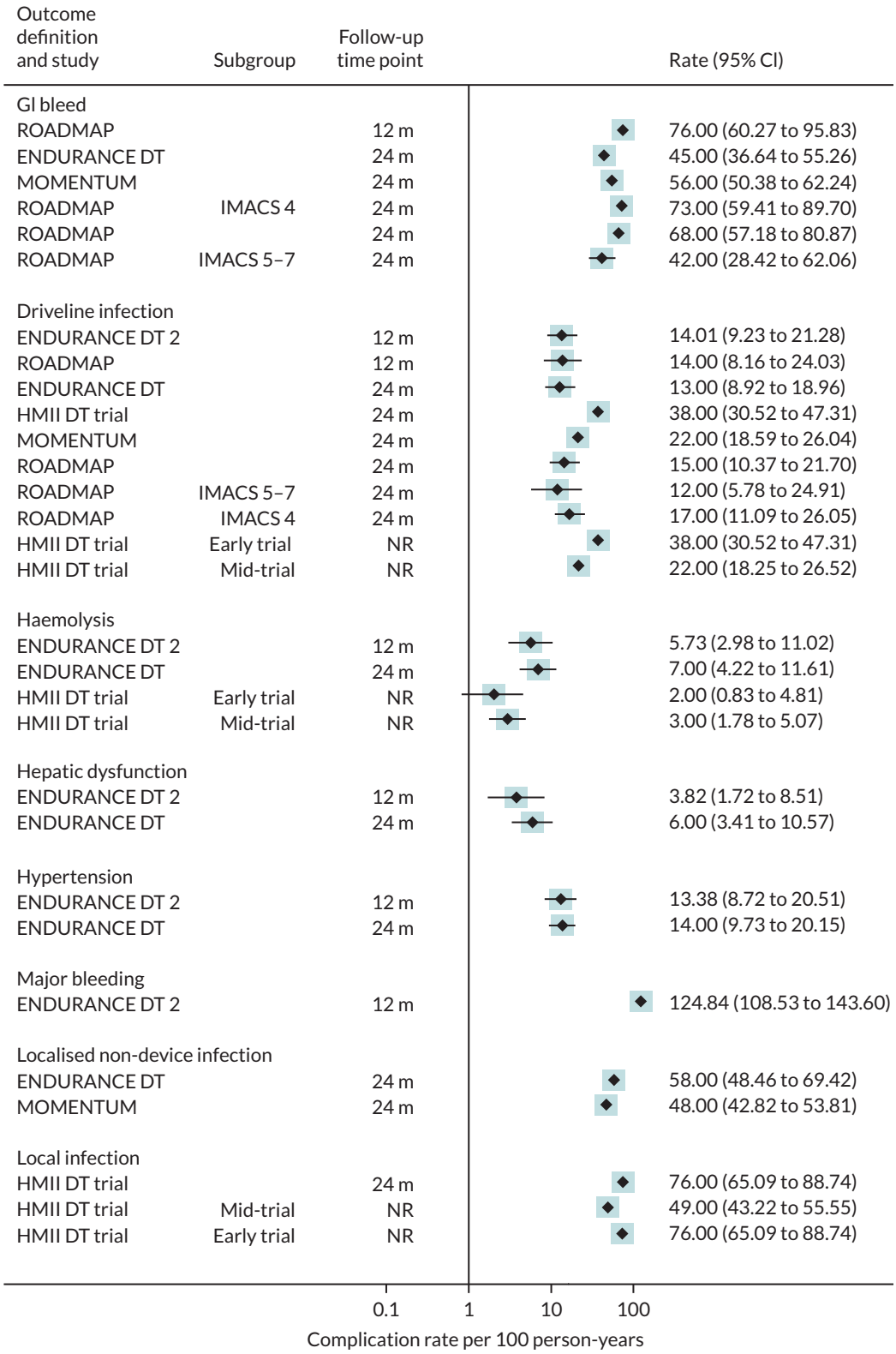

FIGURE 81 A, B and C complication rate per 100 person-years in the HeartMate II at all reported time points. (*continued*)

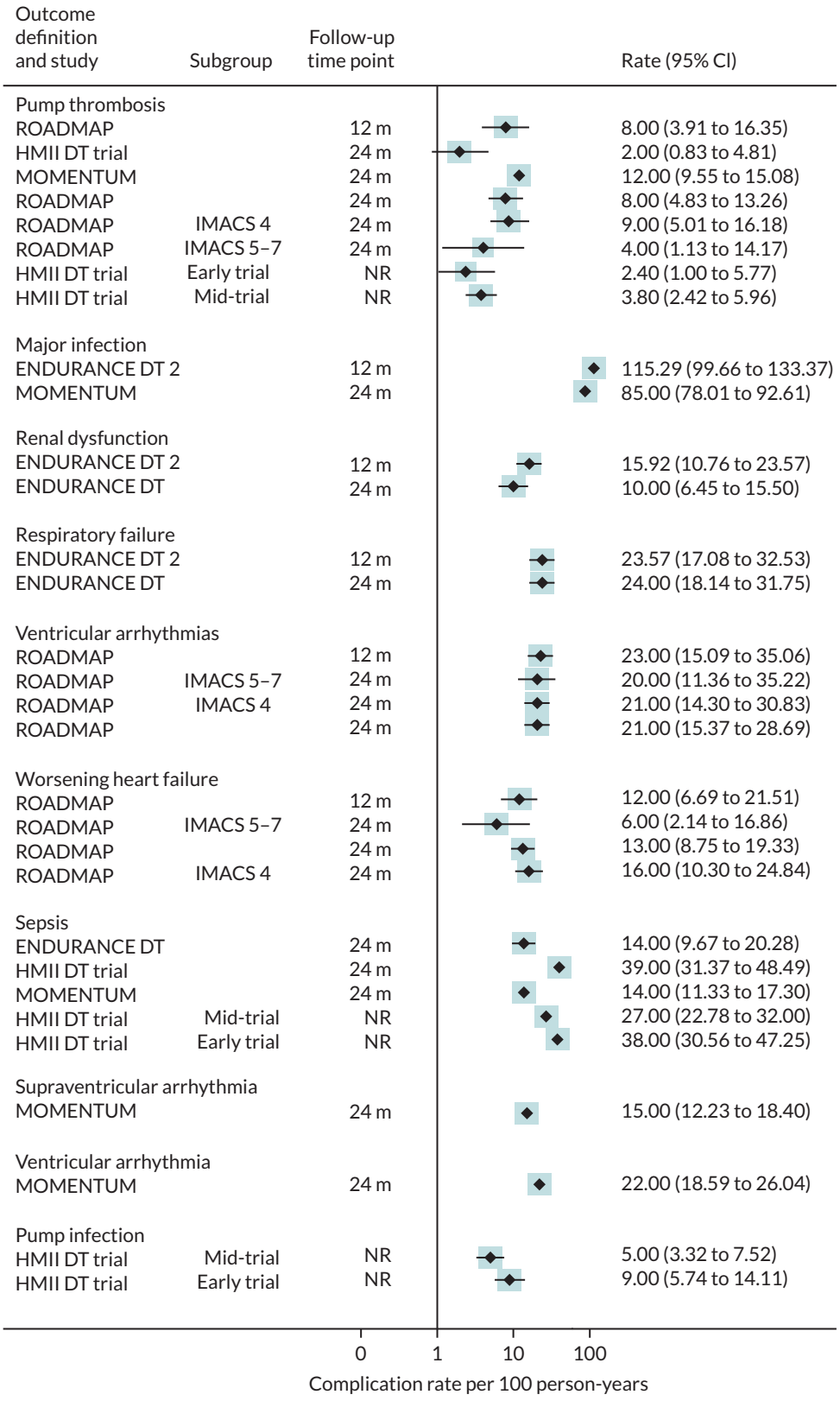

FIGURE 81 A, B and C complication rate per 100 person-years in the HeartMate II at all reported time points. (*continued*)

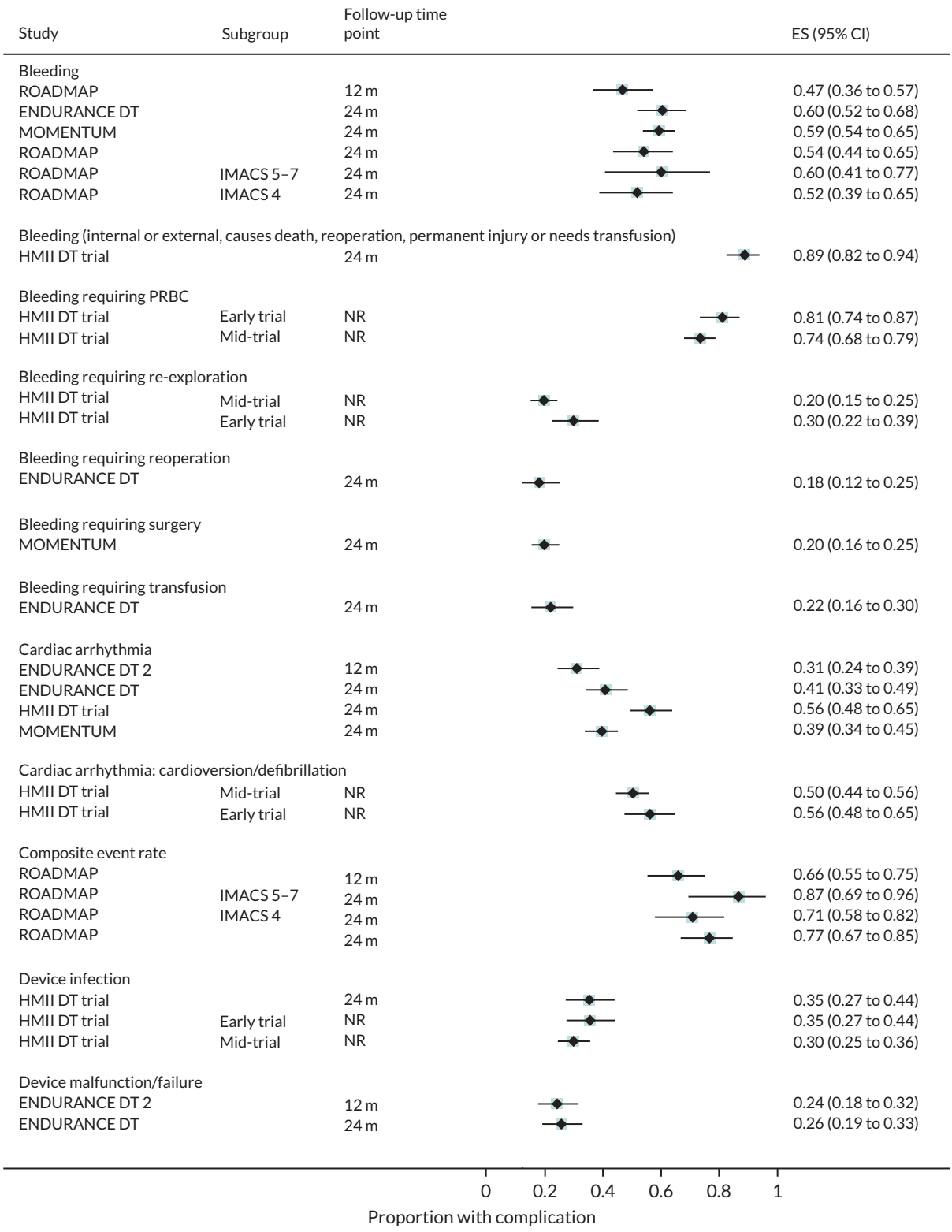

FIGURE 82 A, B and C proportion of people with complications in the HeartMate II at all reported time points.

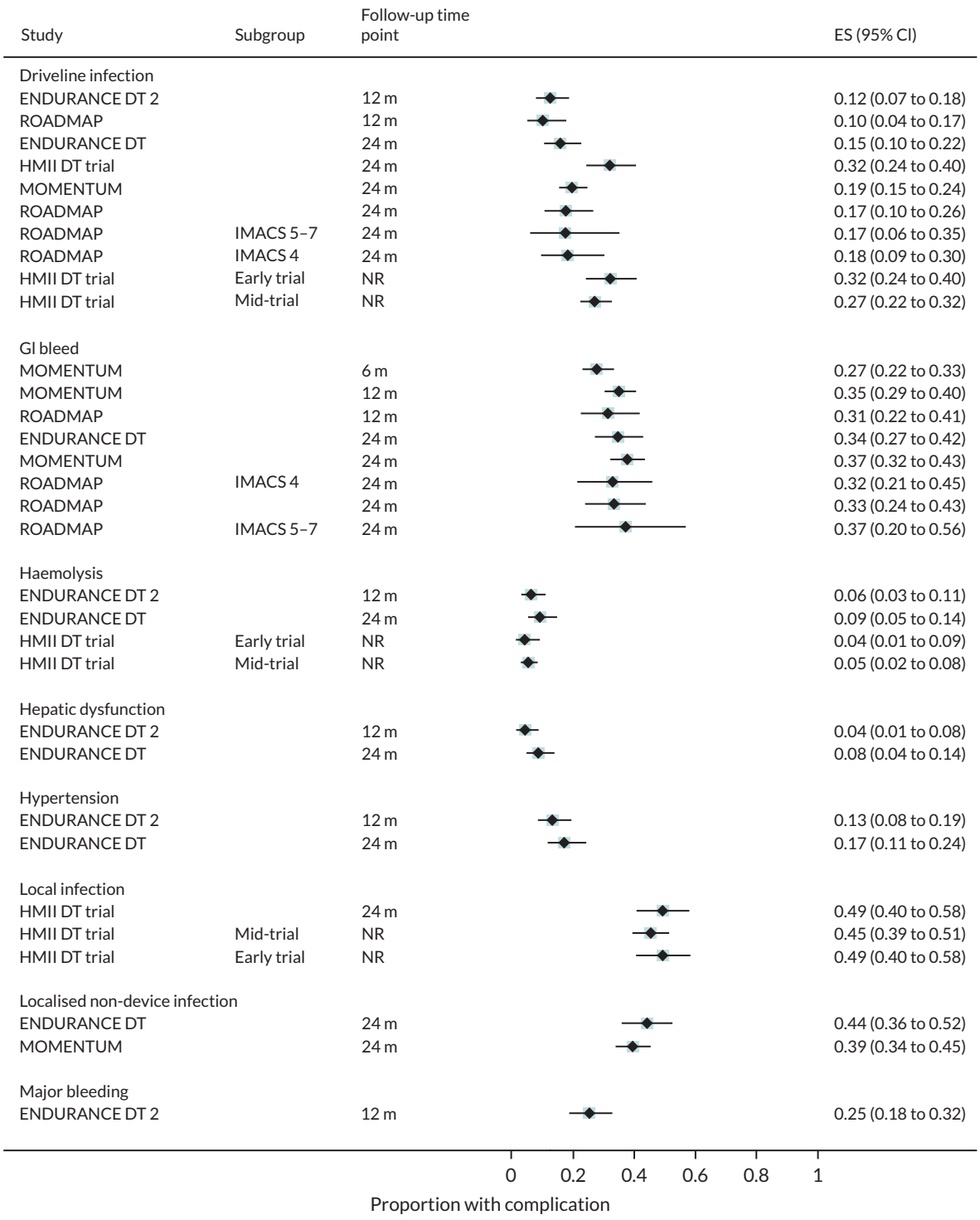

FIGURE 82 A, B and C proportion of people with complications in the HeartMate II at all reported time points. (*continued*)

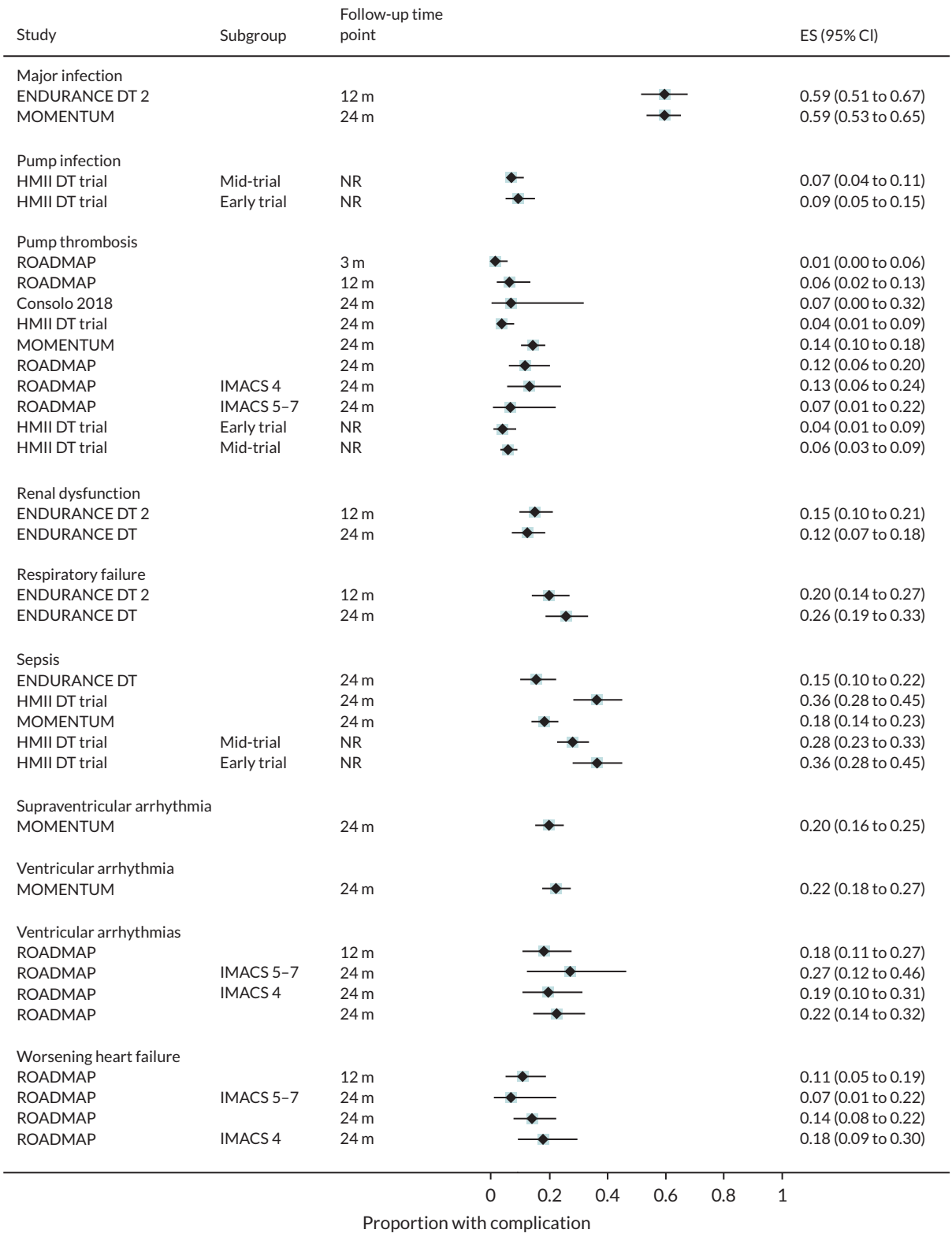

FIGURE 82 A, B and C proportion of people with complications in the HeartMate II at all reported time points. (*continued*)

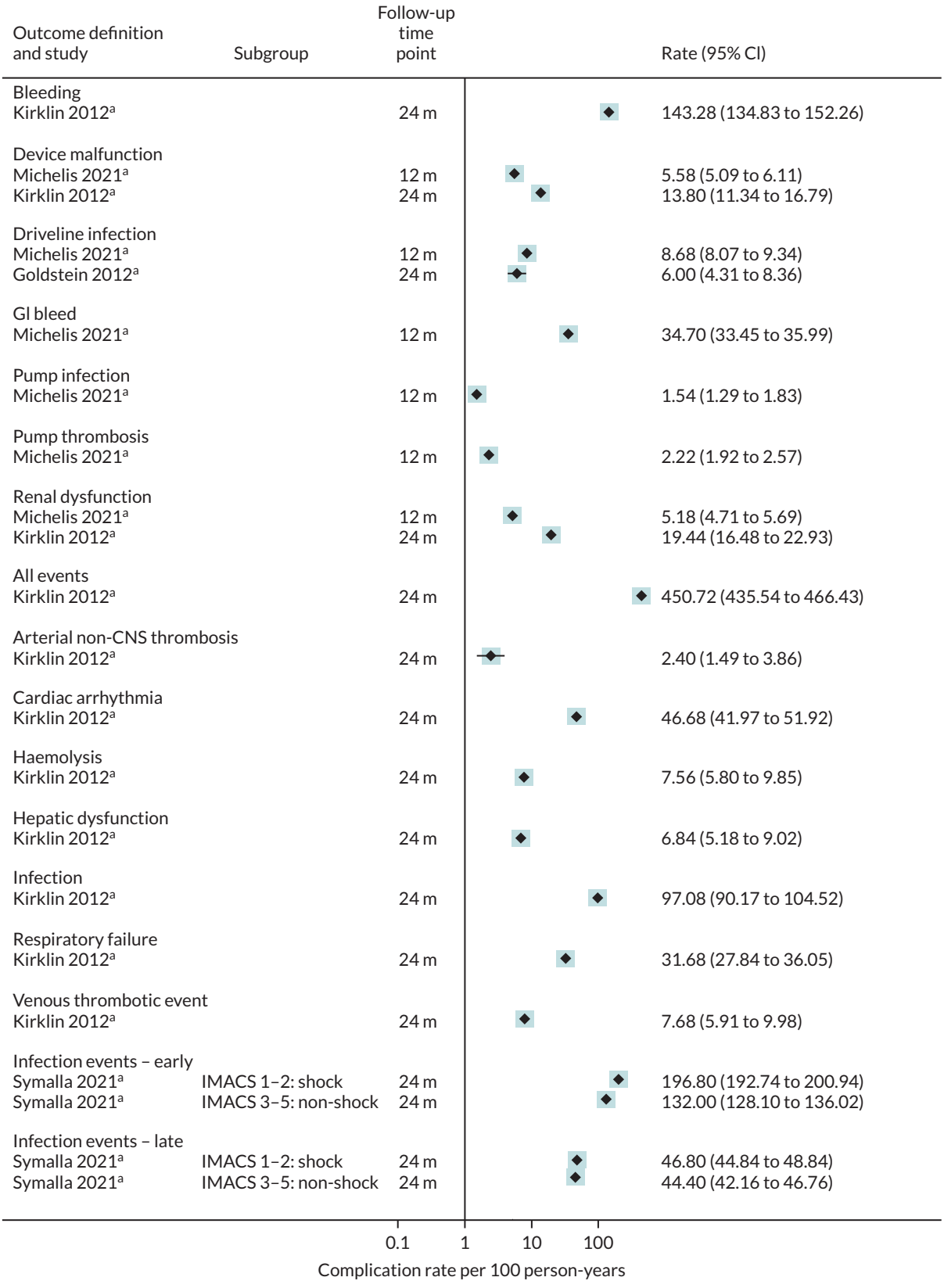

FIGURE 83 Complication rate per 100 person-years in studies with multiple devices at all reported time points. a, Data are from a registry report.

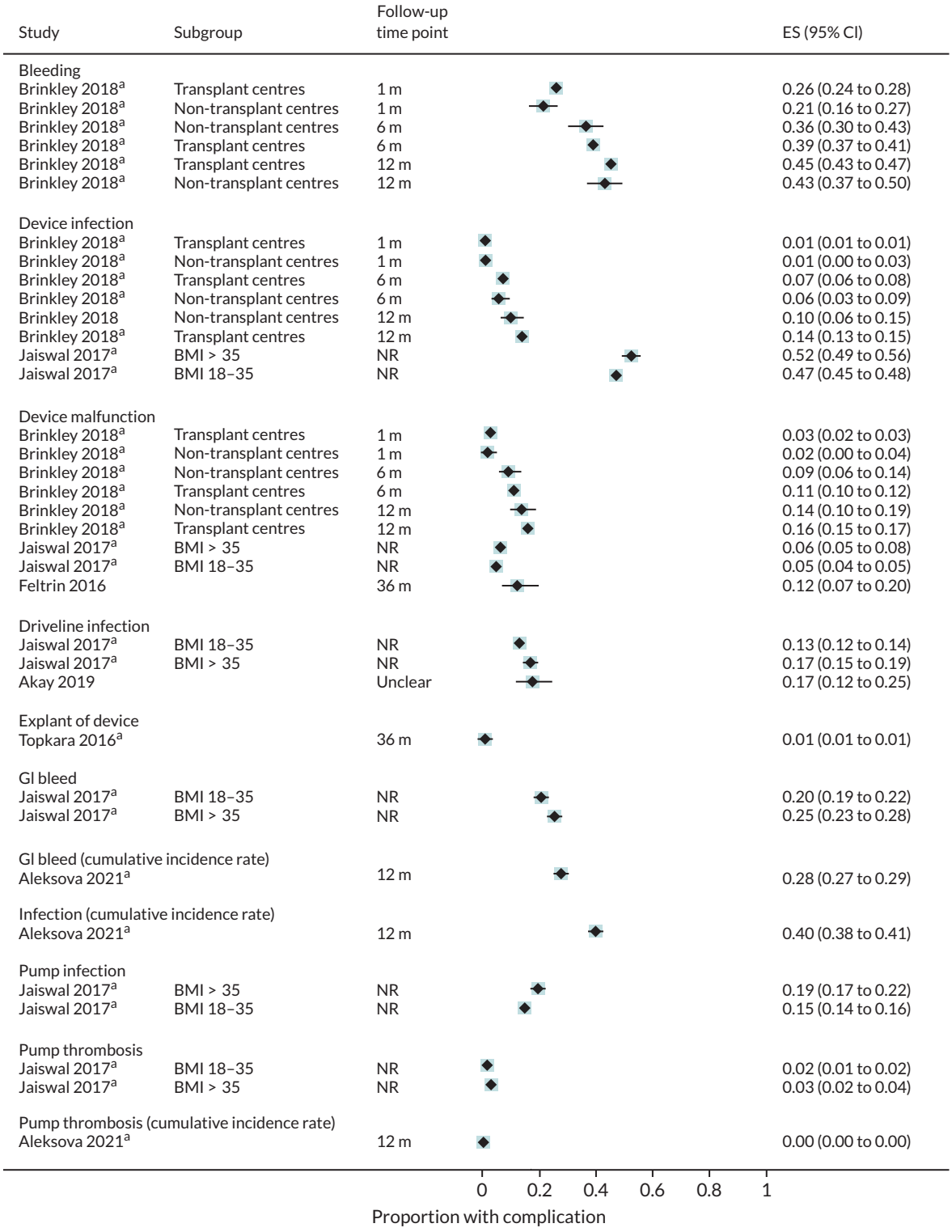

FIGURE 84 Proportion of people with complications in studies with multiple devices at all reported time points. a, Data are from a registry report.

Appendix 6 Observational studies overlapping with INTERMACS

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Adamo 2015	Barnes-Jewish Hospital in St Louis, Missouri	2005–13	269 (86)	1: 89 (33) 2: 146 (54) 3: 17 (6) 4 or more: 17 (6)	55.9 (12.1)	217 (81)	All HMII	Validation and derivation cohort of HMRS	Survival, validity of HMRS for predicting mortality, morbidity (stroke, thrombosis, GI bleed, etc.)	Survival
Aggarwal 2012	Advocate Christ Medical Centre, Illinois	2005–11	101 (94)	NR	GI bleed absent 61.17 (12.63) GI bleed present 64.96 (9.9)	81 (80)	All HMII	GI bleed present or absent	GI bleed, location of GI bleed, survival	All patients are DT so for all outcomes
Aggarwal 2013	Advocate Christ Medical Centre, Illinois	2005–11	79 (69)	NR	Aortic insufficiency 67.67 (8.45) No aortic insufficiency 58.46 (13.2)	67 (85)	All HMII	Aortic insufficiency present or absent	Survival, cause of death, hospitalisations predictors of aortic insufficiency	No. DT with aortic insufficiency
Anwer 2019	Mayo Clinic College of Medicine, Rochester	2007–15	278 (178 DT, 64)	INTERMACS 1–2 70 (39) overall	Median 62 (IQR 52.5–69) overall	226 (81)	HMII 223 (84) HVAD 28 (10) Jarvik 2000 9 (3) VentrAssist 6 (2) DuraHeart 2 (1)	Successful implant vs. 'failure'	Successful or failure implant, survival, re-admissions, adverse events	DT as predictor of failure, success rate in DT, survival
Asleh 2017	Mayo Clinic College of Medicine, Rochester	2007–16	341 (216)	Median 3 (IQR 2–4)	62 (IQR 52–68.9)	272 (80)	HMII 269 (78.8) HVAD 51 (15) HM3 4 (1.2) Jarvik 2000 9 (2.6) VentrAssist 6 (1.8) DuraHeart 2 (0.6)	Diabetes vs. non-diabetes	All-cause mortality, LVAD-related complications (stroke, pump thrombosis, DI/PI)	Mortality, device-related infection, composite non-fatal events, composite nonfatal and fatal events

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Assouline-Dayan 2018 (conference abstract)	University of Iowa	2010–15	104 (DT NR)	NR	Median 55.8 overall	80 (76.9)	NR	N/A	GI bleed, survival	GI bleed
Auvil 2019	Perelman School of Medicine, University of Pennsylvania, Philadelphia.	2008–18	221 (122 DT, 55)	NR	Median 57 overall	190 (85)	HMII and HVAD	No, mild and moderate aortic insufficiency	Mortality, RHF, functional exercise capacity	DT as a predictor of 2-year mortality, 6-minute walking distance and RHF
Bryce 2016 (conference abstract)	Unclear	2011–4	100 (69 DT 69)	NR	55.6 (12.29) overall	78 (78)	NR	N/A	Cognitive function, survival, rehospitalisation	Cognitive function
Bryce 2018 (conference abstract)	Unclear	2011–4	100 (69 DT 69)	NR	55.6 (12.29) overall	78 (78)	NR	N/A	Cognitive function, survival, rehospitalisation	Cognitive function
Cagliostro 2015	Columbia University Medical Centre	2009–13	266 (DT 89)	NR	Group A 58.71 (13.24) Group B 57.81 (13.78)	214 (80) overall	HMII 238 (89) HVAD 28 (11)	Implanted before June 1, 2011 (Group A) Implanted after that time point (Group B)	DI rates, freedom from infection, re-admissions	Number of DI events
Corral 2020	Mayo Clinic and National Inpatient Sample (hospitalisations)	2012–8	1344 (DT 407, 30.3) 55 LVAD patients from the general National inpatient sample	NR	DT patients 63.1 (0.7)	DT patients 320 (78.6)	NR	HF controls, DT, LVAD then heart transplant, heart transplant and inpatients from NIS	Acute pancreatitis, all-cause mortality	Incidence of acute pancreatitis
Corral 2020 (conference abstract)	Mayo Clinic	2012–8	1344 (407 DT)	NR	60.9 (14.3) overall	987 (73.4) overall	NR	LVAD DT, transplanted or LVAD BTT and controls with no therapy	Deaths, incidence of acute pancreatitis, predictors of acute pancreatitis	LVAD DT as predictor of acute pancreatitis

continued

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Coyle 2010	Advocate Christ Medical Centre, Illinois	2004–7	58 (all DT)	NR	Normal BMI 66 (11) Obese 55 (13)	Normal BMI 33 (87) Obese 14 (70)	HMII 36 (62) HeartMate XVE 22 (38)	Normal BMI vs. obese	In-hospital mortality, survival, postoperative complications	All patients are DT so for all outcomes
Critsinelis 2018	Texas Heart Institute/Baylor College of Medicine	2003–16	526 (243 DT, 46)	INTERMACS 1 75 (14) 2 173 (33) 3 200 (38) 4 55 (21) 5 14 (3) 6 2 (0.5) 7 7 (1.5)	NR for whole cohort	411 (78)	HMII 403 (77) HVAD 124 (23)	Normal, moderate or severe hypoal-buminemia	Survival, re-admission, neurological dysfunc-tion, GI bleed, RHF	DT as predictor of mortality
Daneshmand 2010	Duke University Medical Center	2000–8	60 DT LVAD 93 heart transplant	NR	DT median 60 (IQR 52–69)	DT 47 (78)	'Most' were HeartMate XVE	No- DT LVAD vs. extended criteria-alternate list heart transplant	Survival, post-op length of stay, post-op wound infections, driveline/PI, renal insufficiency	All outcomes
Daneshmand 2015	Duke University Medical Center	2005–12	146 DT LVAD 62 heart transplant	DT: not determined – 1 (0.1) 1–13 (9) 2–67 (46) 3–39 (27) 4–18 (12) 5–8 (6)	DT: median 67 (IQR 59–73)	DT: 108 (74)	All HMII	No. DT LVAD vs. extended criteria-alternate list heart transplant	Overall survival, eGFR, index hospitalisations length of stay and mortality, stroke, stroke-free survival, re-admission rate per year of support	All outcomes
Dunlay 2014	Mayo Clinic College of Medicine, Rochester	2007–12	99 (all DT)	Median 4 (IQR 3–5)	65.1 (9.4)	81 (81.8)	HMII 94 (95) HVAD 5 (5)	By frailty index	Mortality, cause of death, rehospitalisations	All patients are DT so for all outcomes
Dunlay 2016	Mayo Clinic College of Medicine, Rochester	2007–14	89 (all DT)	NR	64.5 (10.7)	71 (80.7)	HMII 84 (94.4) HVAD 3 (3.4) HeartMate XVE 2 (2.2)	N/A	Patients who died on LVADs Cause of death, clinical course before death	All patients are DT so for all outcomes

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Fukuhura 2016	Columbia University	2004–14	340 (89 DT, 26.2)	1–2 253 (74.4) 3–4 87 (25.6) overall	56.6 (13.9) overall	274 (80.6) overall	HeartMate II 281 (82.6) HeartWare 36 (10.6) Ventrassist 9 (2.6) DuraHeart 8 (2.4) DeBakey VAD 6 (1.8)	Those with aortic valve repair vs. those without	Survival, predictors of and freedom from aortic insufficiency, adverse events (bleeding, infection, device malfunction, pump thrombosis, RHF)	Freedom from aortic insufficiency
Grady 2018 (conference abstract)	13 USA sites	2015–8	71 DT	NR	67.6 (4.5)	NR	NR	N/A	HRQoL	HRQoL
Grady 2019 (conference abstract)	13 USA sites	2015–8	137 DT	NR	68.6 (5.1)	NR	NR	N/A	HRQoL	HRQoL
Grady 2020 (conference abstract)	13 USA sites	2015–8	154 DT	NR	68.6 (5.2)	NR	NR	N/A	HRQoL	HRQoL
Grady 2021	Multiple INTERMACS sites	2008–13	1620 (862 DT)	INTERMACS 1 69 (8), 2 293 (34), 3 302 (35), 4–7 198 (23)	≥ 50,750 (82)	707 (82)	NR	DT is long-term group ineligible for transplant, also analyse short-term and uncertain groups	HRQoL, factors associated with HRQoL	All outcomes
Grady 2021 (conference abstract)	13 USA sites	2015–8	154 DT	NR	68.6 (5.2)	NR	NR	N/A	HRQoL	HRQoL
Han 2016 (conference abstract)	Columbia University	2004–13	341 (85 DT, 25)	NR	56 (14) Overall	283 (83)	NR	N/A	Re-admissions and predictors of re-admissions	Rate of admission compared to BTT

continued

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Hernandez 2015	Texas Heart Institute	2008–12	148 (83 DT, 56.1)	INTERMACS 1 or 2 50 (60.2)	DT 54.2 (12.8)	DT 69 (83.1)	All HMII	DT vs. BTT	Hospital re-admissions (planned or unplanned), reasons for re-admissions, predictors of re-admissions, survival	Re-admissions, unplanned re-admissions compared to BTT
Jedeon 2019 (conference abstract)	University of Minnesota Heart Institute	2010–8	341 (153 DT, 45)	≤ 2 in 65.5 patients overall	58 (14) overall	278 (81.5)	NR	Early vs. late ventricular arrhythmias	Ventricular arrhythmias and association with mortality	Early ventricular arrhythmias in DT associated with mortality
Jedeon 2021	University of Minnesota Medical School	2010–8	344 (155 DT)	INTERMACS ≤ 2 100 (64.9)	64.4 (12.9)	125 (80.6)	HeartMate II 110 (71.9) HeartMate III 25 (16.3) HeartWare HVAD 18 (11.8)	DT/BTT, early ventricular arrythmia vs. no early ventricular arrythmia	Predictors of ventricular arrythmias, mortality	All outcomes
John 2016	University of Minnesota	2005–14	267 (DT 58, 21.1)	Mean score 3.8 (1.6) overall	57.2 (14.2) overall	214 (81.4) overall	All HMII	Compared by time period of implantation	Survival, serious complications (including GIB, pump thrombus, haemolysis, neurological dysfunction, DI)	Survival, DT as predictor of haemolysis, stroke, GIB, DI, PE
Katz 2015	27 open heart centers that contribute to INTERMACS	2009–12	276 (DT 176, 64)	DT: 1 17 (10), 2 52 (30), 3 72 (41), 4–7 35 (20)	DT ≤ 59 49 (28), 60–69 65 (37), ≥ 70 62 (35)	DT 145 (82)	All HMII	DT vs. BTT, INTERMACS score (survival only)	Survival, operative mortality, major adverse events, length of stay in hospital, rehospitalisations, physical status, QoL	Survival (and by INTERMACS score), adverse events, length of hospital stay, rehospitalisations, QoL

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Kilic 2018	University of Pittsburgh Medical Center	2006–15	238 (DT 142, 60%)	DT 1 7 (5), 2 52 (37), 3 41 (29), 4 19 (14), 5 1 (1)	DT normal glomerular filtration rate: 57 (16) Reduced glomerular filtration rate: 64 (1)	DT 118 (85)	HMII 187 (79) overall No details on other devices included	Normal glomerular filtration rate and reduced glomerular filtration rate	Survival, major postoperative complications (e.g. bleeding, stroke, sepsis, arrythmias, etc.), recovery of renal function	Survival, postoperative complications
Kyvernitakis 2019	Allegheny General Hospital, Pittsburg	2006–16	212 (DT 86, 41)	Overall 1 53 (25) 2 104 (49) 3 26 (12) 4 + 29 (14)	Median 60 (range 25–80) overall	170 (80)	HMII 170 (80), HVAD 42 (20) overall	N/A	Bloodstream infections, all-cause mortality	Bloodstream infections, DT as predictor of infection, survival
Lamba 2018 (conference abstract)	Baylor College of Medicine, Texas	1999–2017	615 (unclear but > 50 DT)	NR	54.1 (13.7) overall	485 (78.9)	HMII 493 HVAD 140 Jarvik 81 HM3 9 DuraHeart 2 From a wider cohort	By device	Survival, neurological deficit, acute kidney injury, GI bleed, infections, RVAD	Survival
Maltais 2016	University of Michigan, Mayo Clinic College of Medicine, and Vanderbilt Heart and Vascular Institute	2004–13	614 (250 DT)	LVAD alone mean INTERMACS score 2.9 (1.1) LVAD with concomitant procedure 2.7 (1) overall	LVAD alone 56 (12) LVAD with concomitant procedure 59 (13)	497 (81)	HeartMate II 492 (80) HeartWare 122 (20)	LVAD alone vs. LVAD with concomitant procedure at time of implant	Survival, time to first device-related event, complications (haemolysis, suspected or confirmed pump thrombus, right ventricular failure, stroke, and GIB)	DT as predictor of survival or adverse events vs. BTT
Maltais 2017	24 centres many included in INTERMACS for example Mayo clinic, Vanderbilt Medical, University of Colorado hospital	2014–015	300 (234 DT)	Profile 1 38 (13) 2 90 (30) 3 121 (40) 4–7 51 (17)	57 (13)	248 (83)	All HMII	N/A	Adverse events, rehospitalisations, pump thrombosis, survival	No. with pump thrombosis, survival

continued

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Mohamedali 2017	Advocate Christ Medical Centre	NR	212 (all DT)	INTERMACS 1 14 (7) 2 77 (36) 3 99 (47) ≥ 4 22 (10)	Mean arterial pressure CVP ≥ 7.5 63.2 (11) Mean arterial pressure CVP < 7.5 62.3 (11.6)	168 (79)	All HMII	Mean arterial pressure CVP ≥ 7.5 vs. mean arterial pressure CVP < 7.5	Post-LVAD RVF and major adverse outcomes, including death, HF hospitalisation, GIB, stroke/transient ischemic attack, intracranial haemorrhage, haemolysis, thrombosis, and infections, all-cause mortality	All patients are DT so for all outcomes
Morgan 2014	Henry Ford Hospital	2006–12	126 (52)	INTERMACS 1 8 (6) 2 55 (43) 3 30 (24) 4 26 (21) 5 6 (5) 6 1 (1%)	< 70 years 52.8 (11.4) ≥ 70 years 72.2 (2.3)	34 (27)	HMII 113 (90) HVAD 13 (10)	Age < 70 or ≥ 70	Perioperative mortality, postoperative Survival, overall hospital length of stay, postoperative complication rates for bleeding requiring re-exploration, infection, stroke, respiratory failure, renal failure, RV failure, GIB, AI, re-admission rates, and causes of death	Survival
Morgan 2016	Henry Ford Hospital	2006–15	231 (DT 113, 47.1)	NR	58.2 (11.4) DT	86 (76.1)	HMII 205 (89) HVAD 35 (11)	BTT vs. DT	Survival, complications (bleeding, drivelines infections, pneumonia, RHF, stroke, aortic insufficiency, pump thrombosis)	Survival, complications
Nakagawa 2018	Columbia University Medical Center	2010–6	89 (59 DT, 66)	NR	DT 64.3 (12.4)	DT 49 (83.1)	HMII 49 (83) HVAD 10 (17)	DT vs. BTT patients who died on LVAD	Indicators of good-quality palliative care, cause of death, time on LVAD, renal replacement therapy, LVAD deactivation	All outcomes

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Okoh 2018 (2 conference abstracts)	Beth Israel Hospital, Newark	NR	91 (all DT)	NR	Males 59 (9) Females 52 (6)	70 (77)	NR	By sex AF vs. normal sinus rhythm	In-hospital death, all-cause mortality, post-LVAD implant morbidity Survival, post-LVAD adverse events (e.g. infection, thrombosis, rehospitalisation), AF as predictor of events	All outcomes
Okoh 2019	Unclear	2008–17	91 (all DT)	NR	55 (3)	70 (77)	All HMII	≥ Moderate mitral regurgitation vs. < moderate mitral regurgitation	Mitral regurgitation, survival, hospitalisation, complications (including device malfunction, thrombosis, major infection, stroke)	All outcomes
Olmstead 2019	Baylor College of Medicine and Texas Heart Institute	2009–16	437 (236, 54)	Overall 1 60 (13.7) 2 140 (32.0) 3 174 (39.8) 4 40 (9.2) 5 14 (3.2) 6 2 (0.5) 7 7 (1.6)	55.6 (12.8) overall	342 (78.3) overall	HMII 314 (71.9) HVAD 123 (28.1)	Severe infection vs. no severe infection	Infection rates, survival	DT as a predictor of mortality
Schechter 2014	Duke University Medical Center	2003–12	342 (201 DT 58.8)	NR	Median 65 (IQR 53–71)	DT 148 (73.6)	HMII and HeartMate XVE	Primary LVAD implant vs. replacement procedures	Survival, adverse events (renal failure, right ventricular function), length of hospital stay, stroke, DI	Survival
Schultz 2018 (conference abstract)	University of Minnesota	NR	366 (146 DT, 40)	NR	NR	NR	NR	By indication, DT vs. BTT	Cause of death, survival	Survival, cause of death

continued

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Sharma 2012	Mayo Clinic College of Medicine, Rochester	2007–11	143 (all DT)	NR	61.3 (12.2)	123 (86)	All HMII	DI vs. no DI	No. with drivelines infection, no. with associated pocket infection, microbiological profile, postoperative morbidities	All patients are DT so for all outcomes
Singh 2015	Cleveland Clinic	2000–12	391 (DT 110, 28.1)	NR	53.9 (14.2) overall	317 (81.1)	HeartMate XVE 132 (33.8) HMII 236 (60.4) *Also included total artificial heart, which is not relevant to this review*	GI bleed vs. no GI bleed	GI bleed and causes	No. of DT patients with GI bleed
Slivnick 2020 (conference abstract)	13 US sites	2015–8	109 DT	NR	NR	NR	NR	N/A	HRQoL	HRQoL
Snipelisky 2015	Mayo Clinic College of Medicine, Rochester	2007–13	136 (all DT)	Median 3 (IQR 2–4)	63.6 (11.8)	113 (83.1)	NR	N/A	Mortality, hospital re-admissions Associations between psychosocial factors characteristics and all-cause re-admissions and death	All patients are DT so for all outcomes
Steinberg 2020	Emory University Hospital	2012–6	569 (DT 81, 14.2)	NR	51.7 (12.7) overall	178 (31.3) overall	NR	Male vs. female	Eligibility for heart transplant or DT LVAD, Stanford Integrated Psychosocial Assessment for Transplant scores, survival	Stanford Integrated Psychosocial Assessment for Transplant scores, survival

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Stulak 2015	Mayo Clinic College of Medicine, Rochester	2004–13	493 (192 DT)	NR	Median age overall 60 (range 18–79)	395 (80)	NR	Causes of death by follow-up interval and indication	Cause of death	Cause of death
Stulak 2017	University of Michigan Health System, Mayo Clinic College of Medicine, and Vanderbilt Heart	2004–14	560 (264 DT)	INTERMACS 1–3 387 (69)	Median age overall 59 (range 18–82)	465 (83)	HMII	Percutaneous driveline fracture vs. those without	Repair of driveline fracture, survival	No. with percutaneous driveline fracture
Suarez 2020	Mayo Clinic College of Medicine, Rochester	2007–17	203 (122 DT)	NR	63 DT	166 DT (82)	NR	By indication	Association of depressive symptoms (PHQ-9) with outcomes including mortality, rehospitalisation, major bleeding, neurological events	Severity of depressive symptoms
Takeda 2015	Columbia Presbyterian Medical Center	2004–13	293 (DT 78, 27)	NR	No RHF overall 56.6 (13.9) RHF overall 57.4 (13.3)	243 (83%) Overall	HMII 252 (86), VentrAssist 6 (2) DuraHeart 7 (2) DeBakey 4 (1) HVAD 24 (8)	RHF vs. no RHF	Incidence and significance of late RHF, freedom from RHF, requirement of RVAD, survival, major adverse events requiring hospitalisation (e.g. bleeding, device-related events, cerebral events, infections)	Incidence of RHF, survival by RHF or no RHF
Tsiouris 2015a	Henry Ford Hospital	2006–14	200 (DT 102, 51)	NR	58.4 (10.7) DT	78 (76.5)	HMII 179 (89.5) HVAD 21 (10.5)	BTT vs. DT	Complications (bleeding, stroke, RHF, renal failure, pneumonia, pump thrombosis), no. transplanted, survival, cause of death	Complications, survival

continued

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Tsiouris 2015b	Henry Ford Hospital	2006–13	149 (DT 68, 45.6)	NR	57.6 ± 10.4 DT	47 (71)	HMII 136 (91) HVAD 13 (9)	BTT vs. DT	Survival, complications (bleeding, DI, pneumonia, RHF respiratory failure, renal failure stroke aortic insufficiency, pump thrombosis)	Survival, complications
Uppalapati 2019 (conference abstract)	13 US sites	2015–8	137 DT	NR	68.6 (5.1)	NR	NR	Stratify results by age and gender	HRQoL	HRQoL
Vaddiparti 2018 (conference abstract)	Hartford Hospital	2012–6	78 (51 DT, 65)	NR	Median 65 overall	66 (84)	HMII 63 (81) HVAD 15 (19)	N/A	Stroke incidence, predictors of stroke, time to stroke, mortality from stroke	Incidence of stroke
Verdoorn 2017	Mayo Clinic College of Medicine, Rochester	2009–13	107 (all DT)	NR	64.3 (10.7)	90 (84)	HMII 102 (95) *other devices not reported*	N/A	Number of deaths	Number of deaths
Vidula 2018 (conference abstract)	University of Rochester	2008–16	197 (65 DT, 33)	INTERMACS profile 1 or 2 (59) overall	56 (12) overall	160 (81)	All HMII	N/A	Late RHF, predictors of late RHF	DT as risk factor for late RHF
Vorovich 2019 (conference abstract)	13 US sites	2015–8	155 DT	NR	NR	NR	NR	N/A	Neurocognitive outcomes	Neurocognitive outcomes
Welden 2018	University of Alabama	2009–13	102 (DT 50, 49.02)	NR	53.6 overall	83 (81.37) overall	HMII 76 (74.5) HVAD 25 (24.5)	Patients with GI bleeds vs. those without GI bleeds	GI bleeds, re-admissions for bleeding	Re-admission for bleeding compared to BTT
Willey 2016	Columbia University Medical Centre	2008–15	301 (DT 101 33.6)	NR	Stroke 54.7 (14.1) No stroke 58 (13.7)	238 (79) overall	HMII 266 (88) HVAD 35 (12)	Those with and without stroke	Mortality, number of strokes, transplantation, cause of death	Number of patients with stroke, number transplanted

TABLE 31 Study characteristics of observational studies with patients that overlap with Interagency Registry for Mechanically Assisted Circulatory Support (*continued*)

Study ID	Centre	Implant years	Total no. patients (No. DT)	INTERMACS profiles (*n*, %)	Mean age (SD)	Male (*n*, %)	Device types (*n*, %)	Subgroups analysed	Outcomes reported	DT data reported
Yalcin 2020	University Medical Centre Rotterdam, the Netherlands Johns Hopkins Hospital, Baltimore, USA; and the Medical University Hospital, Charleston, South Carolina	2004–17	400 (DT 154, 39)	1 67 (17) 2 120 (30) 3 135 (34) ≥ 4 62 (16) Overall (only 384 had available score)	53 (14)	298 (75)	HMII 339 (92) HM3 22 (6) HVAD 48 (12)	By severity of chronic kidney disease	Chronic kidney disease, kidney function, survival	No. DT with chronic kidney disease
Yost 2021	Advocate Christ Medical Centre/ University of Michigan Hospitals	2005–16	677 (DT 602, 89)	NR	Primary LVAD Implantation 59.07 (12.99) All pts with LVAD exchange 58.52 (13.12)	513 (76)	HMII 527 (78) HVAD 142 (22)	Patients with LVAD exchange, patients exchanged with infection and without infection	Postoperative length of stay, in-hospital mortality, and 30- and 365-day mortality	No. DT patients exchanged and with/without infections

AI, aortic insufficiency; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; HMRS, HeartMate Risk Score; HRQoL, health-related quality of life; IQR, interquartile range; NIS, National Inpatient Sample; NR, not reported; N/A, not applicable; RHF, right heart failure; RV, right ventricular; VAD, ventricular assist device.

Appendix 7 Risk-of-bias assessment for cost-effectiveness review

TABLE 32 Risk of bias of cost-analysis and cost-effectiveness studies

		Cost-analysis and cost-effectiveness studies									
	CHEC criteria	CETS 2000	Clegg 2007	Droogne 2014	Girling 2007	Messori 2009	Chimanji 2016	Mehra 2018	Oz 2003	Slaughter 2011	Health Qual. On. 2016
1	Is the study population clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Are competing alternatives clearly described?	Y	Y	Y	Y	N	Y	Y	N/A	Y	Y
3	Is a well-defined research question posed in answerable form?	N	P	Y	P	N	Y	Y	Y	Y	Y
4	Is the economic study design appropriate to the stated objective?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Y	N	N	N	Y	N	N	N	N	N
6	Is the actual perspective chosen appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Are all important and relevant costs for each alternative identified?	N	N	N	N	N	Y	Y	Y	Y	N
8	Are all costs measured appropriately in physical units?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Are costs valued appropriately?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10	Are all important and relevant outcomes for each alternative identified?	N	N	N	N	N	Y	Y	N/A	Y	Y
11	Are all outcomes measured appropriately?	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y
12	Are outcomes valued appropriately?	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Y	Y	Y	Y	Y	N	Y	N/A	N	N
14	Are all future costs and outcomes discounted appropriately?	Y	N/A	N/A	N/A	Y	N/A	N/A	N/A	N/A	N
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	N	Y	N	N	Y	N	N	N	Y	N
16	Do the conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

TABLE 32 Risk of bias of cost-analysis and cost-effectiveness studies (*continued*)

		Cost-analysis and cost-effectiveness studies									
	CHEC criteria	**CETS 2000**	**Clegg 2007**	**Droogne 2014**	**Girling 2007**	**Messori 2009**	**Chimanji 2016**	**Mehra 2018**	**Oz 2003**	**Slaughter 2011**	**Health Qual. On. 2016**
17	Does the study discuss the generalisability of the results to other settings and patient groups?	N	N	N	N	P	N	N	N	N	N
18	Does the article indicate that there is no potential conflict of interest of study researchers and funders?	N	N	N	N	N	Y	N	N	N	N
19	Are ethical and distributional issues discussed appropriately?	N	N	N	N	N	N	N	N	N	N
	Overall score	12	9	11	11	12	13	13	8	13	11

N, no; N/A, not applicable; P, partly; Y, yes.

TABLE 33 Risk of bias of modelling studies

		Modelling studies								
	Philips criteria (for modelling studies)	Baras 2017	Chew 2017	Long 2014	Neyt 2013	Rogers 2012	Silvestry 2019	Adang 2006	Schueler 2021	Lim 2021
S1	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the primary decision-maker specified?	N	N	N	Y	N	N	N	Y	Y
	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y	N	Y	Y
S2	Are the model inputs consistent with the stated perspective?	N	Y	Y	Y	Y	Y	Can't tell	Y	Y
	Has the scope of the model been stated and justified? (I.e. have any choices or assumptions been explained sufficiently, in the context of available evidence?)	N	N	N	N	N	N	N	N	N
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	N	Y	Y	Y	Y	Y	Can't tell	Y	Y
S3	Has the evidence regarding the model structure been described?	N	N	N	N	N	N	Y	Y	Y
	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are the sources of data used to develop the structure of the model specified?	N	N	N	N	N	N	N	Y	Y
	Are the causal relationships described by the model structure justified appropriately?	N	N	N	N	N	N	N	N	N
S4	Are the structural assumptions transparent and justified?	N	N	N	N	N	N	N	Y	Y
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	N	N	N	N	N	N	N	Y	Y
S5	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Have all feasible and practical options been evaluated?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is there justification for the exclusion of feasible options?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
S6	Is the chosen model type appropriate, given the decision problem and specified causal relationships within the model?	Y	Y	Y	Y	Y	Y	Y	Y	Y

TABLE 33 Risk of bias of modelling studies (*continued*)

	Philips criteria (for modelling studies)	Modelling studies								
		Baras 2017	Chew 2017	Long 2014	Neyt 2013	Rogers 2012	Silvestry 2019	Adang 2006	Schueler 2021	Lim 2021
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	Y	Y	Y	Y	Y	Y	N	Y	Y
	Is the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	Y	Y	Y	Y	Y	Y	N	N/A	Y
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	N	N	N	N	N	N	N	Y	Y
S9	Is the cycle length defined and justified in terms of the natural history of the disease?	N	N	Y	Y	Y	Y	N	Y	N
D1	Are the data identification methods transparent and appropriate, given the objectives of the model?	N	N	N	N	N	N	N	Y	Y
	Where choices were made between data sources, are these justified appropriately?	N	N	N	N	N	N	N	N	N
	Was particular attention paid to identifying data for the important parameters in the model?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	N	N	N	N	N	N	N	N	N
	Has the quality of the data been assessed appropriately?	N	N	N	N	N	N	N	N	N
	Where expert opinion was used, are the methods described and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
D2	Is the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?	Y	Can't tell	Y	Can't tell	Y	Y	Can't tell	Y	Y
	Is the choice of baseline data described and justified?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are transition probabilities calculated appropriately?	Y	Can't tell	Y	Can't tell	Y	Y	Can't tell	Can't tell	Y
	Has a half-cycle correction been applied to both cost and outcome? If not, has this omission been justified?	N	N	N	Y	N	N	N	N	N

continued

TABLE 33 Risk of bias of modelling studies (*continued*)

		Modelling studies								
	Philips criteria (for modelling studies)	**Baras 2017**	**Chew 2017**	**Long 2014**	**Neyt 2013**	**Rogers 2012**	**Silvestry 2019**	**Adang 2006**	**Schueler 2021**	**Lim 2021**
	If relative treatment effects were derived from trial data, have they been synthesised using appropriate techniques?	Y	Y	Y	Y	Y	Y	N/A	Y	Y
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Y	Y	Y	Y	Y	Y	N/A	Y	Y
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	N	N	N	N	Y	N	N/A	N	N
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Are the utilities incorporated into the model appropriate?	N	N	N	N	N	Y	Y	Y	Y
	Is the source for the utility weights referenced?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are the methods of derivation for the utility weights justified?	N	Y	Y	Y	Y	Y	Y	Y	Y
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	Y	N	N	N	Y	Y	Y	Y	Y
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Is the process of data incorporation transparent?	Y	N	Y	N	Y	Y	N	Y	Y
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	N	N	N/A	N	N/A	N	Y	N/A	N
	If data have been incorporated as distributions, is it clear that second-order uncertainty is reflected?	Y	Y	N/A	Y	N/A	Y	N	N/A	N
D4	Have the four principal types of uncertainty been addressed? If not, has the omission of particular forms of uncertainty been justified?	N	N	N	N	N	N	N	N	N
	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Y	Y	Y	Y	Y	Y	N	N	N

TABLE 33 Risk of bias of modelling studies (*continued*)

		Modelling studies								
	Philips criteria (for modelling studies)	**Baras 2017**	**Chew 2017**	**Long 2014**	**Neyt 2013**	**Rogers 2012**	**Silvestry 2019**	**Adang 2006**	**Schueler 2021**	**Lim 2021**
	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	N	N	N	N	N	N	N
	Has heterogeneity been dealt with by running the model separately for different subgroups?	Y	N	N	N	N	N	N	N	Y
	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	N	N	N	N	N	N	N	N	N
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	N	N	N	N	N	N	N	N	N
C2	Are the conclusions valid given the data presented?	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are any counterintuitive results from the model explained and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	If the model has been calibrated against independent data, have any differences been explained and justified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Have the results of the model been compared with those of previous models and any differences in results explained?	Y	Y	Y	Y	Y	Y	Y	Y	Y

Appendix 8 Supplemental data used to inform the economic evaluation

TABLE 34 Monthly mortality probabilities in four different estimates

Monthly mortality risks	Non-comparative, net weight estimates	Non-comparative, weighted estimates for MM	Comparative estimates mapped to MM in REMATCH	Comparative estimates mapped to LVAD in MOMENTUM
DT (LVAD) mortality risk	**Mean**	**Mean**	**Mean**	**Mean**
1–3 months	0.021	0.021	0.021	0.021
4–6 months	0.021	0.021	0.021	0.021
7–12 months	0.008	0.008	0.008	0.021
13+ months	0.007	0.007	0.007	0.021
RR of mortality in LVAD compared to MM	N/A	N/A	0.247	0.247
MM mortality risk	**Mean**	**Mean**	**Mean**	**Mean**
1st month	0.085	0.0770	0.084	0.085
2–6 months	0.085	0.0770	0.084	0.085
7–12 months	0.085	0.0789	0.031	0.085
13+ months	0.085	0.0793	0.029	0.085

TABLE 35 Monthly probabilities and health utilities in the base-case analyses

Parameters	Mean/month	SE	Trial/database
Mortality			
Mortality risk in LVAD in the non-comparative, net weight estimates (*Mehra 2021*)[126]			
1–6 months	0.021	0.0009	MOMENTUM
7–12 months	0.008	0.0002	
13–24 months	0.007	0.0004	
25+ months	0.007	0.0004	
Mortality risk in LVAD in the comparative estimates mapped to MM in REMATCH (*Mehra 2021*)	Same as above		MOMENTUM
Mortality risk in MM in the non-comparative, net weight estimates (*Rose 2001*)	0.085	0.0085	REMATCH
RR of mortality used in the comparative estimates mapped to MM in REMATCH	0.247	0.0861	Our estimate (see *Chapter 3*)
Mortality risk in MM in the comparative estimates mapped to MM in REMATCH	0.084	0.0084	Our estimate
	0.084	0.0084	
	0.031	0.0031	
	0.029	0.0029	

continued

TABLE 35 Monthly probabilities and health utilities in the base-case analyses (*continued*)

Parameters	Mean/month	SE	Trial/database
Morbidity			
First stroke in LVAD patients *(Kirklin 2020)*			
1–3 months	0.017	0.0059	INTERMACS
4+ months	0.003	0.0022	
Probability of a second stroke after a non-disabling stroke *(Kirklin 2020)*	0.002	0.0016	Same as above
Proportion of disabling stroke in patients experiencing stroke *(Milano 2018)*	0.28	0.028	ENDURANCE DT
RHF in LVAD patients			
1 month *(Teuteberg 2020)* – early RHF	0.140	0.0067	INTERMACS 9th
2+ months *(Teuteberg 2020)* – hospitalisation due to late RHF	0.002	0.0010	
Proportion requiring RVAD placement in patients with LVAD *(Rogers 2017)*	0.125	0.0523	ENDURANCE DT
Severe AR in LVAD patients *(Jorde 2014)*	0.004	0.0048	Columbia Uni Med. Centre
Proportion of AR patients requiring operation for valve replacement *(Jorde 2014)*	0.33	0.0355	Same as above
Stroke in MM patients *(Homma 2012)*	0.001	0.0007	WARCEF trial
GIB in LVAD patients – *12-month follow-up*			
1–3 months (includes surgical bleeding)	0.032	0.0043	(Meta-analysis)
4+ months	0.010	0.0003	
DI in LVAD patients	0.011	0.0001	(Meta-analysis)
PI in LVAD patients *(Tattevin 2014)*			
1st month	0.008	0.0035	ASSIST-ICD 19 centres
2+ months	0.003	0.0021	
PE in LVAD patients (any reason) *(Kirklin 2017)* – *device malfunctions over 72 months*	0.002	0.0003	INTERMACS
Arrhythmia in LVAD patients – *12-month follow-up*	0.018	0.0015	(Meta-analysis)
Probability of re-admission apart from stroke in MM patients *(Ambardekar 2019)*	0.068	0.0356	MEDAMACS
Mortality within 30 days of major events			
Death due to stroke in LVAD patients *(Milano 2018)* – *12-month follow-up*	0.25	0.0475	ENDURANCE
Death due to stroke in MM patients[a] *(Freeman 2011)*	0.085	0.013	N/A
Death due to early RHF[b]	0.021	0.0012	Expert view
Death due to AR[b]	0.021	0.0012	Expert view
Long-term mortality in patients with major events (monthly)			
Mortality risk in disabling stroke survivors *(Kirklin 2020)*	0.024	0.0119	INTERMACS
Mortality risk in AR survivors *(Truby 2018)*	0.021	0.0112	INTERMACS
Mortality risk in RHF survivors	0.085	0.013	Expert view

TABLE 35 Monthly probabilities and health utilities in the base-case analyses (*continued*)

Parameters	Mean/month	SE	Trial/database
QoL (health utility)			
Utility in DT (LVAD)			
1 month	0.51	0.014	(Meta-analysis)
2–6 months	0.76	0.011	
7–12 months	0.77	0.010	
13+ months	0.77	0.014	
Utility in MM	0.51	0.014	(Meta-analysis)
Utility loss after stroke *(Post piet 2001, Chaisinanunkul 2015)*	0.11	0.0255	N/A
Utility loss after disabling stroke *(Post piet 2001, Chaisinanunkul 2015)*	0.67	0.067	Same as above
Utility in patients experiencing RHF[c]	0.405	0.0120	Expert view
Utility in patients experiencing AR[b]	0.405	0.0120	Expert view
Utility loss after GIB *(Silvestry 2019)*	0.048	0.0048	Expert view and previous model
Utility loss after DI and PI *(Long 2014)*	0.156	0.0156	Expert view and previous model
Utility loss after PE *(Silvestry 2019)*	0.24	0.024	Expert view and previous model
Utility loss after arrythmia			
Utility loss after AF *(Witassek 2019)*	0.012	0.001	MOMENTUM
Utility loss after VF *(Mark 2008)* (0.58 of all arrythmia cases were assumed to be VF) *(Mehra 2019)*	0.063	0.006	

SE, standard error.
a It was 0.082 in the study but assumed to be 0.085 so that it is not lower than the overall mortality in MM patients.
b Based on expert view, it was assumed that AR patients would have the same QoL as MM patients and for model simplicity it was assumed that valve replacement wouldn't make any impact on QoL.
c Based on expert view, it was assumed that RHF patients would have the same QoL as MM patients.

Note
In the PSA, beta distribution was used for all the probabilities and health utilities. Random sampling method was used to generate the parameters in the PSA unless the parameter was time-dependent in which case the difference method was used.

TABLE 36 Cost inputs in the base-case analyses

One-off cost items	Currency codes	Cost (2019)	SE
Complex LVAD implant cost (applied for 10% of the LVAD patients)	ED08Z	£130,914	£13,091
Standard LVAD implant (applied for 90% of the LVAD patients)	ED09Z	£90,484	£9048
Average LVAD implant cost	ED08Z/9Z	£94,527	£9453
Complex heart transplantation	ED04Z	£61,070	£6011
Stroke	AA35A-F	£3417	£341
RHF	EB03A-E	£1972	£197
Aortic valve replacement for AR	ED24A-ED25C	£12,928	£1292
GIB	FD03A-H	£1235	£124
DI and PI	HE81A-C	£3478	£348
PE for any reason (assumed to be same as average LVAD implantation)	ED08Z	£94,527	£9453
RVAD placement (operation cost assumed to be same as DI)	N/A	£13,740	£1374
Arrhythmia	EB07A-E	£952	£95
Death[36]	N/A	£9775	£255
Monthly ongoing costs			
Monthly cost for LVAD patients (outpatient) (Chew *et al.* 2017)[106]	N/A	£958	£244
Monthly outpatient costs for MM patients (Clegg *et al.* 2007)[108]	N/A	£644	£64
Cost per re-admission apart from stroke in MM patients (Clegg *et al.* 2007;[108] Girling *et al.* 2007)[109]	N/A	£3389	£339

SE, standard error.

TABLE 37 Parameters used in the deterministic sensitivity analysis for heart transplant

Parameters	Mean
Overall mortality risk in BTT (LVAD) *(Kirklin 2017)*[137]	
1–12 months	0.013
13–24 months	0.008
25–36 months	0.008
37–48 months	0.010
Monthly mortality risk in HT *(Clarke 2014)*[156]	
1st month	0.050
2–12 months	0.014
13+ months	0.009
Transition from DT to BTT (LVAD) *(Goldstein 2020)*[157]	0.006

TABLE 37 Parameters used in the deterministic sensitivity analysis for heart transplant (*continued*)

Parameters	Mean
Transition from BTT (LVAD) to HT *(Kirklin 2017)*[137]	
1–12 months	0.028
Stroke in HT patients *(Kirklin 2017)*[137]	
1–12 months	0.012
Monthly re-admission in HT patients apart from stroke *(Jalowiec 2008)*[158]	0.088
Utility in BTT (LVAD) *(Clarke 2014)*[156]	0.74
Utility in HT *(Clarke 2014)*[156]	0.83

TABLE 38 Parameters used in the one-way sensitivity analyses

Parameter	Value 1	Source	Base-case	Value 2	Source
LVAD implantation cost	£91,162	Schueler 2020[116]	£94,527	£109,140	Lim 2021[110]
End-of-life care cost is doubled for MM	–	–	£9775	£19,550	Steering committee
Monthly outpatient costs in MM patients (outpatient)	£72	Lim 2021	£644	£2951	Silvestry 2019[115]
Outpatient costs for LVAD patients	£72	Lim 2021	£958	£1952	Clegg 2007[108]
Cost per re-admission per MM patient	£2711	0.80 × £3389	£3389	£9041	Baras Shreibati 2017[101]
Proportion of RHF patients receiving RVAD after a LVAD	0.116	Kirklin 2017	0.125	0.138	*Chapter 3*
Probability of RHF hospitalisation after the 2nd month	0.001	0.002/2	0.002	0.004	0.002 × 2
Probability of severe AR	0.002	0.004/2	0.004	0.008	0.004 × 2
Probability of stroke in LVAD patients	0.008 and 0.003	Starling 2017[159]	0.017 and 0.003	0.017 and 0.008	Starling 2017
Probability of stroke in MM patients	–	–	0.001	0.002	Baras Shreibati 2017
GIB in LVAD recipients	0.016 and 0.40	Kirklin 2017	0.032 and 0.010	0.04 and 0.06	Kirklin 2017[137]
DI in LVAD recipients	0.006	0.011/2	0.011	0.024	Tattenvin 2019[160]
Utility loss after disabling stroke	0.450	Scheuler 2020	0.670	0.7	0.67 × 1.05
Utility loss after non-disabling stroke	0.09	(0.11/0.14) × 0.11	0.11	0.14	Luengo-Fernandez 2013[161]
Utility in MM patients	0.40	Baras Shreibati 2017	0.51	0.64	Silvestry 2019
Utility in LVAD recipients (12 months)	0.70	Baras Shreibati 2017	0.77	0.85	Chew 2017[106]
MM mortality risk	0.070	Scheuler 2020	0.085	0.09	0.085 × 1.05
Reduced LVAD mortality risk after 12 months	0.005	Lim 2021	0.021 and 0.012	0.011	Mehra 2021[126]

TABLE 39 Details of the outpatient cost estimates identified from the literature

Cost description	Estimated cost (2019 £)	Sources	What's included	Study and country
Monthly outpatient costs per LVAD patient	£1952	Papworth Hospital NHS Trust, unpublished BTT data	All costs other than hospital visits	Clegg 2007[120] – UK
	£7529 (first 12 months)	Literature-based details are not provided	All costs other than hospital re-admission	Long 2014[111] – USA
	£2139 (13+ months)	Literature-based details are not provided	All costs other than hospital re-admission	HQ Ontario 2016[91] – Can.
	£957	National hospital costing data	All costs other than hospital re-admission	Chew 2017[106] – Can.
	£958	69 BTT patients	All costs other than hospital re-admission	Neyt 2013[102] – NL
	£986	220 patients' Medicare claims after LVAD	All costs other than hospital re-admission	B. Shreibati 2017[101] – USA
	£2172	83 LVAD patients in COMPANION trial	All costs other than hospital re-admission	Rogers 2012[114] – USA
	£1943	Medicare data details not provided	All costs other than hospital re-admission	Silvestry 2019[115] – USA
	£2598	Abbott internal data	All costs other than hospital re-admission	Lim 2021[110]
	£72			
Monthly outpatient costs per MM patient	£644	Papworth Hospital NHS Trust, unpublished BTT data	All costs other than hospital visits	Clegg 2007 – UK
	£958	National hospital costing data	All costs other than hospital re-admission	Chew 2017 – Can.
	£2457	220 patients' Medicare claims before LVAD	All costs other than hospital re-admission	Rogers 2012 – USA
	£1943	83 LVAD patients in COMPANION trial	All costs other than hospital re-admission	B. Shreibati 2017 – USA
	£2951	Medicare data details not provided	All costs other than hospital re-admission	Silvestry 2019 – USA
	£1187	Not provided	All costs other than hospital re-admission	Neyt 2013 – NL
	£336	Clegg 2007	All costs other than hospital re-admission	Adang 2006[104] – NL
	£14,036 (1 month) £6854 (3+ months)[a]	Sharples 2006[119] – BTT patients' unpublished data Medtronic internal data	Outpatient costs and hospital admissions (incl. stroke)[b]	Clarke *et al.* 2014 Scheuler 2021[116]
	£6430	Abbott internal data	Outpatient and hospital admission costs[b]	Lim 2021
	£72		Outpatient costs only	

a Unclear what this means for MM patients considering they would be on MM for a while before the trial.
b Not included in the analysis since it included the admission costs.

TABLE 40 Parameters for the subgroup analysis by Interagency Registry for Mechanically Assisted Circulatory Support profiles

Model inputs	INTERMACS 1	INTERMACS 2 & 3	INTERMACS 4 & 5
Mortality in LVAD *(Teuteberg 2020)*[46]			
1–3 months	0.037	0.021	0.019
4–12 months	0.015	0.021	0.010
13–24 months	0.015	0.012	0.010
25+ months	0.014	0.012	0.010
	(INTERMACS)	*(INTERMACS)*	*(INTERMACS)*
Mortality in MM			
1 month	0.70[162]	0.085	0.061
2–6 months	0.08[a]	*(REMATCH)*[54]	0.077
7–11 months			0.080
12+ months			*(MedaMACS)*[127]
QoL in LVAD			
1 month	0.37 (0.26 + 0.11)[a]	0.40 – 1st month	0.51
2–6 months	0.37	0.562	0.77
7–12 months	0.76	0.76	0.77
13+ months	0.76	0.77	0.77
	(INTERMACS)	*(REMATCH)*	*(MOMENTUM)*[157]
QoL in MM			
1 month	0.1[a] *(first month)*	0.400	0.51
2+ months	0.26[a]	*(REMATCH)*	*(MOMENTUM BASELINE)*

a Assumption based on expert view.

TABLE 41 Deterministic modelling outcomes for the two options considered in estimating the mortality risks and health utilities

	Non-comparative, weighted estimates for MM			*Comparative estimates mapped to LVAD*		
Lifetime outcomes	**MM**	**LVAD**	**Incremental**	**MM**	**LVAD**	**Incremental**
Expected LYs per patient	0.98	4.66	3.67	0.92	2.86	1.94
Expected QALYs per patient	0.50	3.32	2.82	0.46	2.02	1.56
Cost per patient	£19,528	£171,647	£152,119	£18,886	£145,434	£126,548
Incremental cost per LY			£41,429			£65,200
Incremental cost per QALY			**£53,876**			**£81,298**

EME
HSDR
HTA
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PHR

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