Evidence review: Mechanical assist devices for circulatory support (destination therapy) in people with advanced heart failure

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Contents

1 Introduction

- **Mechanical circulatory support devices (MCSD)** support the circulation of blood in people with advanced heart failure. NHS England commissions the use of left ventricular assist devices (LVAD) as a bridge to transplant (BTT) for patients listed for heart transplant, but does not commission LVAD for patients who are not eligible for a transplant. The focus of this review is on the use of MCSD (specifically LVAD) as destination therapy (DT) for patients who are not eligible for a transplant. DT refers to the device being used as support for the rest of the patient's life.
- **Existing national guidance** In March 2015, NICE issued interventional procedure guidance (IPG 516) on the implantation of a left ventricular assist device (LVAD) as destination therapy in people ineligible for heart transplantation (NICE 2015). NICE concluded that:
    - *"Current evidence on the efficacy and safety of the implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit….*
    - *…Clinicians should enter details on all patients who have a left ventricular assist device for destination therapy onto the UK Central Cardiac Audit Database."*
- This guidance was from NICE's Interventional Procedures Programme, and therefore takes into account safety and efficacy, but not cost-effectiveness. It does not constitute a recommendation that the treatment should be used, rather an indication of the circumstances in which it may be used.
- **Heart failure** occurs when the effectiveness of the heart as a pump is impaired. It leads to reduced blood flow to the body and increased filling pressure in the heart. This can cause congestion and oedema in the lungs, making the patient breathless, or in the body, making the legs swell. Other symptoms include reduced exercise tolerance, fatigue and malaise. People with advanced heart failure have symptoms at rest, may be unable to carry out activities of daily living and may be chair- and bed-bound.
- Heart Failure is classified according to severity of symptoms using the New York Heart Association (NYHA) functional classification[1]. In addition, there are seven clinical profiles of illness severity developed from the INTERMACS[2] registry. INTERMACS profiles 1-5 are all equivalent to NYHA functional class IV, INTERMACS profiles 6 and 7 are equivalent to NYHA IIIB and NYHA class III respectively. Patients with INTERMACS profiles 1-3 are usually non-ambulatory and dependent on continuous inotropes. Survival for advanced heart failure is

[1] The New York Heart Association classifications of heart failure include classes based on symptoms and on objective assessment.
Symptoms
I. Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II. Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III. Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20 to 100 m). Comfortable only at rest.
IV. Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
Objective assessment
A. No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B. Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C. Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D. Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

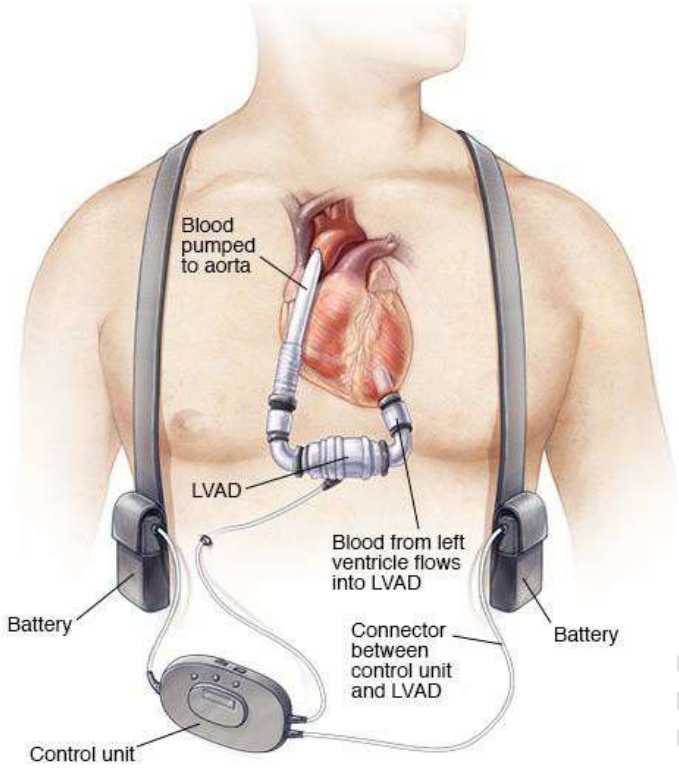
[2] INTERMACS is the Interagency Registry for Mechanically Assisted Circulatory Support, a North American study established in 2005 for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure.

poor: 25% survive to 12 months, and only 8% survive to 2 years (Rose et al 2001).

- NICE (2010) estimates that there are about 900,000 people in the United Kingdom with heart failure, of which about 10% have advanced disease (MacGowan et al 2011, Deng et al 2007). There is uncertainty about the proportion of those with advanced disease in the UK, who no longer respond adequately to optimal medical management (OMM), but a USA study suggests that 5% of patients with heart failure have end-stage disease with symptoms refractory to guideline-based medical therapy (AbouEzzeddine et al 2011).
- **Optimal medical management (OMM)** of heart failure involves drugs such as diuretics and inotropic agents. In addition to OMM, some patients may also have already undergone one or more of the following treatments before heart transplant or MCSD was considered: electrophysiological interventions such as pacemakers and implantable cardioverter defibrillators, revascularisation by percutaneous coronary angioplasty and stenting or coronary artery bypass grafting, valve replacement or repair, and temporary use of intra-aortic balloon pumps. These treatment options were reflected in the population characteristics of studies included in this review. The term OMM therefore included all the interventions above.
- The most recent prognosis data comes from MedaMACS[3] which is a registry of ambulatory heart failure (HF) patients (with INTERMACS profiles 4-7) on OMM. One year survival was 47% (reported in Trachtenberg 2016) using 2011 data.
- **Heart transplantation.** Advanced heart failure refractory to these treatments is sometimes treated with heart transplantation.
- Patients with advanced heart failure may be treated with a mechanical assist device either to augment the circulatory efforts of the failing heart as a bridge to transplant (BTT), or for those ineligible for heart transplantation, as destination therapy (DT).
- Reasons for transplant ineligibility may be absolute or may be potentially reversible. The most frequently cited contraindications are advanced age, renal dysfunction, high BMI, previous malignancy and pulmonary hypertension. Approximately 35% of people listed as transplant ineligible have contraindications which are potentially modifiable. This means that those individuals may recover sufficiently (with device support) to be reconsidered for transplant (Kirklin et al 2012).
- **The intervention.** A mechanical assist device is implanted through a skin incision. Most mechanical assist devices are used to augment the performance of the left ventricle, though right ventricular (RVAD) or bi-ventricular devices (BiVAD) are also available. For left ventricular use, a surgeon attaches one end of the device to the left ventricle and the other end to the aorta. Blood flows from the ventricle into the device, which then pumps the blood out into the aorta, whence it then flows to the rest of the body (Figure 1). With all devices, a fine cable called the driveline connects the device through the skin to a controller, which is outside the body. The controller monitors the device and adjusts its power supply, which is drawn from an external battery pack.

[3] MedaMACS, is the Medical Arm of Mechanically Assisted Circulatory Support (INTERMACS) registry, focusing on the contemporary treatment and outcomes of heart failure patients with INTERMACS Profiles 4-7 and at least one heart failure hospitalization in the prior year, who are neither inotrope-dependent nor listed for cardiac transplantation.

Figure 1: Left ventricular mechanical support device *in situ*



Source: Mayo Foundation for Medical Education and Research (MFMER)

- The pivotal trial by Rose et al in 2001 compared pulsatile flow left ventricular devices (PFVAD) to OMM for 129 patients with end stage heart failure who were ineligible for heart transplantation. They showed a significant improvement in survival (1 year: 52% vs 25%, p=0.002 and 2 years: 23% vs 8%, p=0.09) and quality of life. However, there was 2.35 times the frequency of serious adverse events in the device group (particularly infection, bleeding or device malfunction). Since this initial trial, the device technology has advanced with improved survival outcomes, and reduced adverse events.
- The first generation pulsatile flow devices (PFVAD) have been replaced by second-generation continuous-flow devices (CFVAD). These are quieter, more reliable and smaller, and therefore easier to insert. Third-generation devices propel blood with magnetic forces or hydrodynamic levitation, but without mechanical contact. They are more durable, with less mechanical wear and tear than second-generation devices (Birks 2010, Nguyen et al 2010). The second-generation device most widely used in the NHS is HeartMate II (HMII) (Thoratec Inc, Pleasanton, CA) and was approved by the FDA[4] for BTT support in 2008 and then for DT in January 2010. The most common third-generation device is HeartWare (HW), although it is not licensed for use as destination therapy (HeartWare Inc, Framingham, MA) (Felix et al 2012).
- Data from the INTERMACS registry shows that, between 2006 and 2009, fewer than 10% of ventricular assist devices (VADs) were for destination therapy (Kirklin et al 2011). By 2011, 95% of all devices used (for any treatment strategy) were CFVADs. In 2010-11, all INTERMACS registry patients receiving a device as DT had a CFVAD (Kirklin et al 2012).
- NHS England Specialised Services commissions the provision of mechanical assist devices

[4] United States Food and Drug Administration (FDA) is the Federal Agency responsible for the licensing of medical devices in the USA.

only as a bridge to transplant for patients suitable for and awaiting a heart transplant. To preserve the integrity of the commissioning specification, hospitals are expected, with two minor exceptions, to list the patient for transplant when they insert the device. About 80 devices are implanted annually in the UK, and about 100 British people are alive with a device in place (British Heart Foundation, accessed 30 April 2017).

- NHS England does not commission mechanical assist devices as destination therapy for those in whom transplantation is contra-indicated (NHS Commissioning Board 2013/14). People with advanced heart failure unsuitable for transplant outnumber those who are eligible for the procedure, and usually die from worsening heart failure within 12 months (Long et al 2014)

2 Summary of results

- This evidence review found no controlled studies which reported the outcomes for continuous flow left ventricular assist devices (CFVAD) compared to optimal medical therapy (OMM) in patients ineligible for transplant and dependent on inotropes who were implanted with a device as destination therapy.
- We found one prospective controlled study (patients not dependent on inotropes), one prospective controlled study (control was pre-approval CFVAD, not OMM as per scope of this review), three systematic reviews of uncontrolled studies (or out of scope controlled studies) and seven large retrospective uncontrolled studies suitable for inclusion.
- The main outcome of interest was survival. The survival of CFVAD recipients is 74% and 59% at one and two years for people with a baseline INTERMACS profile 1-3 (Jorde et al 2014). There is INTERMACS registry data reporting 57% survival at 3 years (Kirklin et al 2015). CFVAD appears to offer clear improvement in survival compared to OMM for people needing continuous inotropes since their estimated survival is only 20% at 1 year (Boothroyd et al 2013). Other key outcomes reported were function, quality of life and adverse events.
- Improvements in function were measured using the 6 minute walk distance test (6MWD). In the prospective post approval HMII DT study (Jorde et al 2014), 19% of the 247 HMII recipients were able to complete a 6MWD test. Before HMII implant, the mean baseline 6MWD was 183±97m. Two years post implant, this had increased to 297±118m. It is not known what proportion of HMII recipients became ambulatory after device implant or how an improvement of 114m over six minutes translates to activities of daily living or independence.
- In addition, a large proportion (at least 80%) of HMII recipients who are alive at 6 months and at 2 years achieve and sustain NYHA class I or II, from an initial NYHA IV health state (Boothroyd et al 2013).
- Improvements in quality of life (QoL) have been reported using a wide variety of measures including KCCQ, EQ5D and MLHFQ. KCCQ has been shown to improve from a mean score of 24 at baseline to 68 and 74 at 3 months and 24 months respectively post implant (equivalent to NYHA class II) (Rogers et al 2010, reported in McIlvennan et al 2014). EQ5D was also shown to improve significantly with a 33-35 point improvement between baseline and 12 months (Grady et al 2015). All studies which reported quality of life outcomes reported significant improvements although we noted that some of these were highly selective in recruiting subjects for analysis (i.e. those who died or were too unwell to complete a QoL assessment were excluded from the analysis). This may lead to an over optimistic understanding about the QoL that can be achieved outside of a study environment.
- Adverse events were significant with the most common being bleeding. A significant

proportion of HMII recipients will experience a bleed during the first 24 months after device implant. Jorde et al reported that over 54% of recipients had a bleed which required transfusion and 13% needed further surgery.

- Other common adverse events included infection (sepsis, local device related, non-device related), stroke (haemorrhagic stroke, ischaemic stroke) and device related events such pump thrombosis and device malfunction.
- The three cost effectiveness studies identified were based on outcomes at 2 years modelled over a lifetime (approximately 5 years). The model will have estimated a projected survival as well as QoL (including the impact of adverse events on QoL) based on indirect data from more than one study, and based on assumptions beyond the period of observed data. There was a wide variation in the estimated quality adjusted life years (QALY) and life years gained (LYG) over a lifetime. Despite the weakness of the models, the estimated ICER was consistently high in all studies (£91,299 to £162,388 per QALY). This is not surprising as the LYGs are associated with numerous and serious adverse events which in turn reduce quality of life for the patient and increase the ongoing cost of care.
- The published literature on the use of CFVAD as DT compared to OMM for patients with NYHA class IV dependent on inotropes is of low quality. There is a large volume of uncontrolled, small, observational studies, none of which are suitable for meta-analysis. Most studies report the 'as treated' outcomes only and often exclude some with the poorest outcomes, increasing the uncertainty of the findings.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group (PWG) for the topic (see section 9 for PICO), and further clarifications agreed by correspondence with the PWG.
- The PICO was used to search for relevant for publications between 1st March 2007 and 3rd March 2017 from the following sources: TRIP, NICE Evidence search, PubMed, Embase and Cochrane Library limited to English and last 10 years (see section 10 for search strategy). The search excluded conference papers, letters, commentary and editorials. In addition, due to the large volume of results papers with no authors listed or with no abstracts have been excluded.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Studies of pulsatile-flow devices and those which did not separately report results specific to patients receiving a CFVAD as destination therapy were also excluded.
- Individual studies were also excluded if they were already included in literature reviews selected for inclusion, review articles or editorials on CFVADS, studies that were non-human, studies that focused on surgical techniques, studies that reported on temporary devices or partial support, studies with a heart transplant focus, studies which did not separate data based on CF vs PF device, studies reporting on risk modelling and CFVADS, studies that

were updated by newer publications, and sub-analyses of previously reported results.

- Following agreement with the PWG, further exclusion criteria were agreed including: single centre studies and studies with less than 100 patients.
- Evidence from all full papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- For serial publications updating longitudinal registry findings, we included only the most recent publication that addressed a specific outcome.
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

What is the clinical effectiveness of mechanical circulatory support devices when used as destination therapy (i.e. not as bridge to transplant) in patients with chronic end-stage heart failure?

Clinical Effectiveness Studies

Although it was agreed that the scope of the review could include people with advanced heart failure who were ambulatory and not dependent on inotropes, the main population focus of this review (see section 9 for detail) is patients with chronic end stage heart failure who are ineligible for heart transplant, whose symptoms have failed to respond to OMM, and who are dependent on inotropic therapy (equivalent to NYHA IV, INTERMACS profiles 1-3).

We found **no controlled studies** which reported the outcomes for continuous flow left ventricular assist devices (CFVAD) compared to optimal medical therapy (OMM) in patients ineligible for transplant and dependent on inotropes who were implanted with a device as destination therapy.

We found **one prospective controlled study** (Estep et al 2015) which compared the outcomes for CFVAD with OMM. However, this study recruited only ambulatory patients who were not dependent on inotropes (INTERMACS profiles 4-7).

We found **one prospective, controlled, post approval study** by Jorde et al (2014), which compared the outcomes of 247 consecutive patients, who were implanted with a Heartmate II (HMII) device as destination therapy, with those of patients enrolled in the HMII pre-authorisation study by Slaughter et al (2009).

We found **three systematic reviews** (McIlvennan et al 2014, Boothroyd et al 2013 and Draper et al 2014) reporting outcomes for patients who were implanted with a CFVAD as destination therapy. These three systematic reviews reported different outcomes and are therefore all included in this review. We have reported destination therapy outcomes for CFVAD only. This is because the individual studies of CFVAD as DT from McIlvennan et al (2014) and Boothroyd et al (2013) had comparators which were out of scope of this review (pulsatile flow devices, or with bridge to transplant (BTT) treatment strategies) (Slaughter et al 2009, Rogers et al 2010, Petrucci et al 2012, Park et al 2012) or had no comparator at all (Kirklin et al 2012a).

Because the systematic reviews were unable to perform meta-analysis due to the heterogeneity of the studies (for example due to out of scope comparators and different population

characteristics)), we also included **seven large, retrospective, uncontrolled studies** which reported outcomes for destination therapy patients who received a CFVAD (Arnold et al 2016, Kirklin et al 2015, Grady et al 2015, Fendler et al 2015, Katz et al 2015, Boyle et al 2014, and Kirklin et al 2012).

Cost effectiveness Studies

We found **three relevant published papers** for the cost-effectiveness of CFLVAD as destination therapy for people with chronic end-stage heart failure who are ineligible for heart transplant (Nunes et al 2016, Neyt et al 2014 and Baras Shreibati et al 2017). Two of these were systematic reviews of cost effectiveness studies, the latter focused on the cost-effectiveness of LVAD in ambulatory patients (i.e. INTERMACS profiles 4-7) with advanced heart failure.

In the summary of evidence selection (section 11 of this report), the counts include individual studies reported by the systematic reviews and which were retrieved for further detail on the DT-specific outcomes for CFVAD.

What is the <u>clinical effectiveness</u> of mechanical circulatory support devices when used as destination therapy (i.e. not as bridge to transplant) in patients with chronic end-stage heart failure?

Clinical effectiveness outcomes reported. Commonly reported clinical effectiveness outcomes reported in the studies include survival, event free-survival, recovery, transplantation, attainment of NYHA 1 or II levels of functioning from initial NYHA class IV, physical function, cognitive function, quality of life (QoL) using a range of different measures, resource utilisation, adverse events and risk factors.

Survival was the main clinical effectiveness outcome reported in the studies. There are no controlled studies (randomised or otherwise) which reported survival (for any time period) for CFVAD as DT compared to OMM in patients with chronic end stage heart failure ineligible for transplant, refractory to OMM, who are dependent on inotropes (the focus of this review).

In patients with less severe disease (INTERMACS profiles 4-7), the ROADMAP study by Estep et al (2015) reported no significant difference in the intention to treat (ITT) analysis[5] of survival at 12 months (n=200, HMII 82% vs OMM 81%, p = 0.931).

However, in patients who more closely match the profile concerned in this review, there are survival data up to three years. Early outcomes from Slaughter et al (2009) (reported in McIlvennan et al 2014 and Boothroyd et al 2013) suggest that 68% and 58% of patients are alive at 12 and 24 months respectively (n=133). More recently, the seventh INTERMACS Annual Report (Kirklin et al 2015), has reported actuarial survival for CFVAD as DT of 76% at 12 months and 57% at 3 years. However, this is an estimate of probability of survival projected beyond the survival of those patients actually observed and at risk (i.e. exposed to the intervention) at the specified time points.

This is consistent with the results of the systematic review by Boothroyd et al (2013) which reported survival at 12 months of 68% to 78% (n=817) and at 2 years of 58% to 63% (n=208), as

[5] An analysis in which participants are classified according to the treatment to which they were allocated, even if they do not receive it or receive another, or have an adverse event. The inclusion of the whole cohort in the analysis, rather than a selective subset, ensures that the outcomes reported are more generalizable.

well as the more recent survival outcomes from Katz et al (2015) where outcomes for HMII CFVAD as a destination treatment were reported as Kaplan-Meier survival rate of 70% ± 5% at 12 months and 63% ± 6% at 24 months.

Results from the Katz et al (2015) registry based study of 176 recipients of HMII device as DT suggest that at 6 months and 12 months post implant, the survival rate and number of patients alive is greater for those with a baseline INTERMACS profile 4-7 (ambulatory and not dependent on inotropes) compared to those with INTERMACS profiles 1 and 2 (see below). In particular, those patients with a baseline INTERMACS profile 1, had a likelihood of being alive at 6 months of 60.4% ± 12% which was almost 20% lower than for all other profiles. No INTERMACS profile 1 patient was alive 12 months post implantation. This was based on a small, uncontrolled study with incomplete reporting and the results should be treated with caution.

Source: Katz et al 2015	Time after implantation (number of people included in the analysis)	
INTERMACS profile	At 6 months (n=86)	At 12 months (n=37)
1	63.4% ± 12.0% (7)	N/A
2	82.4 ± 5.7 (28)	64.3 ± 8.5%(16)
3	81.5 ± 5.1% (37)	76.4 ± 5.9%(13)
4-7	87.9 ± 6.7% (14)	72.6 ± 11.5%(8)

There is evidence from one study that only 90% patients are discharged from hospital (Katz et al (2015), and that 30-day mortality may be between 3.4% (n=176) and 14% (n=414) (Katz et al 2015 and Boothroyd et al 2013 respectively).

Importantly, the survival from retrospective studies using INTERMACS registry data is based on the estimated probability of survival rather than observed events for every time point (Kirklin et al 2012, Kirklin et al 2012a, Kirklin et al 2015, Katz et al 2015). Large proportions of device recipients have had their device implanted for a shorter period than the survival time reported. For example, in Kirklin et al 2012, 1128 of the 1160 devices were implanted for less than two full years, 620 of these were implanted for less than one full year at the time of data analysis.

In addition, the INTERMACS registry does not represent the complete sample of DT patients; there is no follow-up data for approximately 9.6% of patients with FDA approved devices (due to lack of informed consent) as well as those who receive a device as part of a clinical trial. It is not known if the incomplete data for device recipients affects the estimated probability of survival. .

In contrast, the survival (74% ± 3% at one year, 61% ± 3% at two years) reported in the prospective, post approval study is based on at least 2 years observation of all 247 consecutive HMII device recipients with patients censored only for transplantation, recovery or withdrawal from the study (Jorde et al 2014). The diagram below shows improvement in survival in the post approval HMII DT study (Jorde et al 2014) since the original HMII DT trial by Slaughter et al (2009). In particular, it highlights the significantly poorer percentage survival at all time periods of patients who were in the OMM control arm of previous clinical trials (Rose et al 2001) as well as the marked survival advantage of the HMII continuous flow device over the pulsatile devices (VE, XVE , Novacor LVADs shown below)

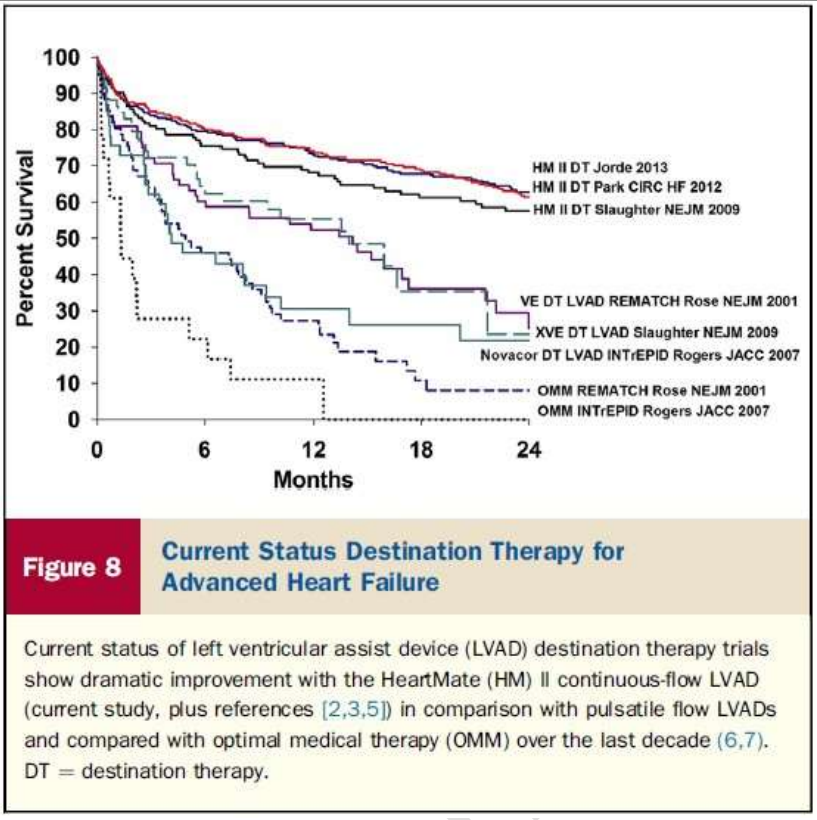


Figure 8 **Current Status Destination Therapy for Advanced Heart Failure**

Current status of left ventricular assist device (LVAD) destination therapy trials show dramatic improvement with the HeartMate (HM) II continuous-flow LVAD (current study, plus references [2,3,5]) in comparison with pulsatile flow LVADs and compared with optimal medical therapy (OMM) over the last decade (6,7). DT = destination therapy.

Diagram 1. Survival between 0 and 24 months for OMM vs HMII LVAD interventions in people with advanced heart failure (Jorde et al 2014).
Note: VE, XVE and Novacor devices were all pulsatile LVADs.

Diagram 2 below highlights the continued improvement in survival between the older devices (pre-2012 including PFVADS) and newer generation CFVADS for destination therapy. The use of LVADS as a bridge to transplant continues to offer a greater clinical effect to patients listed for transplant.

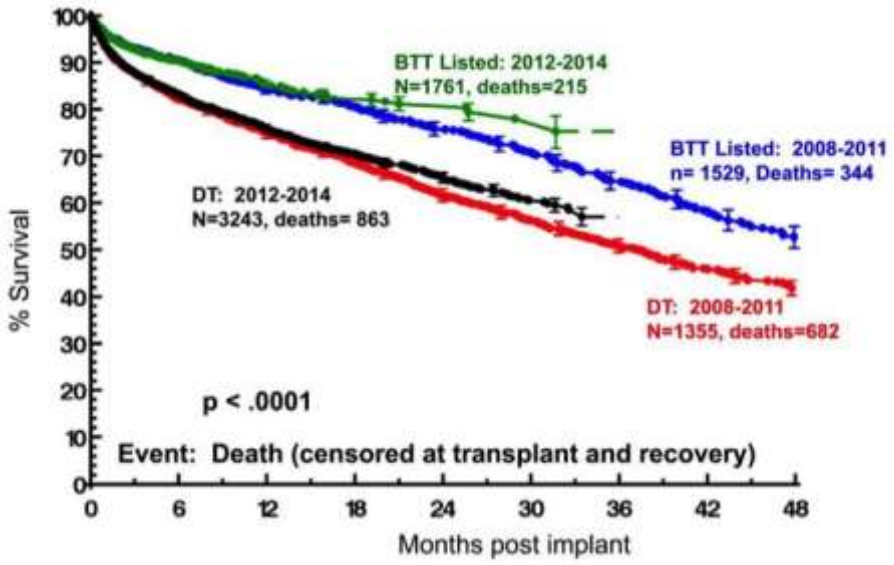


Diagram 2: Proportion of people alive after implantation of a CFVAD (LVAD/BiVAD) 2008-1014, n=12030 (Kirklin et al 2015)
BTT: Bridge to transplant, DT: Destination therapy. The error bars indicate ± 1 standard error.

Event free survival. The multicentre, post approval study of 247 patients (Jorde et al 2014) reported that at 2 years post implant, 54% (n=135) of patients implanted with a HMII device as DT, were alive and free from stroke or any reoperation. They suggested that this was a superior significant outcome (p=0.042) when compared to the outcomes reported in the pivotal HMII DT trial (Slaughter et al 2009), although the comparison of these results should be treated with caution as they are from two different studies, with differences in patient selection and provider/surgeon experience.

The attainment of NYHA class I or II (from a baseline of NYHA IV) is an important measure of function for patients whose heart failure is initially so advanced that they are mostly bedridden and experience symptoms at complete rest. NYHA class I or II symptoms are mild, and do not limit ordinary activity (see footnote 1 above).

Class I: Cardiac disease, but no symptoms and no limitation in ordinary physical activity, for example no shortness of breath when walking, climbing stairs.

Class II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity

The results from the two studies which reported this outcome are too heterogeneous to be pooled. The literature review (Boothroyd et al 2013) estimates that at 6 months 80%-82%, and at 2 years 80%-81%, of HMII devices used as DT achieved NYHA class I or II symptoms from an initial advanced NYHA IV (86% were on intravenous inotropes before implantation).

The ROADMAP trial by Estep et al (2015), which studied 200 patients with less severe heart failure (mostly ambulatory and not dependent on inotropes) reported that at 12 months after implantation, 25% and 52% of HMII recipients achieved NYHA class 1 and II respectively. Although it was a relatively small study, it was a controlled prospective design which compared the HMII device as a destination treatment strategy against optimal medical management (OMM). 55% (39/71) of HMII recipients improved by a minimum of 2 NYHA functional classes compared to 4% (2/52) on OMM. However, the results were incompletely reported since they excluded 68 of the 200 patients (who died, crossed over from OMM to HMII treatment, withdrew from the study or received a heart transplant).

Physical function. In addition to the functional element of the NYHA classification, the main measure of physical function was measured in four studies using the six-minute walk distance test (6MWD).

Patients taking part in the ROADMAP trial were all initially ambulatory (and therefore not the primary patient group of interest for this review), whereas the majority of device recipients included in the systematic literature reviews and the prospective post approval study by Jorde et al (2014) had more severe advanced heart failure. The systematic reviews reported 6MWD from older studies including the pre-approval HMII DT study by Slaughter et al 2009.

The most relevant 6MWD results for DT recipients are from the prospective, post approval HMII study (Jorde et al 2014) which compared the outcomes with the results from the earlier HMII DT

trial (Slaughter et al 2009). Only a limited proportion (19%) of people were able to walk well enough to complete the 6MWD. Of these, the baseline distance (183 ± 97metres) improved significantly to 297 ± 118 metres at two years. As with other studies of MACS, the effect size should be treated with caution as the studies were uncontrolled and small and data reported was analysed on an 'as treated', rather than 'intention to treat' basis. This might inflate the effect size reported.

The ROADMAP trial reported 6MWD for ambulatory patients with NYHA class IV heart failure. For those treated with OMM, there was no significant difference in 6MWD between baseline and 12 months (p=0.325). Treatment with a HMII device did statistically significantly improve the 6MWD from 187m to 263m at 12 months post implant (p<0.001) (Estep et al 2015)

It is not clear what impact the ability to walk an additional 114 metres (from Jorde et al 2014) over six minutes makes on an individual's quality of life, activities of daily living and independence.

Cognitive Function was reported in two of the studies. The initial cognition was reported in a systematic review of the literature (based on one small follow up study of the HMII DT Trial by Petrucci et al (2012). 72/96 recipients had stable or improved cognition at 6 months but 2 years post implant the number of recipients who avoided any deterioration in cognitive function was only 33 of the initial 96 patients.

More recently, an analysis of 4419 patients on the INTERMACS registry selected 1173 patients with cognitive function recorded at baseline (Fendler et al 2015). There were only 349 recipients who had cognitive function recorded at 12 months. Based on the unadjusted analysis of the whole cohort (n=1173), 21% (n=246) had meaningful cognitive decline[6]. However, there was incomplete data for the rest of the cohort (n=927) and the 'modelled' lack of cognitive decline for these subjects is unreliable. There was an increased risk of cognitive decline associated with destination therapy compared with BTT therapy (HR 1.42, 95%CI 1.05-1.92, p<0.001). It is unknown how these results compare to cognitive decline in a similarly matched cohort on OMM treatment strategy.

Quality of life outcomes were reported in six studies, using three different measures. These were the KCCQ[7], the EQ5D and the MLHFQ. The EuroQoL-5D is a measure of health-related quality of life (HRQoL); there are five dimensions (5D) including activity, anxiety, mobility, pain and self-care. A higher score indicates better quality of life with visual analogue scale ranging from 0= worst imaginable health to 100=best imaginable health state. The MLHFQ Scores range

[6] Defined as an increase of 32 seconds or longer (0.5x baseline TMT-B score SD of 64 seconds, corresponding to a moderate effect size) either from one time point to the next or additively over consecutive time points.

[7] Kansas City Cardiomyopathy Questionnaire (KCCQ): a 12-item (23-items before 2014) self-administered questionnaire that assesses specific health domains pertaining to heart failure. Both versions yield an overall summary scale (KCCQ-OS) ranging from 0-100. Higher scores are associated with fewer symptoms, better function, and higher quality of life. KCCQ-OS is reported to correlate roughly to NYHA functional classes as follows:
class 1~KCCQ-OS score 75-100
class 2~KCCQ-OS 60-74
class 3~KCCQ-OS 45-59
class 4~KCCQ-OS 0-44 (population of interest in this review)

from 0 to 105; unlike the KCCQ, a lower score illustrates a better quality of life.

The older studies reported in the two systematic reviews measured QoL using KCCQ (McIlvennan et al 2014) and MLHFQ (McIlvennan et al 2014 and Boothroyd et al 2013). Four studies reported QoL using the EQ5D instrument. One of these studies by Grady et al (2015) found that across 1470 recipients of CFVAD as DT, there was a similar mean improvement of 33-35 points in the EQ5D VAS at 12 months post implant for all three age groups in the study (>70 years old, 60-69 years, <60 years). They also reported that there was no difference in the proportion of patients with a >10point improvement in HRQoL across the three age groups (74.3%, 74.9%, 73.4%) respectively.

The Registry analysis of 1160 CFVAD recipients by Kirklin et al (2012) found statistically significant reductions in the number and proportions of people who were experiencing problems with self-care, usual activities, mobility and anxiety/depression when compared to baseline ($p<0.05$). The improvement from baseline in EQ5D at 3 months was sustained at 6 and 12 months although the number of patients at risk (i.e. those who were able to contribute data) at 12 months was low (n=186) compared to the initial baseline (n=654). This affects the certainty of the findings as well as the size of the effect.

Resource utilisation was reported in three studies. The median initial length of stay for the implant procedure was reported to be 22.5 days (Katz et al 2015) in line with the post approval study by Jorde et al (2014), which reported 21 days.

Katz et al (2015) and McIlvennan et al (2014) also reported readmissions to hospital post device implant. As these were reported from two very small studies, using different measures over different time periods (1.77 hospitalisation readmission events per patient year and 94% rehospitalisation at 24 months respectively), there remains uncertainty about the incidence and frequency of these events. We do not know how this compares to those who remain on OMM.

Safety The main complications of mechanical cardiac support are bleeding, infection, cardiac arrhythmia and respiratory failure (Kirklin et al 2012, Kirklin et al 2015).

In the ROADMAP trial (Estep et al 2015), the composite rate of bleeding, driveline infection, pump thrombosis, stroke, ventricular arrhythmias and worsening heart failure after HMII device implantation was 1.89 events per participant year, compared with 0.83 events per participant year during medical management (relative risk for OMM vs HMII: 0.44, 95% confidence interval 0.35 to 0.56, $p< 0.001$ (Estep at al 2015). More mechanical support patients (80%) than OMM patients (62%) were readmitted within a year of enrolment, most commonly because of bleeding for mechanical support patients and worsening heart failure for OMM patients. However, this study included device recipients who were all ambulatory and not dependent on inotropes. It suggests that the incremental survival benefit experienced by heart failure patients with INTERMACS profiles 4-7, may be eclipsed by the incremental burden of device related adverse events.

Bleeding, stroke and pump thrombosis adverse events post discharge, for patients who were initially dependent on inotropes, were reported by Boyle et al (2014). This study followed up, for at least 2 years, 956 patients (i.e. a total of 1192 patient–years) who had received a HMII device as a participant of a HMII clinical trial; 58% (n=551) were implanted as DT. They reported the

number of adverse events, the proportion and the event rate, expressed as the number of events per patient year.

Almost half of DT HMII recipients (n=258, 47%) experienced bleeding which required blood transfusion once they had been discharged from hospital. Gastrointestinal bleeds occurred in 29% of patients (n=161) and 4% of patients (n=21) experienced bleeds requiring further surgery (Boyle et al 2014).

Of the 551 HMII recipients for DT, 51 (9%) patients had 53 haemorrhagic strokes which equated to 0.04 events per patient year. In addition, there were 45 ischaemic stroke events in 43 patients (8%). 31 patients experienced 36 incidences of pump thrombosis. The adverse events reported by Boyle et al (2014) may be underreported, due to the exclusion of 173 device recipients who were not discharged from hospital.

Jorde et al (2014) reported adverse events for all 247 consecutive HMII recipients. The most frequent were bleeding requiring transfusion (54% of patients, 0.84 events per patient year), local non-device related infection (39%, 0.59 events per patient year) and cardiac arrhythmia requiring cardioversion (37%, 0.40 events per patient year).

The INTERMACS Registry study by Kirklin et al (2012) reported a wider range of adverse events (including psychiatric burden) than Boyle et al (2014), although this was for a shorter follow up time (12 months). They reported that the total burden of adverse events for the 1160 patients was significant (3273 events, 37.56 events per 100 patient months). Once discharged from hospital, the most common complications were bleeding (1040 events, 11.94 events per 100 patient months), infection (705, 8.09), cardiac arrhythmia (339, 3.89) and respiratory failure (230, 2.64). Per patient year, the event rates were approximately 1.43, 0.97, 0.47 and 0.32 respectively.

What is the <u>cost effectiveness</u> of mechanical circulatory support devices when used as destination therapy (not as bridge to transplant) in patients with chronic end-stage heart failure?

We found **three relevant studies** for the cost-effectiveness of CFLVAD as destination therapy for people with chronic end-stage heart failure who are ineligible for heart transplant (Nunes et al 2016, Neyt et al 2014 and Baras Shreibati et al 2017). Two of these were systematic reviews of cost effectiveness studies; Baras Shreibati et al (2017) focused on the cost-effectiveness of LVAD in ambulatory patients (i.e. INTERMACS profiles 4-7) with advanced heart failure.

The studies by Nunes et al 2016 and Neyt et al 2014 were both systematic reviews of cost effectiveness studies and included 17 different studies between them (one study – Rogers et al 2012 was reported in both SRs). The majority of studies were about older generation devices, or compared the cost effectiveness of destination therapy with that of heart transplantation. These were excluded from inclusion in this review.

The remaining three studies in the systematic reviews estimated the incremental cost effectiveness ratio (ICER) of CFVAD compared to OMM using data from existing studies, referencing missing information from other studies and simulating probabilities in order to address the uncertainty. The results of the three studies by Rogers et al 2012, Long et al 2014 and Neyt et

al 2013 could not be pooled due to differences in the methodology and input parameters.

Taking into account post-operative complications and associated costs of receiving a CFVAD, the incremental cost effectiveness ratio ranged from US$207,670 to €107,600 per QALY (95%CI €66,700-€181,100) to CAD$200,166. Converting these to GBP, the ICERs ranged from £91,299 to £162,388.

The ICER was highly dependent on the estimated QALY gain which ranged from 1.5 QALYs to 2.83 QALYs. We noted that the QALY gain varied between the studies but the additional costs of implanting the device and managing the heart failure and adverse events were similar US$297,551 and €299,100 (equating to £232,768 to £253,871) (Neyt et al 2014).

The cost effectiveness was also expressed as the cost per life year gained (LYG), a measure which values only life extension regardless of the quality of life associated with receiving a CFVAD.

The cost per LYG ranged from US$167,208 to €94,100/LYG (95%CI €59,100-€160,100)(Nunes et al 2016, Neyt et al 2014). There was an almost two-fold variation in the assumed LYG between the studies (from 1.78 to 3.23 LYG).

We noted that the study by Baras Shreibati et al (2017) which focused upon people treated with an HMII device who had NYHA IV advanced heart failure but were still ambulatory and not dependent on inotropes yielded an ICER of US$209,400 per QALY gained and US$597,400 per LYG. This was less cost effective than treating patients with more advanced disease. The high costs were attributed to readmissions and outpatient costs associated with long term care of people with an implanted HMII device.

Both Baras Shreibati et al (2017) and Long et al (2014) found that the cost per QALY might be more than halved (to US$86,900 per QALY and US$102,807 per QALY respectively) if post-operative complications and associated costs were significantly reduced or absent.

These results indicate that without data on longer term outcomes based upon observed as opposed to projected life expectancy, complications and associated costs, there is significant uncertainty about the cost effectiveness of CFVAD as destination therapy for advanced heart failure compared to optimal medical management.

Regardless, even the most optimistic ICER of approximately £91,000 per QALY is much higher than the usual cost effectiveness threshold (£20-30,000 per QALY) applied by NICE for health conditions that are not rare.

5 Discussion

The main population focus of this review (see section 9) is patients with advanced heart failure who are dependent on inotropes and ineligible for transplant (equivalent to NYHA IV, INTERMACS profiles 1-3).

We found no controlled studies which reported the outcomes for continuous flow left ventricular assist devices (CFVAD) compared to optimal medical therapy (OMM) in patients ineligible for transplant and dependent on inotropes who were implanted with a device as destination therapy.

In the absence of a directly relevant controlled study, we report the outcomes specific to destination therapy from controlled studies with out of scope comparators (without randomisation) and several uncontrolled, observational studies. Only one of these was prospective in approach (Jorde et al 2014) and was controlled (comparing results of enrolled HMII patients with HMII device recipients from a previous study). In addition, results from one controlled study comparing OMM with CFVAD in patients with less severe heart failure (INTERMACS profile 4-7) are reported (Estep et al 2015).

The mean life expectancy for patients ineligible for transplant treated with OMM is 9.4 months (Long et al 2014). The survival estimates cited in studies vary; Rose et al (2001) report that, in patients with NYHA IV who are not eligible for transplant, 28% people were alive at 1 year, and this was reduced to 8% at 2 years. The expected survival rate for people dependent on inotropes is between 20% and 25% at 1 year (Boothroyd et al 2013, Long et al 2014)).

The survival with a CFVAD is 74% and 59% at one and two years respectively for people with a baseline INTERMACS profile 1-3 (Jorde et al 2014). There is INTERMACS registry data reporting 57% survival at 3 years (Kirklin et al 2015). Despite the lack of controlled studies, there is little doubt that CFLVAD offers significant survival advantage compared to OMM.

There were also improvements in function as measured by the attainment of NYHA class I or II, and demonstrated in in 6MWD tests, as well as quality of life (measured using KCCQ, MLHFQ, EQ5D) along with numerous different adverse events.

The studies were all of limited quality and reliability; there were no relevant controls, the baseline characteristics varied between studies, follow up times were not consistent within studies, and cohort size was often small. Studies often did not report outcomes specific to DT, and included BTT patients (who have different characteristics and there is evidence that BTT outcomes are not generalisable to DT). HMII DT trials were controlled but none had OMM as comparator (McIlvennan et al 2014).

OMM was never described in detail although baseline characteristics clearly showed than non-medical interventions were considered part of OMM (e.g. implantable cardioverters and cardiac resynchronisation therapy). Although we reported survival for OMM based on Rose et al (2001) and Boothroyd et al (2013), it is possible that contemporary OMM survival rates may have improved.

The USA INTERMACS registry data is the most comprehensive registry in the world but analysis of outcomes from it are not necessarily generalisable. The actuarial survival reported (Kirklin et al 2012, Kirklin et al 2012a, Kirklin et al 2015, Katz et al 2015) is the estimated probability of survival rather than observed events for every time point; we do not know if the incomplete data for device recipients affects the estimated probability of survival reported.

Some studies based on registry data, go further and exclude from their analysis patients who died

before discharge (Boyle et al 2014), or who did not have a particular outcome measure (e.g. cognitive decline or KCCQ) recorded, or who had died before three months follow up (Fendler et al 2015, Arnold et al 2015). Even with statistical techniques to minimise the effect of selection bias, these results are difficult to interpret and should be treated with caution.

The lack of standard outcomes across the studies prevents comparison of outcomes between studies and also meta-analysis or pooling of results - a technique that is sometimes used to increase certainty about outcomes from a number of smaller datasets. Even survival was reported using a variety of different measures (Kaplan-Meier survival analysis, actuarial survival) and was also incorporated into a variety of novel composite measures (e.g. 'survival free from stroke and reoperation two years post implant' and 'survival free from stroke, device infection or pump replacement'). Five studies reported event rates: events per patient year (Jorde et al 2014, Katz et al 2015, Boyle et al 2014), events per 100 patient months (Kirklin et al 2012) and events per 100 patient years (Boothroyd et al 2013).

Adverse events were significant with the most common being bleeding (reported as bleeds in general, GI bleeds , bleeds requiring surgery, bleeds requiring PRBC), infection (sepsis, local device related, non-device related), stroke (haemorrhagic stroke, ischaemic stroke) and device related events such pump thrombosis and device malfunction.

There was a lack of studies reporting outcomes specific to DT, mixing of DT/BTT patients or mixing LVAD with BiVAD. We took a pragmatic approach and reported outcomes if the majority of patients in the study met the criteria in the PICO in section 9. However, this decreases the certainty of the outcome occurring. In addition, the methodology between studies was heterogeneous (as well as the patient characteristics and the outcome reporting), for example we noted that studies dealt with missing outcomes (due to loss to follow up, transplant or death) in different ways. Some studies treated all of these as an endpoint, others (Fendler et al 2015 modelled the missing data).

In addition, it is not clear that the classification of 'ineligible for transplant' at the time of listing has a single, standard definition that was consistently applied across all the studies (and all centres participating in the studies), nor is it clear if the NHS in England would apply the same 'ineligible for transplant' criteria as those in the studies. This makes the generalisability of the USA study results to the UK somewhat uncertain.

The cost effectiveness studies were based on outcomes at two years modelled over a lifetime (approximately five years). The model will have estimated a projected survival as well as QoL (including the impact of adverse events on QoL) based on indirect data from more than one study, and based on assumptions beyond the period of observed data. There was a wide variation in the estimated QALYs and LYGs over a lifetime. Despite the weakness of the models, the estimated ICER was consistently high in all studies (£91,299 to £162,388 per QALY). This is not surprising as the LYG are associated with numerous and serious adverse events which in turn reduce quality of life for the patient and increase the ongoing cost of care.

In summary, we reviewed a large volume of poor quality studies subject to confounding and bias (selective retrospective recruitment of subjects, as treated analysis, unblinded subjects, self-reported QoL and function outcomes).

We advise caution in interpreting the results, in particular when considering the balance of overall benefits and harms, as the adverse events are significant in both number and severity and will impact upon the quality of life for the individual patient as well as the cost of ongoing care during their extended life years.

6 Conclusion

In patients with severe heart failure in whom heart transplant is contraindicated, destination therapy with a continuous flow mechanical assist device appears more effective than optimal medical therapy. It is associated with improvements in survival, exercise tolerance, in heart failure symptoms measured with NYHA class, and in quality of life. However the number and severity of adverse events associated with CFVAD implant is considerable; the USA registry study by Kirklin et al (2012) reports the total burden of adverse events to be 37.56 events per 100 patient months. Once discharged from hospital, the most common complications were bleeding (11.94 events per 100 patient months), infection (8.09), cardiac arrhythmia (3.89) and respiratory failure (2.64).

The implantation of a CFVAD as DT is three to six times beyond the usual limits for cost effectiveness accepted by NICE. Consideration of CFVAD as DT needs careful consideration, as the majority of patients will live with the device for the remainder of their life, particularly if the reasons for initial transplant ineligibility are unlikely to be modifiable (for instance advanced age or existing comorbidity).

Although the use of CFVAD as DT is considered a specialised service for commissioning, the condition of advanced heart failure is not rare. The NICE Clinical Guideline on Chronic Heart Failure estimates that around 900,000 people in the UK have heart failure (NICE CG108). While the overall prevalence of advanced heart failure is uncertain, it is estimated that roughly 5% of patients with heart failure have end-stage disease with symptoms refractory to guideline-based medical therapy (AbouEzzeddine et al 2011).

Rather than registry data (and subsequent selective studies based on the registry data), a prospective randomised controlled trial, specific for CFVAD device as DT compared to OMM, in patients who are ineligible for transplant in the UK is needed. This is the only way to fully understand the additional survival offered by the device compared to contemporary OMM, to clearly establish the impact on QoL and particularly to confirm the frequency, severity and consequences of adverse events and cost effectiveness.

Given the very high cost per QALY, commissioners may wish to seek certainty about the benefits and harms of CFVAD as DT, compared to OMM for these transplant ineligible patients.

7 Evidence Summary Table

Use of continuous flow mechanical assist circulatory support devices (specifically LVADS) vs. optimal medical management to treat advanced heart failure in patients ineligible for heart transplant										
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**	
Controlled Study										
Estep et al 2015	P1 Prospective, non-randomised multicentre, observational study comparing LVAD support to OMM. Patients followed for up to 2 years 41 hospitals in the USA October 2011 to July 2013	N=200 Advanced heart failure (NYHA functional class IIIB/IV), ambulatory (6MWD<300m), not dependent on intravenous inotropes. Median age 67 years 73% men.	Implantation of HeartMate II LVAD (HMII) as destination therapy (n=97). vs optimal medical management (OMM) (n=103) Participants had 1 HF admission or 2 unscheduled emergency department/ infusion clinic visits in the previous year, plus functional exercise impairment with a baseline 6MWD<300m. HMII: 17 died, 3 received a heart transplant (2	Primary Clinical effectiveness	Alive, on original therapy, with increase in 6 minute walking distance of at least 75m	<u>At 12 months</u> HMII 39/85 (33%), OMM 17/82 (21%), odds ratio (OR) 2.4, 95% confidence interval (CI) 1.2 to 4.8, p = 0.012.	7	Indirect	All subjects have an INTERMACS profile of 4-7. They are not as unwell as the population specified in the PICO below. Study is non-randomised, with treatment based on patient and physician preference. The main reasons that patients gave for choosing OMM instead of LVAD included not wanting major device surgery (40%), not wanting to depend on a machine (26%), and not feeling ill enough (25%). The main reasons for choosing a device were anticipated improvement in survival (85%) and in quality of life (83%). Patients allocated to LVAD support had worse initial heart failure than those who remained on
				Secondary Clinical effectiveness	Survival: (intention-to-treat analysis)	<u>At 12 months</u> HMII 82%, OMM 81%, p = 0.931				
				Secondary Clinical effectiveness	Survival without urgent heart transplantation or delayed device implantation:	<u>At 12 months</u> HMII 80%, OMM 63%, hazard ratio (HR) 1.71, 95% CI 1.07 to 2.73, p = 0.024.				
				Secondary Clinical effectiveness	NYHA functional class	<u>Baseline vs 12months</u> Class I: HMII 0% vs 25%. OMM 0% vs 0%. Class II: HMII 0% vs 52%. OMM 0% vs 29%. Improvement of at least 2 NYHA functional classes: HMII 39/71 (55%), OMM 2/52 (4%) Overall p < 0.001.				

			urgent and 1 elective), and 3 withdrew from the study within 30 days of enrolment before receiving a device, leaving 74 patients with a device at 12 months. OMM: 18 died, 18 received a device at least 1 month after enrolment and 9 patients withdrew from the study before reaching an outcome, leaving 58 patients alive on original OMM therapy at 12 months.	Secondary Clinical effectiveness	6 minute walking distance:	<u>Baseline vs 12months</u> HMII: 187 m vs 263 m, p < 0.001; OMM: 214 m vs 249 m, p = 0.325.			OMM: • NYHA functional class IV: 52% v 25%, p < 0.001; • INTERMACS profile 4: 65% v 34%, p < 0.001. • lower baseline health-related quality of life EQ-5D:50 v 55, p < 0.001. This may overestimate the effect of LVAD compared to OMM. Participants were not required to be ineligible for heart transplantation, and 3 underwent it.
				Secondary Clinical effectiveness	Improvement in EQ-5D	At 12 months, HMII +29 points, OMM +10 points, P < 0.001.			

Use of continuous flow mechanical assist circulatory support devices (specifically LVADS) vs. CFLVAD (HMII) pre-FDA authorisation to treat advanced heart failure in patients ineligible for heart transplant

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Controlled Study									
Jorde et al 2014	P1 Prospective post approval (PA) observational cohort study 61 centres USA All subjects followed up for at least 2 years post implant	n=247 The first 247 consecutive patients, ineligible for transplant (DT) implanted with HMII device post approval (PA) from FDA Implanted between January to September 2010 70% 60 years or older 83% male 75% white 79% NYHA class IV 80% dependent on inotropes INTERMACS profiles (n/%) 1: 12 (5%) 2:104 (42%) 3: 71(29%) 4-7:60 (24%)	CFVAD (HMII)	Primary Clinical effectiveness	Kaplan-Meier Survival	PA (n=247) vs HMII DT (n=133) % patients alive: At 12months: 74%±3% vs 68%± 4% At 24 months: 61%±3% vs 58%±4% (p=0.2081; log rank test) For INTERMACS profiles 4-7 vs 1-3 At 12months: 82%±5% vs 71%±3% At 24 months: 67%±6% vs 59%±4% p=0.179; log rank test	8	Direct	Compared outcomes to historical control group who received HMII for DT (n=133, Slaughter 2009). Outcomes more generalisable than HMII DT trial (Slaughter et al 2009) due to real world setting. High proportion of patients have INTERMACS profiles 1-3 (76%) as opposed to profiles 4-7. EQ5D QoL outcomes reported in a histogram only, with no absolute data (similar improvement to that reported in the DT trial by Slaughter et al 2009). Statistical analysis was performed by the device manufacturer, Thoratec Corporation.
				Secondary Clinical effectiveness	Survival free from stroke and any reoperation at 2 years post implant	PA (n=247) vs HMII DT (n=133) no. (%) 135 (54%) vs 58 (44%), p=0.042			
				Secondary Clinical effectiveness	Survival free of stroke (haemorrhagic or ischaemic), device related infection or pump replacement	PA (n=247) vs HMII DT (n=133) no. (%) At 12 months: 137(58±3%) vs			

						53(42±4%) At 24months: 100(43±3%) vs 31(24±4%) p(log-rank)<0.001			
				Secondary Clinical effectiveness	Median initial LOS	PA (n=247) vs HMII DT (n=133) 21 days vs 27 days			
				Secondary Clinical effectiveness	Functional status 6MWD	6MWD for 19% of PA and 38% of HMII DT trial patients who were able to walk, PA vs HMII DT Baseline: 183±97m vs 182±140m At 2 years: 297±118m vs 372±191m			
				Secondary Clinical effectiveness	QoL – EQ5D components[8]	Scores appeared lower for all 5 dimensions compared to baseline at all follow up times – from 3 months to 2 years			
				Secondary Safety	Adverse events	PA vs HMII DT (% patients, events per patient year) Bleeding requiring packed red blood cells (PRBC): 54%, 0.84 vs 81%, 1.66 Bleeding requiring re-exploration: 13%, 0.09 vs 30%, 0.23 Infection; Local non-device related: 39%, 0.59 vs 49%, 0.76 Sepsis: 19%, 0.18 vs			

[8] including activities, anxiety, mobility, pain and self-care

						41%, 0.38 Device related: 19%, 0.22 vs 35%, 0.47 Cardiac arrhythmia: 37%, 0.40 vs 56%, 0.69 Renal failure: 18%, 0.15 vs 16%, 0.1 Right heart failure requiring inotropes: 18%, 0.16 vs 23%, 0.16 Right heart failure requiring right ventricular assist device (RVAD): 2.4%, 0.02 vs 3.8%, 0.024 Stroke: 11.7%, 0.083 vs 19%, 0.13 Ischaemic stroke: 4.0%, 0.031 vs 8%, 0.06 Haemorrhagic stroke: 7.7%, 0.052 vs 11%, 0.07 Haemolysis: 6.5%, 0.06 vs 3.8%, 0.024 Pump thrombosis: 3.6%, 0.027 vs 3.8%, 0.024 Pump replacement: 4.0%, 0.026 vs 9%, 0.057			

Use of continuous flow mechanical assist circulatory support devices (specifically LVADS) vs. no control (in scope) to treat advanced heart failure in patients ineligible for heart transplant									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Systematic Reviews									
McIlvennan et al 2014	R1 - Systematic review of literature (SR), no meta-analysis Search date 1st Jan 2007-13th Dec 2013 5/52 studies reported results for continuous flow ventricular assist devices (CFVAD) for destination therapy (DT)	n=3463 adult subjects receiving CFVAD as DT[9] (n=1338 from 4 industry funded trials/registries, n=1694 from INTERMACS 2013 multicentre registry and 431from 6 smaller studies)	HeartMate II (HMII) CFVAD as destination therapy (DT) Results reported for DT were from the pivotal HMII DT Trial (HMII CFVAD vs PFVAD as DT, Slaughter et al 2009, n=200). The outcomes reported by Rogers et al (2010) were from the HMII BTT DT Trial Registry	Primary Clinical effectiveness	Survival at 2 years, free of disabling stroke (stroke with a Rankin score>3) or reoperation to replace the device	n=134 no.(%[95%CI]) 62(46% [95%CI 38%-55%])	8	Direct	The SR only reported DT specific outcomes from 2/52 studies included in the literature review. These were from the HMII DT (Slaughter et al 2009) and the HMII BTT DT Trials (Rogers et al 2010). These two studies were too heterogeneous to allow meta-analysis of results. We have reported DT-CFVAD specific outcomes only, as the
				Secondary Clinical effectiveness	Estimated actuarial survival[10]	n=133 At 12months, 68% At 24months, 58%			
				Secondary Clinical effectiveness	KCCQ-OS[11]	Baseline: 27±16 (n=115) At 3months: 63±19 (n=89) At 12months: 66±20 (n=76) At 24months: 70±19 (n=47)			
				Secondary Clinical effectiveness	KCCQ-OS (Rogers et al 2010)	Baseline: 24 (n=318) 3 months: 68 (n=262) 6 months: 72 (n=240) 12 months: 70 (n=203)			

[9] This includes some subjects who are included in the cohort in more than one study (e.g. the initial trial and then included in the longitudinal registry data as well, or single centre reports and again in registry data analyses.

[10] Actuarial survival is the estimated probability that a participant will survive to a specific time set in advance. The actual dates of the survival events are unknown.

[11] Kansas City Cardiomyopathy Questionnaire (KCCQ): a 23-item self-administered questionnaire that assesses specific health domains pertaining to heart failure
From 2014, the questionnaire used by INTERMACS was the KCCQ version 4.0 which used 12 items with a high concordance between the two versions. Both versions yield an overall summary scale (KCCQ-OS) ranging from 0-100. Higher scores are associated with fewer symptoms, better function, and higher QoL. KCCQ-OS is reported to correlate roughly to NYHA functional classes as follows:
class 1~KCC-OS score 75-100
class 2~60-74
class 3~45-59
class 4~0-44 (population of interest in this review)

			study (n=655).			24 months: 74 (n=97)			comparators (BTT or PFVAD) are out of scope of this review. All outcomes reported from this systematic review are from Slaughter et al 2009 unless otherwise stated. Only the primary outcome from Slaughter was reported using intention to treat analysis. The secondary end points were evaluated using an 'as-treated' analysis of data until the use of the device was stopped. This may overstate improvements in outcomes.
				Secondary Clinical effectiveness	MLHFQ[12]	Baseline: 75±18 (n=116) At 3months: 37±22 (n=89) At 12months: 34±22 (n=76) At 24months: 30±22 (n=44)			
				Secondary Clinical effectiveness	MLHFQ (Rogers et al 2010)	Baseline: 75 (n=323) 3 months: 34 (n=258) 6 months: 32 (n=234) 12 months: 32 (n=197) 24 months: 34 (n=90)			
				Secondary Clinical effectiveness	6MWD[13] (metres)	Baseline:182±140m (n=50) At 3months: 319±191m (n=77) At 12months: 318±164m (n=61) At 24months:, 372±191m (n=36)			
				Secondary Clinical effectiveness	6MWD (metres) (Rogers et al 2010)	Baseline: 204±150m (n=129) 6 months: 350±198m (n=199) 24 months: 360±210m (n=75)			
				Secondary Safety	Bleeding	n=133, At 24months (no. (%)) Bleeding requiring packed red blood cells (PRBC): 108 (81%) Bleeding requiring surgery: 40 (30%)			
					Neurological event	n=133, At 24months (no. (%)): Overall Stroke: 24 (18%) of which: Ischaemic 11 (8%) Haemorrhagic			

[12] Minnesota Living with Heart Failure Instrument (MLHFQ). Scores range from 0 to 105. A lower score illustrates a better quality of life
[13] Six minute walk distance (6MWD) is measured in metres.

						15 (11%) Other 29 (22%)			
					Infection	n=133, at 24months, (no. (%)): LVAD related: 47 (35%) Local non-LVAD: 65 (49%) Sepsis: 48 (36%)			
					Device malfunction – thrombosis requiring exchange	n=133, at 24months: 2%			
					Device malfunction-other requiring exchange	n=133, at 24months: 8%			
					Right heart failure – inotropic support required	n=133, at 24months: n=27 (20%)			
					Right heart failure – RVAD required	n=133, at 24months: n=5 (4%)			
					Arrhythmia – VA or other	n=133, at 24months: n=75 (56%)			
					Rehospitalisation at 24months	n=133, at 24months: n=107 (94%)			
Draper et al 2014	S1 - Systematic review and meta-analysis of 17 case-control/ cohort studies, 5 for CFVAD as DT	1839 LVAD patients including 1697 (92%) had CFVAD 416 patients had CFVAD	CFVAD for DT (device not specified)	Secondary (for destination therapy) Safety	Gastro-intestinal bleeding (GIB)	n=416, 91 patients with GIB vs 325 patients without GIB Destination therapy is associated with increased risk of bleeding: OR 1.85 (95%CI 0.80-4.32), I^2=45%[14], p=0.12	7	Direct	Based on data from 5 unspecified studies (out of 17 included). All were retrospective cohort/case-control studies. However, it is not possible to know the size, primary outcome, time period, LVAD type and country for the studies reporting destination therapy outcomes. The conclusion that DT is not a significant increased risk factor for GIB is based on the meta-analysis of 5 poor quality studies and meta-analysis which is unreliable and

[14] The Cochrane Handbook considers I^2 (a measure of inconsistency) =45% represent moderate heterogeneity*.
http://handbook.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm

									uncertain.
Boothroyd et al 2013	R1 Systematic review of literature (SR), no meta-analysis 14 studies published before 15 June 2012 4/14 studies involved patients deemed ineligible for transplant (DT)	1200 transplant-ineligible (DT) patients (and 1900 BTT) Transplant ineligible patients were 10 years older than BTT group (~60 yrs old) Mean LVEF was 15-17% (across BTT & DT patients) 86% of transplant-eligible and 78% of transplant-ineligible patients (all with a HMII device) were on intravenous inotropes at baseline	CFVAD HMII device was implanted in all DT patients	Primary Clinical effectiveness	Survival (based on up to 3 studies: Slaughter et al 2009, Park et al 2012,Kirklin et al 2012a)	30 days: 86-87% (n=414)[15] 1 year: 68-78% (n=817) 18 months: 73% (n=511) 2 years: 58-63% (n=208)	8	Direct	We reported DT specific results only from the 4/14 studies that studied CFVAD for DT. Data was limited to 2 studies per patient type for each outcome (for HMII) apart from survival which was based on up to 3 studies. Not all studies reported outcomes at all time intervals; hence the number of subjects may differ at different time points. Only one of the studies of DT was a controlled study (Slaughter et al (2009) also reported above). Others were retrospective, observational studies. Results based on more than one study were presented as ranges. Pooling of results or meta-analysis was not possible due to limitations of original study design, heterogeneity of study subjects and comparators outside the scope of this review (e.g. BTT and PFVAD).
				Secondary Clinical effectiveness	Recovery (based on INTERMACS 4 only (Kirklin et al 2012a))	30 days: not reported 1 year: 1% (n=740) 18 months: 1% (n=740) 2 years: 1% (n=740)			
				Secondary Clinical effectiveness	Transplantation (based on 2 studies: Slaughter et al 2009 ,Kirklin et al 2012a)	30 days: not reported 1 year: 3% (n=740) 18 months: 4% (n=740) 2 years: 3-13% (n=874)			
				Secondary Clinical effectiveness	NYHA class I or II (based on 2 studies: Slaughter et al 2009, Park et al 2012)	6 months: 80-82% (n=276) 2 years: 80-81% (n=153)			
				Secondary Clinical effectiveness	Mean/median 6MWD (based on 2 studies: Slaughter et al 2009, Park et al 2012)	Baseline: 181-225m (n=150) 6 months:>340m (n=221) 2 years: >340m (n=134)			
				Secondary Clinical effectiveness	Neurocognition (Petrucci et al 2012)	Baseline: n=96 6 months: stable or improved (n=72) 2 years: stable or improved (n=33)			
				Secondary Safety	Adverse events after 19-21 months of use (based on Slaughter et al (2009) and Park et al (2012)	No. of events per 100 patient years (n=414) Bleeding requiring transfusion 113-166 Bleeding requiring			

[15] Proportion (%) of patients who received an implanted device and were discharged from hospital. Not all studies reported survival at 30 days.

						surgery 14-23 Localised non-device related infection 49-76 Septicaemia 27-38 Percutaneous lead infection 22-38 Pump pocket infection 5-9 Arrhythmias: ventricular or requiring cardioversion/ defibrillation 46-69 Right heart failure requiring inotropes 10-14 Right heart failure requiring RVAD 2-3 Ischaemic or embolic stroke 5-6 Haemorrhagic stroke 3-7 Device replacement 2-6			Outcomes were reported using an 'as-treated' analysis of data until the use of the device was stopped. Gaps in information across various time points. Neurocognition results were based on a very small sample of patients from one follow up study.
				Secondary Cost effectiveness	Incremental cost effectiveness ratio (ICER) of HMII LVAD compared with optimal medical treatment	US$198,184/QALY over 5 year time horizon to CAN$123,700/QALY over lifetime			The ICER is not specific to DT only. Time horizon for the US ICER estimate is short. Estimated ICER is based on maximum observation data of 2 years, and simulated data thereafter. Excluded physician fees and out of hospital medication so not generalisable to NHS England commissioning.
Uncontrolled Studies									

Arnold et al 2016	S2 Retrospective, observational cohort study using data from INTERMACS Registry USA	N=1638 adult patients' ineligible for transplant from INTERMACS registry INTERMACS profiles 1-2: 42% 3: 32.2% 19% women Median age 60-69 years Implantation between May 2012-Sept 2013	LVAD (devices not specified)	Primary Clinical effectiveness	Poor outcome (defined as death or KCCQ<45 during 12 months post LVAD)	29.7% poor outcome comprising: • 22.4%(n=367) died before I year • 7.3% (n=101) had persistently poor QoL	8	Direct	Study based on selective, retrospective analysis of registry data with no intention to treat analysis. At 12months, n=1069/1638 were included in the analysis. Excluded were 569 patients: 367 who died before 12 months and 202 (16%) with missing KCCQ follow up data at 12 months. Uncertainty due to statistical accounting used to adjust for the effect of missing data from 569 patients. Reasons for missing baseline KCCQ data are inadequately explained as 'mostly administrative'. Baseline KCCQ was lower for patients with poor outcomes than for survivors with an acceptable KCCQ (KCCQ: 29.8 vs 35.3, p<0.001). Not clear how these results compare to OMM.
				Primary Clinical effectiveness	Factors associated with poor outcome (compared with patients who experienced a good outcome) at 12 months	Higher BMI: 29.3 vs 28.2kg/m^2, p=0.007 Lower haemoglobin: 11.1 vs 11.4g/dL, p=0.005 Previous cardiac surgery: 47.8% vs 39.8%, p=0.004 History of cancer: 13.8% vs 9.7% p=0.025 Severe diabetes mellitus: 15.6% vs 11.5%p=0.038			

Kirklin 2015 (7th INTERMACS Annual Report)	S2 Retrospective cohort study from INTERMACS Registry: 158 hospitals, 154 in USA & 4 in Canada	15,745 adult recipients of mechanical support devices of which 4598 (38%) recipients were for destination therapy n=3243 recipients for DT implanted 2012-2014.	CFVAD including some biventricular (BiVAD) implants	Primary Clinical Effectiveness	Survival for DT	2012-2014 device era: n=3243, 863 deaths % Survival: At 1 year: 76% At 3 years: 57%	8	Direct	We report DT specific outcomes only. Retrospective analysis of contemporary registry data for CFVAD. DT outcomes include an unspecified proportion of continuous flow Bi-ventricular device (BiVAD) implants. Median age and gender of DT recipients not reported.
Grady et al 2015	S2 Retrospective cohort study from INTERMACS registry	N=1470 adults who had CFVAD between 21st January 2010 and 31st March 2012 Mean age 63.4 yrs 82% male 75% white	CFVAD for destination therapy	Primary Clinical Effectiveness	EQ-5D-3L VAS[16] (HRQOL using the VAS score from baseline to 1 year)	Mean Pre-implant vs mean 1 year post implant (mean change) >70 years: 40 vs 77 (+33) 60-69 years: 33 vs 72 (+35) <60 years: 31 vs 70 (+35)	9	Direct	Uncontrolled retrospective study design. Study attempted to examine differences in QoL between three age groups but there were significant differences in baseline characteristics between the three age groups, particularly baseline INTERMACS profile. Incomplete data for every group at baseline and also at 12months for each age group (<60, 60-69, >70years).
				Primary Clinical Effectiveness	Proportion of patients with a >10point improvement in HRQoL	>70 years: 74.3% 60-69 years: 74.9% <60 years: 73.4%			
Fendler et al 2015	S2	N=4419 adults who had LVAD between	CFVAD for destination	Primary	Trailmaking B Test (TMT-B)[17] at 0,3,6,12	Through 12 months post implant, ,	9	Direct	Retrospective cohort study of non-

[16] Health-related quality of life (HRQoL) measured with EuroQoL 5D (EQ-5D); a higher score indicates better quality of life with visual analogue scale ranging from 0= worst imaginable health to 100=best imaginable health state.

[17] Trailmaking B Test (TMT-B) detects several forms of cognitive impairment including subclinical stroke. Meaningful cognitive decline was defined as a clinically important increase during follow up using a moderate Cohens *d* effect size of 0.5xbaseline standard deviation (32seconds).

	Retrospective study from INTERMACS registry	May 2012-December 2013 1173 had cognitive function measured, 349 included in analysis at 12 months post implant <50 yrs: 24% 50-59 yrs: 24% 60-69 yrs:34% >70 yrs: 18% 80% male 41% INTERMACS profiles 1-2 39% profiles 3-7.	therapy (durable therapy)	Clinical Effectiveness	months	unadjusted analysis of 1173 recipients: 21.0% (n=246/349) had meaningful cognitive decline vs 34.5% improved cognitive function vs 44.5% no change in cognition			consecutive patients, no control arm. TMT-B test not validated for this specific population. Large volume of missing data: 2840 out of 4013 eligible patients on the registry had missing cognitive data at baseline or f/up so could not be included in analysis. The proportion of patients who had cognitive decline is uncertain. Only a subset (n=349) of the final cohort (n=1173) had 12month follow up TMT-B score. It is not possible to confirm that cognitive decline did not occur in the remaining 927 subjects at 12 months. Risk of cognitive decline factors of older age and DT are confounded as older age is also a key factor to being unlikely to be listed for transplant. Selective retrospective review of registry data.
				Primary Clinical Effectiveness	Risk of cognitive decline due to a specific risk factor, compared to those without cognitive decline	Adjusted analysis, Destination therapy (HR 1.42, 95% CI 1.05-1.92), p<0.001			
Katz et al 2015	S2 Retrospective study from INTERMACS registry 27 non-transplant	N=176 adults with advanced heart failure ineligible for transplant (+100 listed for transplant)	CFVAD HMII for destination therapy Average duration of HMII as DT: 7.6±6.8months (maximum 31.2months)	Primary Clinical Effectiveness	% patients discharged after implantation	90%	7	Direct	We have reported DT specific results only as the comparator (BTT) is out of scope for this review. Incomplete reporting of 176 DT recipients. At 6 months and 12
				Primary Clinical Effectiveness	30-day mortality	3.4% (6/176 patients) all with baseline INTERMACS profiles 1 and 2			

	mechanical circulatory support centres, USA Data analysis 31 Dec 2012	DT recipients implanted January 2012-September 2012		Primary Clinical Effectiveness	Kaplan-Meier survival rate	At 6 months: 81±3% 12months: 70±5% 24 months: 63±6%			months, the estimated survival outcomes were based on only 86 and 37 live subjects due to limited number of recipients receiving their device 12 months and 6 months earlier, and also any HMII patients who are no longer alive at the analysis time point. At time of analysis, 7 patients originally listed as ineligible for transplant, had undergone transplant (4%). 20% of the DT cohort had INTERMACS profiles 4-7 (not the focus of this review).
				Primary Clinical Effectiveness	Survival rate(%) and number of patients alive (n) by INTERMACS profile	At 6 months (n=86): 1: 63.4±12.0% (7) 2: 82.4±5.7 (28) 3: 81.5±5.1% (37) 4-7: 87.9±6.7% (14) At 12months (n=37): 1: Nil 2: 64.3±8.5%(16) 3: 76.4±5.9%(13) 4-7: 72.6±11.5%(8)			
				Primary Clinical Effectiveness	Median LOS	22.5 days			
				Primary Clinical Effectiveness	Hospital readmission rate (events per patient year)	1.77 events per patient year, (n=108 readmissions reported for n=176)			
				Secondary Safety	Bleeding	Number of patients (%), number of events, events/pt.-yr Bleeding: 75(43%), 161, 1.47 GI: 34(19%), 74, 0.67 Bleeding requiring surgery: 25(14%), 26, 0.24			
				Secondary Safety	Cardiac arrhythmias	Number of patients (%), number of events, events/pt.yr. 24(14%),39,0.36			
				Secondary Safety	Device infection	Number of patients (%), number of events, events/pt.yr. 13(7%),15,0.14			
				Secondary Safety	Stroke	Number of patients (%), number of events, events/pt.yr. Stroke: 11(6%),12,0.11			

						Haemorrhagic: 4(2%), 4, 0.04 Ischaemic: 4(2%), 5, 0.05 Unknown: 3(2%),3, 0.03			
				Secondary Safety	Right heart failure	Number of patients (%), number of events, events/pt. yr. 21(12%),28, 0.26%			
Boyle et al 2014	S2 Retrospective 2 year evaluation of HMII clinical trials	N=956 post implant adult patients who were successfully discharged from hospital 23% women 82% IV inotropes 56% cardiac resynchronisation devices 28% intra-aortic balloon pump n=551 (58%) were ineligible for transplant (DT) At March 2012, all patients had at least 2 year f/up Baseline characteristics were not reported for the DT group.	CFVAD (HMII) implanted as DT prior to January 2010	Primary Safety	<u>Haemorrhagic events</u>	Patients, n (%) Bleeding requiring surgery 21(4%) Bleeding requiring >2 units PRBC 258(47%) GI Bleeding 161(29%) Haemorrhagic stroke 51 (9%) DT (1192 pt-yrs) Events (Event per Patient Year) Bleeding requiring surgery 23(0.02) Bleeding requiring >2 UPRBC 855(0.72) GI Bleeding 417(0.35) Haemorrhagic stroke 53 (0.04)	9	Direct	We report DT specific results only. Incidence of adverse events associated with LVADs is significant but it is unclear if pre-operative characteristics influence the development of post implant haemorrhagic or thrombotic complications. Retrospective analysis of discharged patients only (excluded 173 patients from HMII DT and BTT clinical trials (per trial data not reported).
				Primary Safety	<u>Thrombotic events</u>	Patients, n(%) Ischaemic stroke: 43(8%) Pump thrombosis: 31 (6%) DT (1192 pt-yrs) Events (Event per Patient Year) Ischaemic stroke: 45(0.04) Pump thrombosis: 36(0.03)			

Kirklin et al 2012	S2 INTERMACS Registry study of 5613 registry patients Data analysis at 31 Dec. 2011 104 institutions USA	N=1160 adults with advanced heart failure, ineligible for transplant Recruited June 2006- Dec 2011 Device Implant by year: Pre 2010: n=32 2010: n=508 2011: n=620	CFVAD as destination therapy 1136 CFLVAD 24 CFBiVAD (out of scope of this review) Device not specified	Primary Clinical effectiveness	Kaplan-Meier survival	n=1160 At 12months: 73%	8	Direct	The 1160 CFVAD as DT recipients include 24 patients (2%) who had biventricular CF device support, so are out of scope of this review. 3% of patients went on to have a heart transplant. Incomplete reporting: large proportion of DT-CFVAD recipients were implanted less than 1 and 2 years before data analysis. Absolute numbers and numbers at risk at different time points are not reported. INTERMACS misses about 9.6% patients (due to consent reasons) and also data from patients who receive a device as part of a clinical trial.
				Secondary Safety	% free from device event	n=1160 6months – 99% 12months- 96% 24months- 94%			
				Secondary Safety	Deaths by INTERMACS level (minimum follow up of 2 years)	Deaths 248, (n=1160) Level 3-7: 110 deaths (n=613), Level 2:106 deaths (n=435) Level 1, 32 deaths, (n=112)			
				Secondary Clinical effectiveness	EQ5D (some and extreme) problems with Self Care	n=1160, p<0.0001 Pre:43%, n=287/668 3m 32%, n =129/407 6m 26% n=90/346 12m 25% n=49/186			
					EQ5D (some and extreme) problems with Usual activities	n=1160, p<0.0001 Pre: 81%, n=543/667 3m: 54%, n=220/405 6m: 46%, n=158/347 12m: 44%, n=81/186			
					% survival by risk (high, medium, low)	6m: 83%, 88%, 94% 12m: 77%,81%, 89% 24m: 72%, 65%, 80% p(overall)=0.13 (no significant difference between risk groups) p(low risk v others)=0.06 Risk factors include presence of BiVAD, previous cancer, BMI>32, serum sodium<130, blood urea nitrogen>50.			

					Adverse event rates	At 12 months: n events, rate (rate/100 patient months) TOTAL burden: 3273, 37.56 Bleeding: 1040, 11.94 Infection: 705, 8.09 Cardiac arrhythmia: 339, 3.89 Respiratory failure: 230, 2.64 Neurologic dysfunction: 162, 1.86 Right heart failure: 151, 1.73 Renal dysfunction: 141, 1.62 Device malfunction: 100, 1.15 Psychiatric episode: 78, 0.90 VTE: 56, 0.64 Haemolysis: 55, 0.63 Hepatic dysfunction: 50, 0.57 Wound dehiscence: 19, 0.22 Arterial non-CNS thrombosis: 17, 0.20 Myocardial infarction:3, 0.03			
Cost Effectiveness									
Nunes et al 2016	R1 Systematic review of 11 cost effectiveness studies 2/11 studies were for CFVAD as destination therapy. Rogers et al (2012)	Adults with advanced heart failure LVAD group: HMII DT Trial OMM group: REMATCH patients	CFLVAD (HMII device) as destination therapy	Secondary Cost effectiveness	ICER for CFVAD compared to OMM	CAN$200,166 per QALY US$198,184 per QALY 1.5 QALYs gained for additional cost $297,551 US$167,208 per LYG 1.78 LYG for US$297,551	6	Direct	We report results for CFVAD for DT only. Only 2/11 relevant studies. No meta-analysis possible due to heterogeneity of 11 studies (different generation devices, different treatment strategies). Indirect comparison of

	• Cost utility study from USA payer perspective, lifetime horizon of 60 months, 3% discounting, Thoratec funded (USA) Long et al (2014 • Cost utility study, societal perspective over a lifetime, 3% discounting (USA)								CFLVAD and OMM (Rogers et al 2012) using data from HMII trial and REMATCH study (for OMM). Pseudo-Markov model, with multiway sensitivity analysis. Results highly sensitive to variation in long term survival probabilities, the cost of implantation, cost of readmissions, and the utility attributed to NYHA class I/II health state.
		Adults with inotrope dependent stage D heart failure, ineligible for heart transplant	CFVAD as destination therapy using 'current era' (devices not specified)	Secondary Cost effectiveness	ICER for CFVAD compared to OMM over a lifetime	US$207,670 per QALY taking into account post-operative complications and associated costs. US$102,807 per QALY if total absence of post-operative complications			Decision analytic model that accounted for post-operative complications. Results highly sensitive to younger age, and poorer prognosis with OMM. Based on US data only. Stated societal perspective was not performed and indirect costs were not measured. Lifetime time horizon not defined. Based on INTERMACS registry data.
Neyt 2014	R1 Systematic Literature review (updated	Adults with advanced heart failure LVAD group: HMII	CFVAD (HMII)	Secondary Cost effectiveness	ICER for CFVAD compared to OMM over a lifetime	<u>Cost per QALY (2010 Euros)</u> €107,600 per QALY (95%CI €66,700-181,100)	6	Direct	Only 1 additional relevant study for CFVAD as DT (others were for earlier PFVAD devices,

	Dec 2013) Neyt et 2013 Dutch health care perspective	DT Trial OMM group: REMATCH patients				2.83 QALYs gained for €299,100 additional cost <u>Cost per LYG (2010 Euros)</u> €94,100/LYG (95%CI €59,100-160,100) 3.23 LYG for €299,100 additional cost			Rogers et al was reported by Nunes et al 2016). There is uncertainty about the reliability of the QALYs and LY gained, with higher estimates than reported in Rogers et al 2012 (who also used HMII DT Trial and REMATCH trial for the model). Lifetime horizon is not defined.
Baras Shreibati 2017	P1 Cost utility analysis with lifetime Markov model simulation using costs from Medicare for LVADS implanted LVAD 2009-2010, 3% discount	Ambulatory, non-inotrope dependent patients, ineligible for transplant	LVAD as DT	Secondary Cost effectiveness	ICER for CFVAD compared to OMM over a lifetime	<u>Cost per QALY (</u>2016 US): US$209,400/QALY (1.74 QALYs gained) <u>Cost per LYG (</u>2016 US): US$597,400/LYG Number of readmissions (LVAD vs OMM): 13.03 vs 6.35			Lifetime horizon not defined. Results sensitive to both LVAD readmission rates and Outpatient care costs.

8 Grade of evidence table

Use of Mechanical Circulatory Support Devices (MCSD) (specifically Continuous Flow Left Ventricular Assist Devices (CFVADS) Vs. Optimal Medical Management (OMM) to treat Advanced Heart Failure in patients unsuitable for Heart Transplant[18]					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Survival	McIlvennan et al 2014	8	Direct	A	Survival is the likelihood of being alive at a specified point in time. It was the primary outcome for the majority of studies of mechanical circulatory support devices (MCSD) for heart failure. The most reliable estimate of survival for people with advanced heart failure who are dependent on inotropes and recipients of a continuous flow left ventricular assist devices (CFVAD) as destination therapy (DT) was from the intention to treat analysis (ITT[19]) of observed events by Jorde et al 2014 which followed up all 247 CFVAD recipients as DT for at least 2 years. They showed that 74% and 61% of patients were alive at 12 and 24 months respectively. Survival was slightly lower in patients who had baseline INTERMACS profiles 1-3 (71% and 59% at 12 and 24 months respectively). This is consistent with the most recent estimated probability of survival analysis from the INTERMACS registry report (Kirklin et al 2015) of CFVAD DT recipients implanted between 2012 and 2014. This reports actuarial survival at one and three years of 76% and 57% respectively. Compared to OMM, where only 20% of people with NYHA class IV end-stage heart failure, dependent on continuous IV inotropes and ineligible for transplant are likely to be alive at one year, CFVAD implantation offers a significant improvement in survival. There are no controlled studies which directly compare survival for CFVAD as DT compared to OMM for people with advanced heart
	Boothroyd et al 2013	8	Direct		
	Estep et al 2015 ITT analysis	7	Indirect		
	Jorde et al 2014	8	Direct		
	Kirklin et al 2015	8	Direct		
	Katz et al 2015	7	Direct		
	Kirklin et al 2012	8	Direct		

[18] This evidence review found no controlled studies which reported the outcomes for continuous flow left ventricular assist devices (CFVAD) compared to optimal medical therapy (OMM) in patients ineligible for transplant and dependent on inotropes who were implanted with a CFVAD as destination therapy.
As none of the studies directly matched the population, intervention and comparators specified in the literature search terms in section 9, this grade of evidence table reports the most reliable evidence for each outcome from all the available studies, and does not distinguish between comparators. This is because these were all out of scope (or because the study design had no control group) or because the study population did not match.

[19] Intention to treat (ITT) analysis includes every subject recruited to a clinical trial according to treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. It most closely resembles the likely outcomes that might be reproduced in real life clinical practice.

					failure who are dependent on inotropes. Actuarial survival rates should be treated with caution as they estimate the probability of survival beyond the time period for which there are observed events.
Survival by INTERMACS profile	Katz et al 2015	7	Direct	B	This is the proportion of people who are alive at a specified time, categorised by the baseline severity of their heart failure. Survival at 12 months (37 patients included in the analysis) INTERMACS profile 1: No survivors available for analysis INTERMACS profile 2: 64.3±8.5%(n=16) INTERMACS profile 3: 76.4±5.9%(n=13) INTERMACS profiles 4-7: 72.6±11.5%(n=8) There is a weak suggestion that at 12 months post device implant, there was a greater likelihood of being alive after CFVAD implantation as DT in people with less severe advanced heart failure (INTERMACS profiles 3 to 7). It may be appropriate for further research to consider if patients with the most severe heart failure will benefit from CFVAD as DT. This was based on weak evidence from a single, small, uncontrolled study of 176 subjects, only 37 subjects were included in the analysis at 12 months and the results should be treated with great caution. The survival benefit and the adverse events associated with device implant need to be considered alongside the survival with OMM alone.
Death by INTERMACS level	Kirklin et al 2012	8	Direct	B	This is number of deaths recorded for each baseline INTERMACS profile. Deaths. There were 248 deaths reported out of 1160 CFVAD recipients. INTERMACS profile 1, n=112, deaths 32 (28.6%) INTERMACS profile 2: n=435, deaths =106 (24.4%) INTERMACS profiles 3-7: n=613, deaths 110 (17.9%) This indicates that the proportion of CFVAD recipients who died was smaller in those people who had less severe advanced heart failure (INTERMACS profile 3-7) (no p-value reported). This was based on actuarial survival which should be treated with caution as it estimates the probability of survival beyond the time period for which there are observed events. The data are from a single, large, uncontrolled registry study.
30 day mortality	Katz et al 2015	7	Direct	B	30-day mortality is the likelihood of dying within 30 days of the CFVAD implantation operation. Six out of the 176 CFVAD recipients died within 30 days. This equated to 3.4%. All of the six deaths occurred in people with baseline INTERMACS profiles 1 or 2.

					For people with very severe advanced heart failure (INTERMACS profiles 1 and 2 in particular), the chances of surviving and recovering from the implantation procedure needs to be carefully considered as this, combined with the lower likelihood of survival at 12 months indicates that the benefit of CFVAD implantation may be limited for these recipients. This was based on weak evidence from a single, small, uncontrolled study of 176 subjects all treated at a 'non-transplant' centre. The results may not be generalisable to the UK and should be treated with caution.
% patients discharged after implantation	Katz et al 2015	7	Direct	B	The proportion of CFVAD recipients who were successfully discharged from hospital post implantation surgery was 90%. This means that 10% of patients did not survive the implantation procedure or peri-operative period. Although specific reasons for lack of discharge were not described, careful consideration about patient selection needs to be made in order to achieve the best survival outcomes reported in the clinical trials. This was based on weak evidence from a single, small, uncontrolled study of 176 subjects all treated at a 'non-transplant' centre in the USA. The results may not be generalisable to the UK and should be treated with caution.
% free from device event	Kirklin et al 2012	8	Direct	B	This is the proportion of the 1160 CFVAD recipients who were free from having a 'device event' at a specified point in time. A device event could include malfunction of the device, pump replacement, device related infection. During the 2 year period after implant, there were an estimated 33 device events across the 1160 CF device recipients. The proportions who were free of a device event were 99%, 96% and 94% at 6 months, 12 months and 24 months respectively. This indicates that the proportion of CFVAD recipients who will have a device related event is initially low but there is a small increase in these events as the duration of living with the device increases. This was based on actuarial survival which should be treated with caution as it estimates the probability of survival and adverse events beyond the time period for which there are observed events. The data are from a single, large, uncontrolled registry study.
Alive on original therapy with an increase in 6MWD of at least 75m	Estep et al 2015	7	Indirect	C	This was a novel composite measure which combined both survival and physical function using the six minute walk distance. The number and proportion of CFVAD recipients who were alive and who could walk an additional 75m compared to baseline was reported.

					At 12 months after implantation, 39 out of 85 HMII device recipients were alive and were able to walk an additional 75m compared to 17 out of 82 patients receiving OMM only. We are 95% confident that HMII recipients are between 1.2 and 4.8 times more likely to achieve this outcome. This study suggests that people with baseline INTERMACS profiles 4-7 are more likely to achieve this outcome than those on OMM. However, less than half of HMII recipients achieved the outcome at 12months, and this result was for people who were already ambulatory before implantation. These results are not generalisable to the population of interest in this review (advanced heart failure, dependent on intravenous (IV) inotropes) as the ROADMAP trial only included ambulatory patients and nearly half of the HMII subjects (n=47) were out of scope (NYHA class IIIB). Although the study recruited 200 subjects, results were only reported for 167, which may produce optimistic results compared to a full ITT analysis. This unique, composite outcome has not been used in any other study rendering any comparison impossible.
Survival free from stroke/any reoperation at 2 years post implant	Jorde et al 2014	8	Direct	B	This is the number and proportion of patients who have had a HMII implant who are alive and have not experienced a stroke or any reoperation 2 years after the HMII implantation. It was measured in a post approval study (PA) and compared the outcome to that reported in the original HMII DT Trial by Slaughter et al in 2009. At 2 years post HMII implant, 54% (135/247) recipients of a HMII device were alive and free from stroke/reoperation compared with 44% (58/133) which was reported in the pre-approval pivotal HMII DT Trial. This showed that in a real life clinical practice setting, that the results of HMII implantation were statistically significantly better (p=0.042) than in the DT Trial. This was a well-conducted, prospective, multicentre study of the first 247 consecutive recipients of HMII in the USA. All device recipients were followed up for at least two years. Although this was a USA study, the post approval nature of the study design means that the results may be generalisable to a clinical practice setting. We note that one employee of the device manufacturer was a study author.

Poor Outcome: Survival and QoL composite measure (KCCQ)	Arnold et al 2016	8	Direct	B	Poor outcome was defined in this study as death or a poor quality of life (KCCQ score less than 45). This was a composite measure specific to this study. 468 (29.7%) of the 1638 CFVAD recipients included in the analysis had a poor outcome during the 12months after device implementation. Of these, 367 (22.4%) died before the end of the 12months, and 101 (7.3%) patients had persistently poor QoL (KCCQ score below 45). Without a direct comparator study, it is not clear how this compares to patients who receive OMM only. Regardless, a substantial proportion of CFVAD recipients who were successfully discharged from hospital experienced a poor outcome during the first 12 months after implantation. These results should be treated with caution. This was based on a single, large, observational, uncontrolled registry study with significant selection bias. The INTERMACS registry excludes patients who died before discharge. Inclusion of these subjects in this analysis may result in a larger number and proportion of patients reported as having a poor outcome. In addition, follow up KCCQ data from 202 (16%) subjects initially selected for inclusion into this study was missing at 12 months. This may further understate the number of poor outcomes. The lack of ITT analysis introduces significant uncertainty about the results.
Attainment of NYHA 1 or II	Boothroyd et al 2013	8	Direct	A	This is a measure of symptom improvement from NYHA functional class IV to NYHA I or II. It represents an improvement in symptoms from being almost bedbound and unable to walk to experiencing only mild symptoms with limited or no symptoms during ordinary physical activity (walking, climbing stairs). The most reliable results for the population of interest in this review are reported as a range (due to data from more than one study which was too heterogeneous to be pooled). At 6 months after HMII device implantation, 80-82% of subjects had achieved NYHA I/II. This proportion was similar (80-81%) at 2 years after device implant (Boothroyd et al 2013). There is weak evidence that a large proportion of HMII recipients who are alive at 6 months and at 2 years achieve NYHA class I or II, from an initial NYHA IV health state. These results should be treated with caution as the two studies that they were based on were relatively small; one was controlled, but against an out of scope device (PFVAD); the other was uncontrolled. Results were based on observation of the 'as treated' population with no ITT analysis.
	Estep et al 2015	7	Indirect		

Physical Function (Mobility 6MWD)	McIlvennan et al 2014	8	Direct	A	This is a measure of physical function using the six-minute walk distance test (6MWD). This is usually performed on a treadmill, and the distance in metres that the patient can walk during 6 minutes is measured. 19% of HMII recipients were able to complete a 6MWD test. Before HMII implant, the mean baseline 6MWD was 183±97m. Two years post implant, this had increased to 297±118m (Jorde et al 2014). It is not clear how much extra distance is a meaningful in a real-life setting. An extra 114m may be a highly important difference if the person is initially unable to walk. If the initial distance is 183m, then it is unclear how this translates to being able to perform activities of daily living. This result should be treated with caution as it includes only a small subset of the recruited study population (n=247) who were initially ambulatory. Although the study was a prospective post approval study, there is no comparative data for 6MWD for patients treated with OMM.
	Boothroyd et al 2013	8	Direct		
	Estep et al 2015	7	Indirect		
	Jorde et al 2014	8	Direct		
Cognitive function	Boothroyd et al 2013	8	Direct	A	Cognitive function post LVAD was measured using the Trailmaking Test, part B (TMT-B). It is a validated measure of cognitive dysfunction, specific for executive dysfunction, attention/concentration, working memory, problem solving and frontal lobe injury as well as overall cognitive function. A longer time to complete the task indicates a worse score and poorer cognition. At 12 months, 246/1173 (21%) CFVAD recipients had meaningful cognitive decline, 34.5% had improved cognitive function and 44.5% had no change in cognition. We are 95% confident that HMII recipients are between 1.05 and 1.92 times more likely to experience cognitive decline. It is not clear how these results translate to activities of daily living and ability to live independently. There is significant selection bias in this single, retrospective, observational study which was based on a subset of the INTERMACS registry. It excluded a large proportion of device recipients who did not survive and who did not have baseline cognitive function scores recorded n=2840). The results should be treated with caution.
	Fendler et al 2015	9	Direct		
Survival free of stroke, device related infection or pump replacement	Jorde et al 2014	8	Direct	B	This is the number and proportion of patients who have had a HMII implant who are alive and have not experienced a stroke, a device related infection or pump replacement 2 years after the HMII implantation. It was measured in a post approval study (PA) which compared the outcome to that reported in the original HMII DT Trial

					by Slaughter et al in 2009. At 12 months post implant, 58%±3% of recipients of a HMII device were alive and free from stroke, infection or pump replacement. At 24 months post implant, the proportion of people who were survival free of stroke/infection and pump replacement had reduced to 43%±3%. This showed that in a real life clinical practice setting, that the results of HMII implantation were statistically significantly better (p=0.0001) than in the HMII DT Trial. This composite measure suggests that approximately half of patients with HMII device have increased survival and the absence of specific adverse events. This was a well-conducted, prospective, observational, multicentre study of consecutive recipients of HMII in the USA. However, because the outcome is unique, and there is no OMM control, we do not know how this compares to people treated with OMM or to outcomes reported in other studies. We noted that bleeding after discharge from hospital (a common, major adverse event) was excluded from the composite outcome).
Quality of Life (KCCQ)	McIlvennan et al 2014	8	Direct	B	The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23 (or 12) item self-administered questionnaire that assesses specific health domains pertaining to heart failure. Both versions yield an overall summary scale (KCCQ-OS) ranging from 0-100. Higher scores are associated with fewer symptoms, better function, and higher QoL. KCCQ was reported in 2 studies in the systematic review. Rogers et al (2010) reported that at baseline the mean KCCQ was 24 for 318 HMII recipients (equivalent to NYHA class IV). By 3 months post implant, the KCCQ score had increased to 68 with similar scores at 12 months (KCCQ 70) and 24 months (KCCQ 74). It seems that the KCCQ scores improved significantly post HMII implant and that this effect was consistently sustained through to 2 years after HMII implant. The improvement in mean KCCQ score from 24 to 74 or better equated to a change in NYHA class IV to class II. This result should be treated with caution. There was no (relevant) control so the comparison with those on OMM remains unknown. The number of HMII recipients exposed to HMII therapy diminished as time progressed with data from only 97 patients at 24 months compared to 318 at baseline.

Quality of Life (Improvement in EQ-5D)	Estep et al 2015	7	Indirect	A	The EQ5D is a measure of quality of life based on 5 dimensions: activities, anxiety, mobility, pain and self-care. A higher score indicates a better quality of life with a visual acuity scale ranging from 0 (worst imaginable health) to 100 (best imaginable health). Across all three age groups (>70 years, 60-69 years and <60 years) there was a mean improvement of between 33 and 35 points between baseline and 12 months post implant. The mean 33-35 point change is significant and given the five dimensions of the EQ5D, this is likely to lead to practical and functional improvements. However, these results were based on retrospective, observational data from the INTERMACS registry and may not be generalisable as the registry excludes some patients, including those that did not survive implantation, those taking part in clinical trials and those that did not have baseline EQ5D scores recorded. The results should be treated with caution.
	Jorde et al 2014	8	Direct		
	Grady et al 2015	9	Direct		
EQ-5D problems with self-care	Kirklin et al 2012	8	Direct	B	This is the proportion and number of 1160 CFVAD recipients with some or extreme self-care problems at a specified point in time after device implantation. Pre-implantation, 287 out of 668 (43%) people had difficulties with self-care. This was reduced to 32%, 26 % and 25% at 3 months, 6 month and 12 months post device implant. This indicates that in real life clinical practice (as suggested by inclusion into the INTERMACS registry), there is a meaningful reduction in problems with self-care, and that this is sustained throughout 3 months to 12 months post implant period. This was based on a single, large, observational, uncontrolled registry study with significant selection bias. The registry is not an ITT analysis as it excludes patients who died before discharge. In addition, there were significantly fewer patients included in the analysis at 12 months compared to baseline. This may understate the complications associated with receiving a CFVAD.
EQ-5D problems with usual activities	Kirklin et al 2012	8	Direct	B	This is the proportion and number of 1160 CFVAD recipients with problems with usual activities at a specified point in time after device implantation. Pre-implantation, 543 out of 667 (81%) people had difficulties with usual activities. This was reduced to 54%, 46% and 44% at 3 months, 6 months and 12 months post device implant.

					This indicates that in real life clinical practice (as suggested by inclusion into the INTERMACS registry), there is a meaningful reduction in problems with performing usual activities, and that this is sustained throughout the 3 months to 12 months post implant period. This was based on a single, large, observational, uncontrolled registry study with significant selection bias. The registry is not an ITT analysis as it excludes patients who died before discharge. In addition, there were significantly fewer patients included in the analysis at 12 months compared to baseline. This may understate the complications associated with receiving a CFVAD.
Quality of Life (MLHFQ)	McIlvennan et al 2014	8	Direct	A	The Minnesota Living with Heart Failure Instrument (MLHFQ) is a measure of quality of life and was used for the HMII as destination therapy clinical trials by Slaughter et al 2009 and Rogers et al 2010 (reported in McIlvennan et al 2014). Scores range from 0 to 105. A lower score illustrates a better quality of life. The larger of these two studies reported a baseline MLHFQ score of 75 in 323 HMII recipients. The MLHFQ score was reduced to 34 or less for all time points between 3 months and 24months. This indicates that in a formal clinical trial setting, there is a meaningful improvement in MLHFQ and that in patients who survive, the improvement in QoL is sustained throughout the 3 months to 24 months post implant period. This was based on observed data from one arm of a non-randomised controlled trial. There was no ITT analysis. In addition, there were significantly fewer patients included in the analysis at 24 months (n=90) compared to baseline (n=323). This may overstate the benefit of HMII device on quality of life as it is likely that the missing data is due to censorship (crossover to heart transplant, death or device explantation)) or due to the patients being too unwell to participate in the study data collection.
	Boothroyd et al 2013	8	Direct		
Length of stay	Katz et al 2015	7	Direct	B	The median length of stay in hospital after implantation with a HMII device was 22.5 days. This indicates that the procedure costs of implantation are likely to be significant, in addition to the device cost and longer term health care still required. This was based on one, small, retrospective, observed registry study of 176 HMII recipients as destination therapy. We do not know how this compares with similar patients who receive OMM and the number of days they need to be in hospital for symptom management.

Adverse events					
Bleeding	McIlvennan et al 2014	8	Direct	A	Bleeding was the most commonly reported adverse event. The most relevant study of bleeding was from Jorde et al (2014) who followed up all 247 HMII recipients for at least 2 years after implantation. (Boyle et al (2014) included only post discharge patients, which may lead to incomplete reporting of adverse events). After two years follow up, 54% of the 247 HMII recipients experienced bleeding sufficient to require a blood transfusion. 13% of the HMII recipients required readmission to hospital and further surgical re-exploration. A significant proportion of HMII recipients experienced at least one severe bleeding adverse event (sufficient to require surgical exploration or a blood transfusion) during months 0-24 post implant. . Health care resources are likely to be required to manage these events. This was a well-conducted, prospective, observational, multicentre study of consecutive recipients of HMII in the USA. However, because there is no OMM control, there remains uncertainty about how this compares to people treated with OMM.
	Draper et al 2014	7	Direct		
	Boothroyd et al 2013	8	Direct		
	Jorde et al 2014	8	Direct		
	Katz et al 2015	7	Direct		
	Boyle et al 2014	9	Direct		
	Kirklin et al 2012	8	Direct		
Neurological event (Stroke)	McIlvennan et al 2014	8	Direct	A	Neurological events are commonly reported adverse events. They include stroke, often differentiated between ischaemic and haemorrhagic stroke. It was reported as the proportion of patients who had a stroke, and as the number of events per patient year. The most reliable study which reported neurological events was the post approval, prospective observational study (n=247) (Jorde et al 2014). (Boyle et al (2014) included only post discharge patients, which may lead to incomplete reporting of adverse events). At 2 years post implantation, 11.7% of HMII recipients had experienced a stroke (0.083 strokes per patient year). There were more haemorrhagic strokes (7.7%, 0.052 events per patient year) than ischaemic strokes (4.0%, 0.031 events per patient year). The chance of having a stroke is not insignificant. There is no information about the severity of stroke, or about the proportion of people who had a stroke who recovered. This was a well-conducted, prospective, observational, multicentre study of consecutive recipients of HMII in the USA. However, there is no OMM control arm and we do not know how this compares to people treated with OMM.
	Boothroyd et al 2013	8	Direct		
	Jorde et al 2014	8	Direct		
	Katz et al 2015	7	Direct		
	Boyle et al 2014	9	Direct		
Neurological dysfunction	Kirklin et al 2012	8	Direct	B	This is the number and the rate (expressed as rate per 100 patient months) of neurological dysfunction at 12 months after device implantation for the 1160 CFVAD recipients.

					Neurological dysfunction was reported in 162 patients out of 1160 CFVAD recipients. This equated to a rate of 1.86 events per 100 patient months. It is not clear how to interpret this data as the study does not define 'neurological dysfunction', no other studies report this outcome and we do not know if patients treated with OMM experience these events. This result should be treated with caution. This was based on a large, multicentre, registry study with significant selection bias due to incomplete reporting. The majority (n=620) of the 1160 subjects did not have one full year of observed follow up as they received their device less than one year before the data analysis. The registry also misses approximately 9.6% of patients due to consent reasons as well as those in a current clinical trial. In addition, the cohort of patients also included 24 patients who received a bi-ventricular CFVADs as DT. Their results are not reported separately.
Infection	McIlvennan et al 2014	8	Direct	A	Infections are a commonly reported adverse event for recipients of HMII devices as DT. They are usually categorised as local non-device related infections, device related infections and sepsis. It was reported as the proportion of patients who had an infection and the number of events per patient year. The most reliable study which reported infection events was the post approval, prospective observational study (n=247) (Jorde et al 2014). At 2 years post implantation, 39% of HMII recipients had experienced a local non-device related infection (0.59 infections per patient year), 19% had had a device related infection (0.22 infections per patient year) and 19% had had sepsis (0.18 infections per patient year). The chance of having an infection is high although we do not know the severity of the infections or the consequences of these reported adverse events (such as explantation or hospitalisation. This was a well-conducted, prospective, observational, multicentre study of 247 consecutive HMII recipients in the USA. However, there is no OMM control arm and we do not know how this compares to people treated with OMM.
	Boothroyd et al 2013	8	Direct		
	Jorde et al 2014	8	Direct		
	Katz et al 2015	7	Direct		
	Kirklin et al 2012	8	Direct		
Wound dehiscence	Kirklin et al 2012	8	Direct	B	Wound dehiscence is the number and the rate (expressed as rate per 100 patient months) with wound breakdown 12 months after device implantation for the 1160 CFVAD recipients. Wound dehiscence was reported in 19 patients out of 1160 CFVAD recipients. This equated to a rate of 0.22 per 100 patient months. It is not clear how to interpret this data as although wound dehiscence is associated with infection, it is a specific event and

					prevents comparison or pooling of the result with other studies. This result should be treated with caution. This was based on a large, multicentre, registry study with significant selection bias due to incomplete reporting. The majority (n=620) of the 1160 subjects did not have one full year of observed follow up as they received their device less than one year before the data analysis. The registry also misses approximately 9.6% of patients due to consent reasons as well as those in a current clinical trial. The cohort of patients also included 24 patients who received a bi-ventricular CFVADs as DT. Their results are not reported separately.
Device Malfunction – thrombosis requiring exchange	McIlvennan et al 2014	8	Direct	A	This occurs when there is clotting of blood cells in the device which requires device exchange in order for the pump to work effectively and to avoid dislodged clots causing serious harm (e.g. stroke, pulmonary embolism). It requires explantation of the implanted device, and implantation of new device. (Boyle et al (2014) included only post discharge patients, which may lead to incomplete reporting of adverse events). After two years follow up, 3.6% (0.027 events per patient year) of 247 HMII recipients experienced device related thrombosis which required exchange (Jorde et al 2014). This is a highly undesirable and serious adverse event as device exchange requires significant resource (both financially and in terms of bed days) as well as exposing the recipient to significant post-operative risk and 30 day mortality. People treated with OMM would not be exposed to this risk. This was a well-conducted, prospective, observational, multicentre study of 247 consecutive recipients of HMII in the USA, and is generalisable to a UK setting.
	Boothroyd et al 2013	8	Direct		
	Jorde et al 2014	8	Direct		
	Boyle et al 2014	9	Direct		
Device malfunction – other requiring exchange	McIlvennan et al 2014	8	Direct	A	Device Malfunction is a serious adverse event as it requires explantation of the implanted device, and implantation of new device. (Boyle et al (2014) included only post discharge patients, which may lead to incomplete reporting of adverse events). After two years follow up, 4% (0.026 events per patient year) of HMII recipients experienced device malfunction which required exchange (Jorde et al 2014) This is a highly undesirable and serious adverse event as device exchange requires significant resource (both financially and in terms of bed days) as well as exposing the recipient to significant post-operative risk. People treated with OMM would not be exposed to this risk. This was a well-conducted, prospective, observational, multicentre study of 247 consecutive recipients of HMII in the USA, and is
	Boothroyd et al 2013	8	Direct		
	Jorde et al 2014	8	Direct		

					generalisable to a UK setting.
Right Heart failure- inotropic support	McIlvennan et al 2014	8	Direct	A	A known consequence of left ventricular circulatory support is the development of right ventricular heart failure. This may require inotropic support. It was reported as the proportion of patients who had right heart failure requiring inotropic support and the number of events per patient year. The most reliable study which reported this adverse event was the post approval, prospective observational study (n=247) (Jorde et al 2014). At 2 years post implantation, 18% of HMII recipients had experienced right heart failure requiring inotropic therapy. This equated to 0.16 new events per patient year), Although the development of RHF is not the most common adverse event, it is a serious adverse event which affects the ability of the patient to benefit from the LVAD, and may eventually lead to implantation of another device, if the response to inotropes is insufficient. This was a well-conducted, prospective, observational, multicentre study of consecutive recipients of HMII in the USA. However, there is no OMM control arm and we do not know if people treated with OMM also develop right heart failure requiring treatment.
	Boothroyd et al 2013	8	Direct		
	Jorde et al 2014	8	Direct		
	Katz et al 2015	7	Direct		
	Kirklin et al 2012	8	Direct		
Right heart failure (RHF) – Right ventricular assist device (RVAD)	McIlvennan et al 2014	8	Direct	A	The post approval study of 247 HMII recipients reported cases of right heart failure which required the implantation of a right ventricular assist device (RVAD) (Jorde et al 2014). The number and the rate (expressed as rate per 100 patient months) who had RHF and subsequent RVAD within the 12month period after device implantation is reported for CFVAD recipients. After two years follow up, 2.4% (0.02 events per patient year) of HMII recipients developed right heart failure which required RVAD implantation. The development of RHF following left ventricular assist device implantation is a known consequence of this intervention. The implantation of a RVAD is used in patients with more severe symptoms who do not respond to inotropes. This has significant resource requirements and exposes the individual to major additional risks associated with surgery. This result should be treated with caution. Patients treated with OMM are not exposed to this adverse event. This was a well-conducted, prospective, observational, multicentre study of 247 consecutive recipients of HMII in the USA, and the incidence of this adverse event is likely to be generalisable to a UK setting.
	Boothroyd et al 2013	8	Direct		
	Jorde et al 2014	8	Direct		
Arrhythmia- VA or other	McIlvennan et al 2014	8	Direct	A	Arrhythmia is a disturbance to the heart's usual rhythm. Ventricular arrhythmias can cause severe symptoms and may be fatal. Cardiac

	Boothroyd et al 2013	8	Direct		arrhythmia events observed after implant are reported as the proportion of patients who experienced the event and the rate (expressed as event rate per patient year). After two years follow up, 37% (0.4 events per patient year) of HMII recipients developed cardiac arrhythmias which required cardioverter defibrillation (Jorde et al 2014). The development of arrhythmia post device implant in over one third of device recipients is a serious adverse event which may require further treatment (such as medication or an implantable cardioverter defibrillator). This result should be treated with caution. We do not know what proportion of patients treated with OMM experience cardiac arrhythmia. This was a well-conducted, prospective, observational, multicentre study of 247 consecutive recipients of HMII in the USA, and the incidence of this adverse event is likely to be generalisable to a UK setting.
	Jorde et al 2014	8	Direct		
	Katz et al 2015	7	Direct		
	Kirklin et al 2012	8	Direct		
Renal failure	Jorde et al 2014	8	Direct	A	Renal failure/dysfunction occurs when the kidneys no longer work effectively to filter and clean blood, causing unsafe levels of waste products to build up and without treatment, this can cause death. After two years follow up, 18% (0.15 events per patient year) of HMII recipients developed renal failure (Jorde et al 2014). The development of renal dysfunction post device implant is a serious adverse event which requires treatment of the cause (e.g. medicines for high or low blood pressure) and dialysis for a short time. If untreated, chronic renal failure can lead to end stage kidney diseases, requiring dialysis and eventually a kidney transplant. This result should be treated with caution. We do not know what proportion of patients treated with OMM experience renal failure. This was a well-conducted, prospective, controlled, multicentre study of 247 consecutive recipients of HMII in the USA, and the incidence of this adverse event is likely to be generalisable to a UK setting.
	Kirklin et al 2012	8	Direct		
Haemolysis	Jorde et al 2014	8	Direct	A	Haemolysis is premature damage and destruction of red blood cells due to the mechanical action of the implanted ventricular assist device. After two years follow up, 6.5% (0.06 events per patient year) of HMII recipients developed haemolysis (Jorde et al 2014). This result should be treated with caution. This was a well-conducted, prospective, controlled, multicentre study of 247 consecutive recipients of HMII as DT in the USA, and the incidence of this adverse event is likely to be generalisable to a UK setting.
	Kirklin et al 2012	8	Direct		

Adverse Events - Other	Kirklin et al 2012	8	Direct	B	The most commonly reported adverse events were bleeding, infection, cardiac arrhythmia and respiratory failure. Additional adverse events rates during the first 12 months after implant, were reported as n (number of events), rate (events per 100 patient months). Respiratory failure 230, 2.64 Psychiatric episode 78, 0.90 Venous Thromboembolism 56, 0.64 Hepatic dysfunction 50, 0.50 Arterial non- CNS thrombosis 17, 0.20 Of note, there were 3273 adverse events experienced by 1160 CFVAD recipients during the first year post implant. The total burden of adverse events is significant, with consequences for individuals, and also for health care resources (financial, bed days, waiting list). These specific adverse event measures were not reported in other studies, and because of the variation in currency, it is not possible to compare outcomes with other studies. This result should be treated with caution. This was based on a large, multicentre, registry study with significant selection bias due to incomplete reporting. The majority (n=620) of the 1160 subjects did not have one full year of observed follow up as they received their device less than one year before the data analysis. The registry also misses approximately 9.6% of patients due to consent reasons as well as those in a current clinical trial. In addition, the cohort of patients also included 24 patients who received a bi-ventricular CFVADs as DT. Their results are not reported separately.
Re-hospitalisation	Katz et al 2015	7	Direct	B	The hospital readmission rate was 1.77 events per patient year, for recipients of devices as DT, highlighting that complications associated with an implanted CFVAD commonly require readmission. The most common reasons for readmission were bleeding including gastrointestinal bleeding, infection and neurological events. Rehospitalisation is an important indicator of severity of an adverse event, and contributes significantly to the overall costs associated with survival with a CFVAD. This was based on one, small, retrospective, observed registry study of 176 HMII recipients as destination therapy. We do not know how this compares with similar patients who receive OMM.

Cost effectiveness	Boothroyd et al 2013	8	Direct	B	Cost effectiveness is expressed as the incremental cost effectiveness ratio (ICER) for a treatment (CFVAD) against a comparator (OMM). The ICER is a composite measure of both the life years gained with each treatment and the quality of life for those years. Typically, the National Institute for Health and Care Excellence (NICE) considers an ICER of less than £30,000 per QALY to be cost effective and affordable. The estimated incremental cost effectiveness ratio over the projected lifetime (5 years) ranges from £91,299 to £162,388 [20]per quality adjusted life year (QALY). None of the modelled ICER estimates were more reliable than any other. The ICER range reflected a wide range of assumptions about the likely QALYs gained (1.5 to 2.83). This arose because the models were based on studies with a maximum follow up of two years, and assumptions were made about the additional life years and the quality of life for the remaining duration. The incidence of adverse events reduces the quality of the life years gained and increases the ICER. These results should be treated with caution. The studies used as the basis of the models were observational studies with no OMM comparator. In addition, the modelling of life years gained, adverse events and quality of life beyond the trial period introduces significant uncertainty. None of the cost effectiveness models were based in a UK setting and the results may not be generalisable to the NHS in England: the ICER (from an NHS payer perspective) may be different to Canada and the Netherlands, even though these most closely align with the NHS health care system. Despite the uncertainty about the ICER for CFVAD as DT, even the most optimistic estimate is 3 times higher than that usually accepted by NICE.
	Nunes et al 2016	6	Direct		
	Neyt et al 2014	6	Direct		
	Baras Shreibati et al 2017	6	Indirect		

[20] Based on conversion of euros and US dollars to GBP using currency exchange rates on 27 April 2017

9 Literature Search Terms

Search strategy Indicate all terms used in the search	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients with chronic end-stage heart failure (New York Heart Association Class IV end-stage left ventricular failure for at least 90 days with a life expectancy of less than 2 years), who are not candidates for heart transplantation, and meet all of the following conditions: • The patient's Class IV heart failure symptoms have failed to respond to optimal medical management, including dietary salt restriction, diuretics, digitalis, beta-blockers, and ACE inhibitors (if tolerated) for at least 60 of the last 90 days; • The patient has a left ventricular ejection fraction (LVEF) < 25%;and • The patient has demonstrated functional limitation with a peak oxygen consumption of < 12 ml/kg/min; or the patient has a continued need for intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion.
I – Intervention Which intervention, treatment or approach should be used?	Mechanical circulatory support devices for circulatory failure, specifically left ventricular assist devices such as HeartMate 2, Ventracor VentrAssist, HeartWare HVAD, Jarvik 2000 or sometimes called FlowMaker, MicroMed DeBakey, subsequently re-branded as ReliantHeart HeartAssist 5, Berlin Incor, Terumo DuraHeart, EvaHeart, any other LVAD devices reported.
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Best supportive medical therapy, cardiac re-synchronisation therapy and non-transplant cardiac surgery if indicated
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* Survival, quality of life, Adverse effects including infection, bleeding, pump thrombosis and stroke, *Important to decision-making:* Any other outcomes reported

Assumptions / limits applied to search
Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc. This review will need to include all evidence published in peer-reviewed journals in the English language in the last 10 years relevant to the research question and not be restricted to randomised controlled trials. It will need to include register and natural history studies for both the intervention and comparator groups, including non-concurrent comparisons. The review should only include modern devices in current use.

Following consultation with the Policy Working Group on 17th March 2017, we agreed that in addition to the interpretation described below, we will not undertake a specific evidence review of the natural history of end stage heart failure, but that we will include a brief reference to this in the introduction (section 1 of the NHS England Evidence Review template). We also confirmed that we will exclude single centre studies and case series <100 subjects as there are both systematic reviews and also very large registry studies which eclipse these.

- **NYHA class IV patients:** we will include studies where at least 75% of the patients are NYHA class IV.
- **'for at least 90 days'**: will not be applied strictly
- **LE<2 years**: will not be applied strictly
- **Not candidates for heart transplant:** will be applied as requested
- **Failed to respond to OMM for 60/90 days:** days will not be applied strictly
- **LVEF<25%:** will be applied as requested
- **Functional limitation** will be interpreted more broadly, specifically, ambulatory patients who are able to complete a 6MWT, and those patients who are not dependent on IV inotropic drugs may be included

10 Search Strategy

Embase: search date 3rd March 2017

# ▲	Searches
1	"rose$" [Author Surname] and "heart failure" [Article Title] and "2001" [Publication Year]
2	*heart failure/
3	heart failure.ti,ab.
4	2 or 3
5	*heart assist device/
6	exp left ventricular assist device/ or *ventricular assist device/
7	((left ventric* or lv) adj (assist device* or support device*)).ti,ab.
8	(mechanical circulat* adj2 (support device* or assist device*)).ti,ab.
9	(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.
10	5 or 6 or 7 or 8 or 9
11	mortality/ or cardiovascular mortality/ or hospital mortality/ or exp mortality rate/ or surgical mortality/
12	exp survival/ or exp treatment outcome/
13	exp "quality of life"/
14	cerebrovascular accident/
15	exp thrombosis/

16 bleeding/ or application site bleeding/ or postoperative hemorrhage/ or wound hemorrhage/
17 infectious complication/ or exp device infection/ or postoperative infection/ or surgical infection/
18 (mortality or death? or survival).ti,ab.
19 ("quality of life" or qol or hrqol or "quality adjusted life year?" or qaly?).ti,ab.
20 (infection? or sepsis or septic*).ti,ab.
21 stroke.ti,ab.
22 (thrombo* or embolism? or embolus).ti,ab.
23 (complication? or adverse event? or adverse effect? or side effect?).ti,ab.
24 outcome?.ti. or outcome assessment?.ti,ab.
25 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 4 and 10 and 25
27 (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.
28 26 or 27
29 4 and 10
30 limit 29 to "reviews (maximizes specificity)"
31 limit 29 to "economics (maximizes specificity)"
32 28 or 30 or 31
33 limit 32 to (english language and yr="2007 -Current")
34 conference*.pt.
35 33 not 34
36 (exp animals/ or nonhuman/) not human/

11 Evidence Selection

- Total number of publications reviewed: 362
- Total number of publications considered potentially relevant: 47
- Total number of publications selected for inclusion in this briefing[21]: 22

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[21] Including relevant studies reported in the systematic reviews and retrieved separately

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INTERMACS levels (University of Alabama)

INTERMACS 1: Critical cardiogenic shock describes a patient who is "crashing and burning", in which a patient has life-threatening hypotension and rapidly escalating inotropic pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels. This patient can have modifier A or TCS (see 'Modifiers' below).

INTERMACS 2: Progressive decline describes a patient who has been demonstrated "dependent" on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator. Patient profile 2 can also describe a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions cannot be maintained due to tachyarrhythmias, clinical ischemia, or other intolerance. This patient can have modifiers A or TCS.

INTERMACS 3: Stable but inotrope dependent describes a patient who is clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal). It is critical to monitor nutrition, renal function, fluid balance, and overall status carefully in order to distinguish between a patient who is truly stable at Patient Profile 3 and a patient who has unappreciated decline rendering them Patient Profile 2. This patient may be either at home or in the hospital. Patient Profile 3 can have modifier A, and if in the hospital with circulatory support can have modifier TCS. If patient is at home most of the time on outpatient inotropic infusion, this patient can have a modifier FF if he or she frequently returns to the hospital.

INTERMACS 4: Resting symptoms describes a patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with activities of daily living (ADL). He or she may have orthopnea, shortness of breath during ADL such as dressing or bathing, gastrointestinal symptoms (abdominal discomfort, nausea, poor appetite), disabling ascites or severe lower extremity edema. This patient should be carefully considered for more intensive management and surveillance programs, which may in some cases, reveal poor compliance that would compromise outcomes with any therapy. This patient can have modifiers A and/or FF.

INTERMACS 5: Exertion Intolerant describes a patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound. This patient has no congestive symptoms, but may have chronically elevated volume status, frequently with renal dysfunction, and may be characterized as exercise intolerant. This patient can have modifiers A and/or FF.

INTERMACS 6: Exertion Limited also describes a patient who is comfortable at rest without evidence of fluid overload, but who is able to do some mild activity. Activities of daily living are comfortable and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes of any meaningful physical exertion. This patient has occasional episodes of worsening symptoms and is likely to have had a hospitalization for heart failure within the past year. This patient can have modifiers A and/or FF.

INTERMACS 7: Advanced NYHA Class 3 describes a patient who is clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent. This patient is usually able to walk more than a block. Any decompensation requiring intravenous diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower. This patient may have a modifier A only.

MODIFIERS of the INTERMACS® Patient Profiles:

A - Arrhythmia. This modifier can modify any profile. Recurrent ventricular tachyarrhythmias that have recently contributed substantially to the overall clinical course. This includes frequent shocks from ICD or requirement for external defibrillator, usually more than twice weekly.

TCS –Temporary Circulatory Support. This modifier can modify only patients who are confined to the hospital, Patient Profiles 1, 2, and 3 (a patient who is listed as Patient Profile 3 stable on inotropes who has been at home until elective admission for implantable VAD cannot have a TCS modifier); support includes, but is not limited to, IABP, ECMO, TandemHeart, Levitronix, BVS 5000 or AB5000, Impella.

FF – Frequent Flyer. This modifier is designed for Patient Profiles 4, 5, and 6. This modifier can modify Patient Profile 3 if usually at home (frequent admission would require escalation from Patient Profile 7 to Patient Profile 6 or worse). Frequent Flyer is designated for a patient requiring frequent emergency visits or hospitalizations for intravenous diuretics, ultrafiltration, or brief inotropic therapy. Frequent would generally be at least two emergency visits/admissions in the past 3 months or 3 times in the past 6 months. Note: if admissions are triggered by tachyarrhythmias or ICD shocks then the modifier to be applied to would be A, not FF.