A report for Universitätsklinikum Schleswig-Holstein/Campus Kiel on Shared Decision Making for the implantation of left ventricular assist device in the treatment of cardiac insufficiency

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May 2019

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LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
BTT	Bridge to transplantation
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
DARE	Database of Abstracts of Reviews of Effects
EQ-5D	European quality of life-5 dimensions
FAQ	Frequently asked question
GIN	Guidelines International Network
HF	Heart failure
HTA	Health technology assessment
KSR	Kleijnen Systematic Reviews Ltd
LVAD	Left ventricular assist device
MA	Meta-analysis
MM	Medical management
NA	Not applicable
NMA	Network meta-analysis
NR	Not reported
NS	No significant difference
PICOS	Participants, intervention, comparators, outcomes and study design
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
QoL	Quality of life
RCT	Randomised controlled trial
RD	Risk difference
RR	Risk ratio
SD	Standard deviation
SDM	Shared decision making
SF-36	Medical outcomes study short-form 36
SR	Systematic review
UK	United Kingdom
USA	United States of America

1. PROJECT OBJECTIVE

A key aim of the research project “Making SDM a reality” is to create interactive websites to inform patients as part of shared decision making (SDM).

To support this, Kleijnen Systematic Reviews Ltd (KSR) has prepared an evidence report with a synthesis of the literature underpinning the supporting evidence table of the relevant treatment options.

The objective of this evidence report is to present a comparative summary of outcomes resulting from the implantation of a left ventricular assist device (LVAD) versus medical management (MM) for the treatment of cardiac insufficiency.

2. METHODS

2.1 INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question was framed in terms of participants, intervention, comparators, outcomes and study design (PICOS), see Table 1.

As detailed below, literature searches were carried out using a stepwise approach to identify relevant studies according to study design. In the first step, searches aimed to identify relevant systematic reviews and guidelines. For this project, no topic-wide searches for randomised controlled trials (RCTs) or observational studies were conducted as relevant results were extracted from the identified literature.

Table 1: Inclusion criteria for searches

PICOS	
Patients	Patients with cardiac insufficiency
Intervention treatment	Left ventricular assist device (LVAD) This includes either as a destination therapy (DT) or as a bridge to heart transplantation (BTT).
Control treatment	No LVAD, continued Medical Management (MM)
Outcomes	Primary outcomes: • Survival Secondary outcomes • Heart failure (decreased risk of) • Heart transplantation (decreased need of) • Adverse events/side effects: stroke, device-related infections, serious bleeding • Invasiveness of procedure • Health-related quality of life (physical, psychological, emotional) • Hospitalisations/time in hospital • Costs from treatment (including inconvenience) • Impact on activities of daily living (driving, power source for device, water precautions, carry equipment, co-medication) • Role of caregivers
Study design	Systematic reviews (SR), meta-analyses (MAs) of randomised controlled trials (RCTs) or of studies of lower evidence levels (non-randomised/observational studies)
Effect modification/ Subgroups	Any indication of a specific effect modification or subgroup of patients from the evidence review

In consultation with the commissioner, questions frequently asked by patients (in respect of outcomes identified in the literature) were developed into an evidence table outline.

2.2 LITERATURE SEARCHES

Literature searches were carried out using a stepwise approach to identify relevant studies according to study design:

1. Systematic reviews and guidelines
2. Randomised controlled trials
3. Observational studies
4. Supplementary searches

Only in the event of no relevant systematic reviews or guidelines being identified (Step 1) were further searches to be conducted to identify RCTs (Step 2). If no RCTs were identified, only then would searches be undertaken to identify observational studies (Step 3).

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to 2012-2018. Where appropriate, searches were limited to remove animal studies. Searches were not limited by language or publication status.

Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling. Individual records within the EndNote libraries were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enabled the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

Quality assurance within the search process

The main Embase strategy was independently peer reviewed by a second KSR Information Specialist. Strategy peer review was informed by items based on the Canadian Agency for Drugs and Technologies in Health (CADTH) checklist.[1]

2.3 SEARCH SOURCES

Systematic reviews and guidelines

The following systematic review specific databases were searched from 2012 to present:

- KSR Evidence (Internet): up to 2018/08/24 (https://ksrevidence.com/)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 8 of 12, August 2018
- Database of Abstracts of Reviews of Effects (DARE) (https://www.crd.york.ac.uk/CRDWeb/) up to April 2015
- Health Technology Assessment (HTA) database (https://www.crd.york.ac.uk/CRDWeb/) up to October 2016
- Epistemonikos (Internet): up to 2018/08/24

The following guidelines resources were searched from 2012 to present:

- Guidelines International Network (GIN) (Internet): up to 2018/08/24 (http://www.g-i-n.net/library/international-guidelines-library)
- NICE Evidence (Internet): up to 2018/08/24 (www.evidence.nhs.uk/)

Full details of all search strategies are presented in Appendix 1.

RCTs

As the search for secondary sources and, thereby, reference checking was sufficient, no additional searches for primary studies were undertaken.

Observational studies

As the search for secondary sources was sufficient, no additional searches for observational studies were undertaken.

Supplementary searches

The bibliographies of included studies, guidelines, health technology appraisals and review articles were checked for additional relevant articles.

2.4 METHODS OF STUDY SELECTION, QUALITY ASSESSMENT AND DATA EXTRACTION

Two reviewers independently inspected the title and abstract of each reference identified by the search and determined the potential relevance of each article. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected, and inclusion criteria applied. Any disagreements were resolved through discussion.

Data extraction

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence table. Where more than one study could provide evidence for the table, the most relevant studies were extracted using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations representative of the general target population preferred). Where there were gaps in the evidence table (no meta-analysis, systematic review or guideline available), as described before, relevant RCTs would have been searched for and extracted, and where no RCTs would have been identified, observational studies would have been used.

For each study, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus.

3. RESULTS

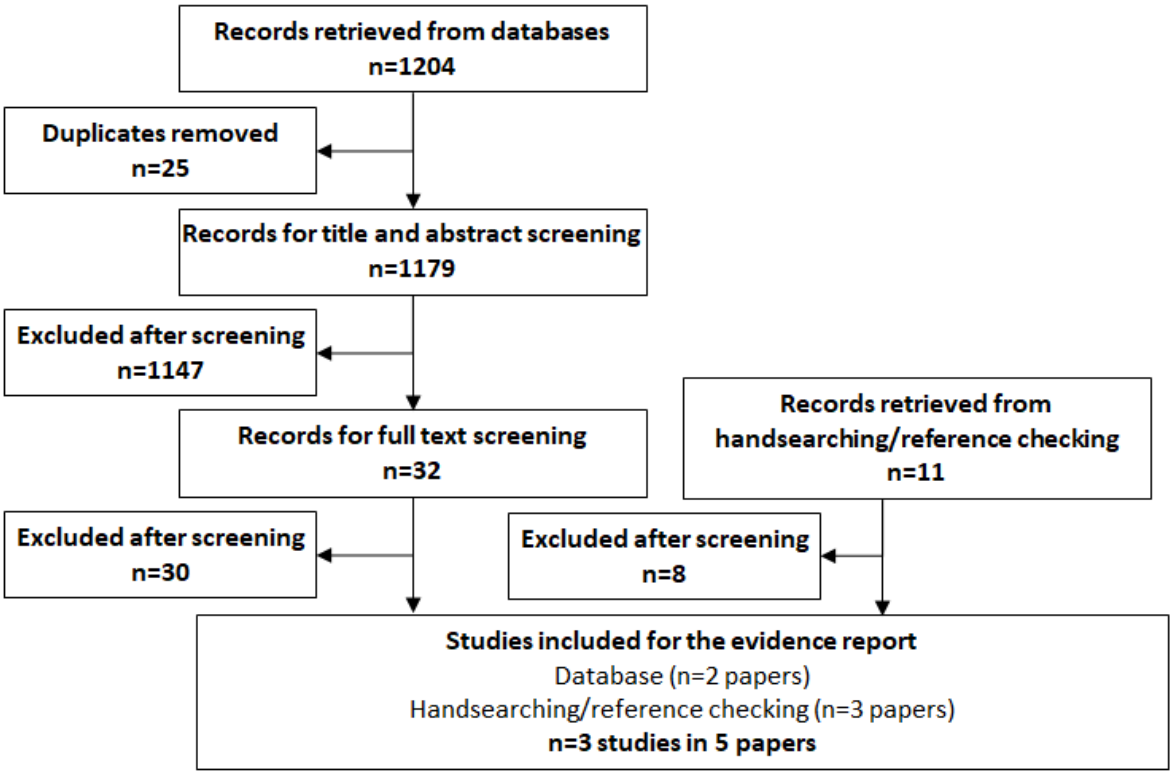
3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

For this evidence report, systematic searches for systematic reviews and guidelines were supplemented by hand searches.

Systematic searches were conducted on 24 August 2018 to identify relevant questions (frequently asked questions; FAQs) and to answer the clinical questions focusing on systematic reviews, meta-analyses and evidence-based guidelines. A total of 1,204 references were retrieved from these literature searches. After de-duplication, 1,179 titles and abstracts were screened by two reviewers. Full papers were obtained for 32 citations alongside 11 which were obtained from reference checking. Key documents used to check references were Health Quality, Ontario, 2016[2, 3] and NICE, 2015.[4] After further review, three studies were selected for this project, i.e. 30 were excluded from those found from literature searching and eight from those identified through reference checking.

A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.

Figure 1: Study selection process



3.2 Overview of the evidence

Table 2 describes the outcomes for which the included studies were employed as a source of evidence. Technologies of interest in Germany are HeartWare and HeartMate III. As a result of this, it was decided to compare these specific technologies to medical management, where evidence permitted. However, for some research questions, evidence for these technologies was not found. In such instances, it was decided to assess evidence for other (older) forms of LVAD (for example, HeartMate II, HeartMate XVE/VE and Novacor) in comparison to medical management but to add a caveat that results for more recent versions of LVAD have not been reported and might be different.

Table 2: Studies populating the evidence table

Study ID	Study type/name if appropriate	How long might I live?	How might I feel?	What complications might occur?	How will my life change?	How will my family be impacted?
Cavarretta 2018[5] ǂ	Meta-analysis of HeartMate XVE/VE; HeartMate III; HeartMate II; HeartWare	**x**		**x**		
Starling, R.C. 2017[6-8] ǂ	Prospective nonrandomised observational study/ROADMAP	*	**x**	*	**x**	
Rose E.A.2001[9] ǂ	RCT/REMATCH	See Cavarretta 2018 [5]	**x**	See Cavarretta 2018 [5]	**x**	

ǂ Sourced from reference checking/hand search

** Data were presented for HeartMate II versus medical management which is less informative where comparisons between Heartmate III/HeartWare can be made.*

What is it and how does the treatment work

Details of the two treatments and how these work are summarised in Table 3.

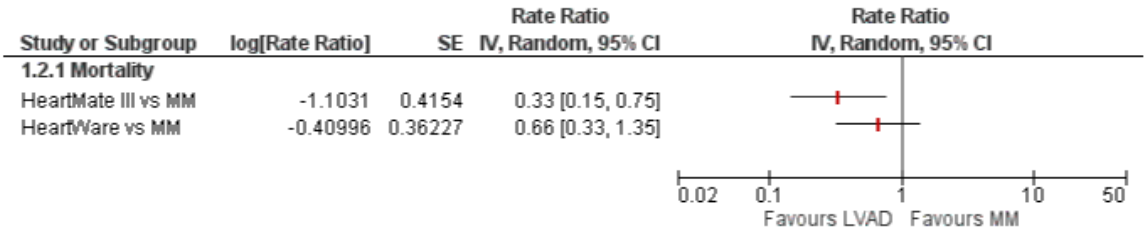
Table 3: What is it and how does the treatment work?

Left ventricular assist device (LVAD)
An LVAD is a mechanical device that helps your heart to pump blood. The LVAD is surgically implanted An LVAD in a patient who will never get a transplant is called "destination therapy" (or LVAD (DT)). This means that the patient will have the device for the rest of his or her life. An LVAD in a patient who is potentially eligible for heart transplant is called "bridging therapy" (or LVAD (BT))[10]
Medical Management (MM)
Medication and other support to relieve symptoms, pain and stress.
Most people with heart failure are treated with medication. Often you will need to take two or three different medicines. Some of the main medicines for heart failure include: • ACE inhibitors • Beta-blockers • Angiotensin receptor blockers (ARBs) • Hydralazine with nitrate • Diuretics • Aldosterone antagonists • Sacubitril valsartan • Ivabradine • Digoxin Source: https://www.nhs.uk/conditions/heart-failure/treatment/

How long might I live?

Improved survival was noted for patients treated with LVAD compared to MM, although the degree and significance of improvement was influenced by the type of LVAD implanted. The clinical evidence for the decision aid is presented in Figure 2. It is based on the meta-analysis undertaken in Appendix Figure 2s by Cavarretta 2018[5] which was originally based on four RCTs involving five treatments (medical management, HeartMate XVE/VE; HeartMate III; HeartMate II; HeartWare). Cavarretta judged these studies to be *"of high quality, notwithstanding the inherent limitation of the open design".* Only RCT evidence was used to evaluate effects and results have been recalibrated for this report by making medical management the comparator to forms of LVAD which are of interest. The network of interventions from which these results are derived is presented in Figure 3 enabling comparison to MM. Analysis in Figure 4 focuses only on the two LVAD treatments of interest in Germany (namely HeartMate III and HeartWare). This network does not include a link to MM or earlier incarnations of LVAD and so is more reflective of current practice, technologies and effects. It is presented in Figure 5. It is worth noting that the nature of MM may well have changed since the work of Rose 2001[9] so it is not clear whether comparisons with more contemporary versions of MM would produce different results.

Figure 2: Survival over the next year: Forest plot of HeartMate III and HeartWare against MM



Information used to calculate Figure 2 is based on results of the trials REMATCH[9], HEARTMATE II[11], ENDURANCE[12] and MOMENTUM 3.[13] – see Figure 3.

Figure 3: Network meta-analysis from Cavarretta 2018

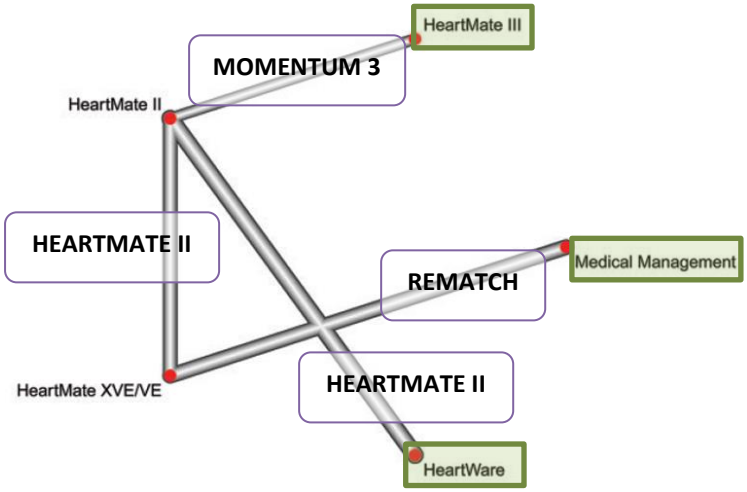
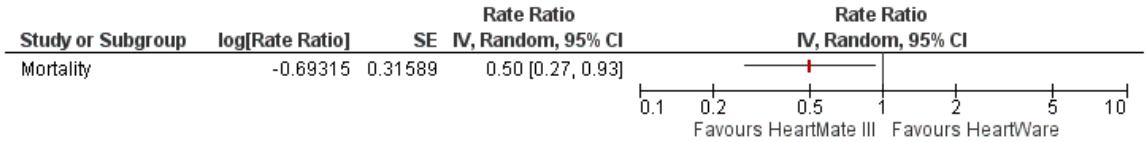
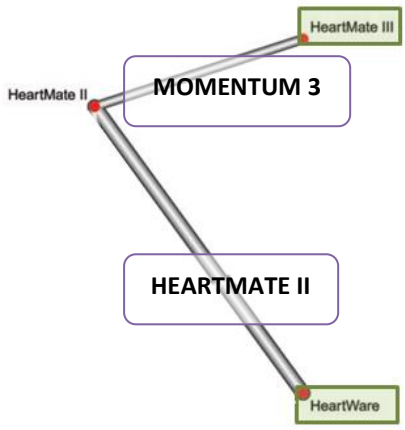


Figure 4: Survival over the next year: Forest plot of HeartMate III against HeartWare



Information used to calculate Figure 4 is based on results of the trials HEARTMATE II[11] and MOMENTUM 3.[13] – see Figure 5.

Figure 5: Network meta-analysis adapted to reflect more contemporary evidence



How might I feel?

With one year of follow up data, LVAD was found to have significant advantages over MM in terms of likelihood of depression, physical health, emotional wellbeing and overall wellbeing. With two years of follow up, LVAD was found to have a significant advantage over MM in terms of overall wellbeing and an, albeit non-significant, advantage in terms of likelihood of depression. The clinical evidence for the decision aid is presented in Table 4, with risk of bias assessment of those studies set out in Tables 9 and 10.

Table 4: How might I feel?

			LVAD				MM				Diff	
Study ID	**Study [Design]**	**Effects**	**Baseline Mean (±SD)**	**N**	**Mean effect (±SD)**	**N**	**Baseline Mean (±SD)**	**N**	**Mean effect (±SD)**	**N**	**Mean diff*** **	**p**
At 1 year												
Rose 2001 [9]	REMATCH [RCT]	Depressed (Beck Depression Inventory)	19 (± 9)	68	8 ± 7	22	16 ± 8	61	13 ± 7	5	-5[Δ]	0.04
		Physically healthy (SF-36 Physical Function)	19 (± 19)	68	46 ± 19	23	18 ± 19	61	21 ± 21	6	+25 [Δ]	0.01
		Emotionally healthy (SF-36 Emotional Role)	33 (± 42)	68	64 ± 45	23	25 ± 38	61	17 ± 28	6	+47 [Δ]	0.03
Starling 2017[6-8]	ROADMAP [Observational]	Change in EQ-5D VAS	42* (NR)	66	+29 (NR)	66	60*(NR)	52	+10 (NR)	52	+19	<0.001
		Depressed; decrement of (PHQ-9)	11**(NR)	67	-4.7 (NR)	67	7**(NR)	53	-0.6 (NR)	53	-4.1	<0.001
At 2 years												
Starling 2017[6, 7]	ROADMAP [Observational]	Change in EQ-5D VAS	44 (± 19)	53	+27 (± 24)	53	66 (± 18)	28	+8 (± 20)	28	+19	<0.001
		Depressed; decrement of (PHQ-9)	10.0 (± 5.6)	54	-4.6 (±6.9)	54	6.8 (± 6.4)	27	-1.8 (± 6.3)	27	-2.8	0.084

** Figures estimated from Figure 6[8]*

*** Figures estimated from Figure 7[8]*

**** Positive mean differences favour LVAD, except for depression scores, where negative means differences favour LVAD.*

[Δ] Mean difference is not matched to scores for same patients at baseline, therefore results should be treated with caution

What complications might occur?

With one year of follow up following treatment-initiation, MM was found to have a significant advantage in terms of likelihood of bleeding that requires surgery as well as likelihood of stroke and/or sepsis (albeit that a non-significant advantage was found when HeartMate III (rather than HeartWare) was implanted. The clinical evidence for the decision aid is presented in Figure 6. It is based on the meta-analysis undertaken by Cavarretta 2018[5] which was originally based on four RCTs involving five treatments (medical management, HeartMate XVE/VE; HeartMate III; HeartMate II; HeartWare). The network of interventions from which these results are derived is presented in Figure 3 enabling comparison to MM. Analysis in Figure 7 focuses only on the two LVAD treatments of interest in Germany (namely HeartMate III and HeartWare). This network does not include a link to MM or earlier incarnations of LVAD and so is more reflective of current practice, technologies and effects. It is presented in Figure 5.

Figure 6: Complications: Forest plot of HeartMate III and HeartWare against MM

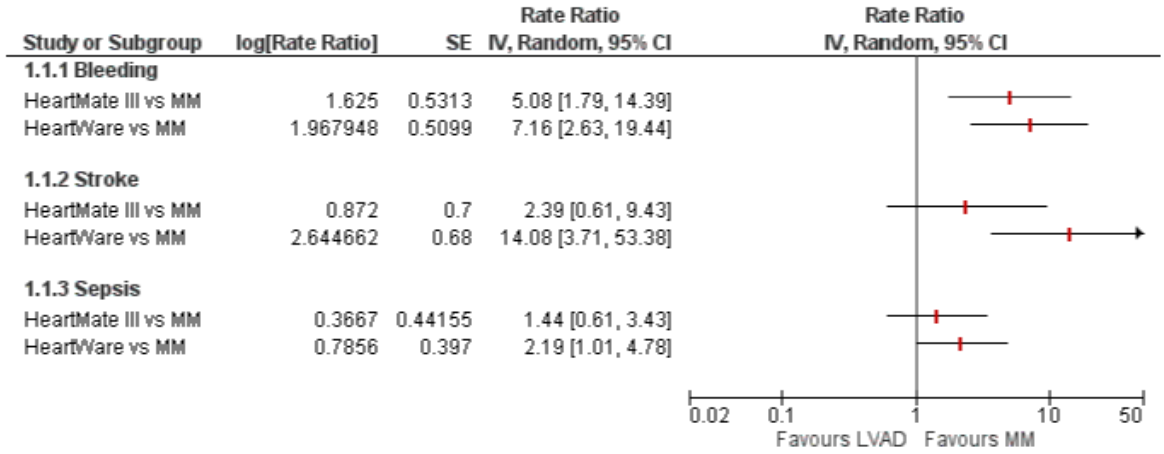
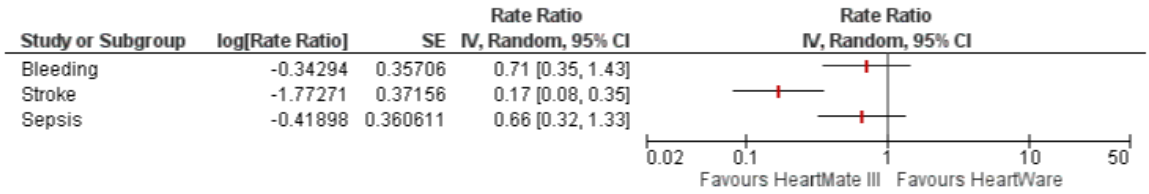


Figure 7: Complications: Forest plot of HeartMate III against HeartWare



How will my life change?

With one year of follow up data, LVAD was found to have significant advantages over MM in terms of climbing stairs (one flight and several flights) and ability to walk around one block. Over the same time period, a non-significant advantage was found for LVAD over MM in terms of longer distance walking (one block, over a mile and 6-minute walking time) as well as for ability to bathe/dress. With two years follow up data, LVAD was also found to have advantages over MM in terms of 6-minute walking time (but this advantage was non-significant). MM did have advantages over LVAD in terms of likelihood of spending days in

hospital whether relating to MM/LVAD management or any other reason. However these advantages were found to be non-significant in statistical terms. The clinical evidence for the decision aid is presented in Table 5. Two studies contributed to the evidence: Rose 2001[9] and Starling 2017[6, 7]. The former is a randomised controlled trial whilst Starling 2017 is prospective observational study. The sample size (N) for the population who completed the test is noted next to the outcome result for each indicator measure.

Table 5: Specific life changes as a result of the intervention

Study ID	Design	Follow-up (months)	Device	Effects	LVAD		MM		RR (or other)	p
					Outcome	N	Outcome	N		
At 1 year										
Rose 2001 [9]	REMATCH [RCT]	12	HeartMate XVE/VE	Climbing one flight of stairs -Limited a lot (n)	3	23	3	6	0.2609	0.006
				Climbing several flights of stairs -Limited a lot (n)	8	23	6	6	0.3478	0.008
				Walking one block -Limited a lot (n)	1	23	3	6	0.0870	0.004
				Walking several blocks -Limited a lot (n)	7	23	3	6	0.6087	0.18
				Walking more than a mile -Limited a lot (n)	15	23	4	6	0.9783	0.72
				Bathing or dressing – Limited a lot (n)	3	23	2	6	0.3913	0.43
Starling 2017[6-8]	ROADMAP [Observational]	12	HeartMate II	6MWD mean change from baseline (meters)(±SD)	Baseline 190*, Change +75	66	Baseline 220*, Change +35	46	Mean Diff 40	NS
Less than 2 years										
Rose 2001 [9]	REMATCH [RCT]	[5-14]	HeartMate XVE/VE	Days spent in hospital / Days alive (medians)	88/408	NR	24/150	NR	1.3480	NS
				Days spent in hospital for MM or implantation of LVAD / Days alive (medians)	29/408	NR	5/150	NR	2.1324	NS
At 2 years										
Starling 2017[6, 7]	ROADMAP [Observational]	24	HeartMate II	6MWD mean change from baseline (meters)(±SD)	Baseline 180 (±88), Change 74 (±141)	39	Baseline 213(±81), Change 64 (±103)	22	Mean Diff 10	NS

NS: No significant difference, 6MWD: 6-minute walking distance

** Figures estimated from Figure 5[8]*

*** RR <1 favour LVAD, RR>1 favour MM*

How will it affect my family?

No quantitative evidence was found to inform how families would be impacted. However, the needs assessment which was undertaken in support of this topic suggested clear advantages of MM when compared to LVAD in terms of the needs to care for and maintain equipment. No clear advantages for one technology over another could be suggested in terms of ability to care for others (including care of younger children). These issues are highlighted in Table 6.

Table 6: Observations on family impact

Family Impact Issues	Potential differences between LVAD and MM
How will care of young children be impacted?	It could reasonably be expected that improved functional/emotional status and increased longevity would result in greater ability to care for others. No evidence was found for the psychological impact on young children in regard of different approaches to treatment.
Care, maintenance of equipment	LVAD is associated with considerable equipment requirements which will undoubtedly place responsibility on patients, their carers and any dependents.
Caring for others	It could reasonably be expected that improved functional/emotional status and increased longevity would result in greater ability to care for others
Interactions with other family members	It could reasonably be expected that improved functional/emotional status and increased longevity would result in greater ability to care for others. No evidence was found as to how carers felt different approaches to treatment might impact their own circumstances.

3.3 Assessment of the clinical review evidence

Details of the three studies are presented in Table 7.

Table 7: Overview of studies comparing LVAD to MM

Study ID	Participants	Device(s)	Country	Study Design	Follow up period	N
Cavarretta 2018 [5]	End-stage heart failure eligible or ineligible for heart transplantation	HeartMate XVE/VE; HeartMate III; HeartMate II; HeartWare	Multinational evidence	Systematic review and Network Meta-Analysis	2 years	1,141
Starling 2017[6-8]	NYHA functional class IIIb/IV patients ineligible or not immediately eligible for heart transplantation	HeartMate II	USA	Prospective non-randomised observational study	1 year; 2 years	200
Rose 2001[9]	End stage heart failure ineligible for heart transplantation	Heartmate XVE/VE	USA	RCT	150 days; 408 days	129

Details of the four trials and related technologies forming the NMA presented by Cavarretta, 2018 [5] are presented in Table 8 with quality assessment of those studies presented in Table 9. Summary risk of bias for the observational study by Starling 2017[6] is presented in Table 10.

Table 8: Overview of RCTs used in meta-analysis performed by Cavarretta 2018

Study ID	Study Name	Risk of Bias (see Table 9)	Participants	Comparator A	Comparator B	Country	N
Mehran 2018[13]	MOMENTUM 3	Limitations due to open design and incomplete outcome data	Patients with advanced heart failure, irrespective of the intended goal of support (bridge to transplantation or destination therapy).	**HeartMate III**	HeartMate II	USA	366
Rogers 2017[12]	ENDURANCE	Limitations due to open design	Patients with advanced heart failure who were ineligible for heart transplantation.	**HeartWare**	HeartMate II	USA; Canada	446
Slaughter 2009 [11]	HEARTMATE II	Limitations due to open design and lack of clarity on allocation concealment	Patients with advanced heart failure who were ineligible for heart transplantation.	**HeartWare**	HeartMate II	USA	200
Rose 2001[9]	REMATCH	Limitations due to open design and lack of clarity on allocation concealment	End stage heart failure ineligible for heart transplantation	Heartmate XVE/VE	**Medical Management**	USA	129

Table 9: Assessment of the internal validity of included randomized trials according to The Cochrane Risk of Bias Tool.

Study	Rose 2001[9]	Slaughter 2009[11]	Rogers 2017[12]	Mehran 2018[13]
Bias	**REMATCH**	**HEARTMATE II**	**ENDURANCE**	**MOMENTUM 3**
Random sequence generation (selection bias)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Allocation concealment	Unclear	Unclear	Low risk of bias	Low risk of bias
Blinding of participants and personnel	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Blinding of outcome assessment	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Incomplete outcome data	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Selective reporting	High risk of bias	High risk of bias	High risk of bias	High risk of bias

Table 10: Assessment of observational study using ROBINS-1 checklist

Study	Starling 2017[6]
Bias	**ROADMAP**
Confounding	Moderate
Selection of participants	Moderate
Classification of Interventions	Moderate
Deviations from intended interventions	No Information
Missing Data	Moderate
Measurement of outcomes	Moderate
Selection of reported result	Moderate
Overall risk of bias judgement	Moderate

4. DISCUSSION

4.1 STRENGTHS, LIMITATIONS AND UNCERTAINTIES

We can be reasonably confident that all relevant RCTs have been included given the recency of the NMA undertaken by Cavarretta 2018[5]. Evidence from these RCTs suggests improved survival for patients treated with LVAD compared to MM, although the degree and significance of improvement was influenced by the type of LVAD implanted. The same sources also suggest that MM has significant advantage compared to LVAD in terms of likelihood of bleeding that requires surgery as well as likelihood of stroke and/or sepsis although, once again, the degree and significance of improvement was influenced by the type of LVAD implanted. No direct comparisons have been found between medical management and either Heartmate III or HeartWare applications of LVAD. The NMA undertaken by Cavarretta[5] suggested that *"new generation devices (HeartMate III and HeartWare) proved better than older generation devices for bleeding, device thrombosis, hepatic dysfunction, renal dysfunction, respiratory dysfunction, right ventricular failure and sepsis with significant differences among them".* For these reasons, it was felt important to focus on these precise applications where evidence permitted. This was possible, via NMA, for two key FAQs namely *"How long might I live?"* and *"What complications might occur?".* The analysis presented in Cavarretta 2018[5] compared four technologies to Heartmate XVE/VE. The analysis we present uses the same underlying data but refocuses it to compare HeartMate III and HeartWare to MM. Additional results were also obtained when comparing HeartMate III and HeartWare to one another, without having to include data from an earlier study of MM (which was relatively small and associated with relatively high levels of uncertainty around effect estimates). This additional analysis does suggest marked differences between HeartMate III and HeartWare with the former having statistically significant favourable outcomes in terms of overall survival and stroke.

A key area of uncertainty relates to the age of some of the primary studies included and a lack of reliable recent evidence of survival rates. Clinical experts have identified two recent publications of data from two registries INTERMACS[14] and EUROMACS[15] which shed some light on survival. Both studies report on patients undergoing continuous flow left ventricular devices. This technology has largely replaced earlier forms of LVAD which were pulsatile volume displacement pumps. These first generation pumps tended to be larger, more complicated and less durable than the continuous flow devices.[16] This is important, in that earlier evaluations of LVAD compared to MM will have been based on pulsatile volume displacement pumps rather than continuous flow LVAD. Based on the INTERMACS database of >20,000 patients from 2008 to 2016, the overall survival of patients receiving continuous flow LVADs with or without right ventricular assist device was 81% at 12 months and 70% at 24 months. Comparative data were not available for medical management patients. This means that the patient group reported in INTERMACS might be different to that in the rest of this review in that some, for whatever reason, may not have been eligible for medical management. Similar analyses of survival rates were provided in EUROMACS[15] over a

period 2011 to 2016. EUROMAC related to 2268 adult patients with a continuous LVAD with or without right ventricular assist device. n this follow-up study, overall survival was 66% at 12 months and 53% at 24 months.

Both of these databases represent evidence which is widely regarded as inferior in quality (higher risk of bias) than evidence from either systematic review or meta analysis of RCTs. Nevertheless they do provide a crude outline of overall survival estimates associated with LVAD (though not medical management). INTERMACS identified changes in patient profile; patients who were stable but dependent on drugs which increase the strength of heart contractions (inotropes) represented 25.2% of patients in 2008-2011, 31.6% of patients in 2012-2014 and 37.5% of continuous flow LVAD patients in 2015-2016. Over the same period, proportions of patients considered to be in a state of progressive decline despite intravenous inotropic support have decreased from 40.8% in 2008-2011, to 35.8% in 2012-2014 and 33.7% of continuous flow LVAD patients in 2015-2016.[14]

It was not possible to make comparisons between HeartMate III/HeartWare and MM for two of the other FAQs ("How might I feel?" and "How will my life change?"). In the absence of such evidence, assessment of MM against different forms of LVAD was presented. Both FAQs were addressed using evidence from one RCT (REMATCH)[9] which was relatively small and based on an early version of pulsatile volume displacement LVAD (HeartMate XVE/VE) and also from one larger more recent observational study Starling 2017[6-8]. Results from these studies were in broad agreement and suggested that LVAD would be favourable to MM, albeit with different degrees of statistical significance.

The remaining FAQ, identified through needs assessment, was *"How will my family be impacted?".* No comparative evidence for this was identified from the literature but instead "plausible" assessments have been suggested in the absence of evidence.

Results for all evidence identified are summarised in Table 9 below.

Table 11: Summary of effect of LVAD vs MM

Evidence	LVAD	MM	Notes
How long might I live?			
Risk of dying over the next year	✓		Improved survival is observed for patients treated with LVAD compared to MM, although the degree and significance of improvement was influenced by the type of LVAD implanted. There is evidence that treatment by either HeartWare or HeartMate III results in longer life expectancy than with Medical Management. This was significant in the case of HeartMate III but not HeartWare. HeartMate III was also found to have a significant improvement in survival when compared to HeartWare in a separate analysis based only on recent evidence.
How might I feel?			
Likelihood of depression over the next year	✓		Evidence based on 1 RCT and 1 observational study
Likelihood of depression over the next two years' time	✓		Evidence based on 1 observational study
Physical health in one years' time	✓		Evidence based on 1 RCT
Emotional wellbeing over the next year	✓		Evidence based on 1 RCT
Overall wellbeing over the next year	✓		Evidence based on 1 observational study
Overall wellbeing over the next two years	✓		Evidence based on 1 observational study

Evidence	LVAD	MM	Notes
What complications might occur within the next year?			
What is the likelihood of stroke over the next year?		✓	MM has significant advantage compared to LVAD although the degree and significance of improvement was influenced by the type of LVAD implanted. Likelihood of stroke was higher with HeartMate III/HeartWare than medical management, however for HeartMate III this was not statistically significant. Separate analysis suggested that likelihood of stroke was higher with HeartWare than HeartMate III and this difference was significant.
What is the likelihood of sepsis over the next year?		✓	MM has significant advantage compared to LVAD although the degree and significance of improvement was influenced by the type of LVAD implanted. Likelihood of sepsis was higher with HeartMate III/HeartWare than medical management, however for HeartMate III this was not statistically significant. Separate analysis suggested that likelihood of sepsis was higher with HeartWare than HeartMate III but this difference was not significant.
What is the likelihood of bleeding that will require surgery over the next year?		✓	MM has significant advantage compared to LVAD. Likelihood of bleeding which requires surgery was higher for HeartMate III/HeartWare than medical management and this difference was of statistical significance. Separate analysis suggested that likelihood of bleeding was higher with HeartWare than HeartMate III but this difference was not significant.
How might my life change?			
Severe limitations climbing one flight of stairs over the next year	✓		Whilst the evidence suggests a statistically significant improvement in outcome this is based on an older version of LVAD (HeartMate XVE/VE) and small numbers in the trial providing the evidence.
Severe limitations climbing several flights of stairs over the next year	✓		Whilst the evidence suggests a statistically significant improvement in outcome this is based on an older version of LVAD (HeartMate XVE/VE) and small numbers in the trial providing the evidence.
Severe limitations walking one block over the next year	✓		Whilst the evidence suggests a statistically significant improvement in outcome this is based on an older version of LVAD (HeartMate XVE/VE) and small numbers in the trial providing the evidence.
Severe limitations walking several blocks over the next year	✓		Whilst the evidence suggests a statistically non-significant improvement in outcome this is based on an older version of LVAD (HeartMate XVE/VE) and small numbers in the trial providing the evidence.

Evidence	LVAD	MM	Notes
Severe limitations walking more than a mile over the next year	✓		Whilst the evidence suggests a statistically non-significant improvement in outcome this is based on an older version of LVAD (HeartMate XVE/VE) and small numbers in the trial providing the evidence.
Severe limitations bathing or dressing over the next year	✓		Whilst the evidence suggests a statistically non-significant improvement in outcome this is based on an older version of LVAD (HeartMate XVE/VE) and small numbers in the trial providing the evidence.
Improvement in 6-minute walking distance over the next year	✓		Evidence based on 1 observational study
Improvement in 6-minute walking distance over the next two years	✓		Evidence based on 1 observational study
Likelihood of spending days in hospital		✓	Evidence based on 1 RCT
Likelihood of spending days in hospital relating to either MM or LVAD		✓	Evidence based on 1 RCT
How will it affect my family?			
How will care of young children be impacted?	✓		It could reasonably be expected that improved functional/emotional status and increased longevity would result in greater ability to care for others. No evidence was found for the psychological impact on young children in regard of different approaches to treatment.
Care, maintenance of equipment		✓	No evidence is required since LVAD is associated with equipment requirements, whereas medical management is not

Evidence	LVAD	MM	Notes
Caring for others	✓		It could reasonably be expected that improved functional/emotional status and increased longevity would result in greater ability to care for others. No evidence was found as to how carers felt different approaches to treatment might impact their own circumstances.
Interactions with other family members	✓		It could reasonably be expected that improved functional/emotional status and increased longevity would result in more meaningful and rewarding interactions with other family members

KEY	
✓	better but not statistically significant
✓	significant difference for HeartWare but not HeartMate III
✓	statistically significantly better

5. REFERENCES

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APPENDIX 1: SEARCH STRATEGIES

Shared Decision Making: Q7 – LVAD
Rapid Appraisal searches

Database	Dates	Results
CDSR	2012 - Iss 8, August 2018	515
DARE	2012-2018	0
HTA	2012-2018	6
NICE	up to 23 August 2018	27
KSR Evidence	2015-2018	577
Epistemonikos	2012-2018	40
GIN	2012-2018	39
Total		**1204**
Total after de-duplication		**1179**

SDM database searches

Database	Dates	Results
Embase	1974-2018 August 28	86
MEDLINE	1946-2018/August week 3	77
MEDLINE IP, DU & Epub	July 19, 2018	10
CENTRAL	2012 - Iss 6, Jun 2018	51
Handsearch		
Total		**224**
Total after de-duplication		**178**

Strategies

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 8 of 12, August 2018
Searched: 23.8.18

ID Search Hits
#1 MeSH descriptor: [Heart Failure] explode all trees 7858
#2 (heart OR cardiac) NEAR/2 (failure or decompensation) 22435
#3 (LVAD OR ((ventricle OR ventricle OR ventricular OR heart) NEAR/2 assist NEAR/2 device) OR "artificial ventricle" OR "mechanical circulatory support") 470
#4 MeSH descriptor: [Heart-Assist Devices] explode all trees 150
#5 #1 or #2 or #3 or #4 22676

Limit to 1.1.2012 – 30.8.2018
CDSR = 515

Database of Abstracts of Reviews of Effects (DARE): up to April 2015
Health Technology Assessment (HTA) database: up to August 2018
https://www.crd.york.ac.uk/CRDWeb/
Searched: 29.8.18

Results for: ((LVAD)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN DARE, HTA FROM 2012 TO 2018

6 records retrieved

Epistemonikos (Internet): up to 2018 Aug 24
https://www.epistemonikos.org/en/
Searched: 24.08.18

(advanced_title_en:((LVAD)) OR advanced_abstract_en:((LVAD))) [Filters: protocol=no, classification=systematic-review, cochrane=missing, min_year=2012, max_year=2018] **40 records**

International Guideline Library (GIN) (Internet): up to 24 August 2018
Searched 24.8.18
http://www.g-i-n.net

Search terms	**Results: 2012-2018**
"Heart Failure"	39
LVAD	0
Heart assist	0
"left ventricular assist device"	0
"artificial ventricle"	0
"cardiac failure"	0
"mechanical circulatory support"	
Total retrieved	**39**
Total (without duplicates)	**39**

KSR Evidence (Internet): Database last updated 2018 Aug 24
www.ksrevidence.com
Searched: 24.08.18

1 heart failure in Title 512
2 LVAD in All text 28
3 ventricular assist device in All text 39
4 heart assist device in All text 38
5 artificial ventricle in All text 13
6 mechanical circulatory support in All text 14
7 #1 or #2 or #3 or #4 or #5 or #6 577

Database last updated 10 Aug 2018, 5:43 p.m.

National Institute for Health and Care Excellence (NICE): Guidelines
Searched 23.8.18
https://www.nice.org.uk/

NICE Guidance; Conditions and diseases; Heart Failure

27 Products:
Pathways 2

NICE Guidelines 2
Quality Standards 2
Technology appraisal guidance 3
Interventional procedures guidance 9
Medical technologies guidance 1
Medtech innovation briefings 2
In development 6

Targeted SDM searches

Embase: 1974-2018 Aug 28
Searched: 29.8.18

1 (LVAD or ventricle-assist device or ventricular assist device or heart-assist device or heart-assist pump or artificial ventricle or mechanical circulatory support).ti,ab,ot. (18842)
2 exp left ventricular assist device/ (11222)
3 1 or 2 (21221)
4 shared decision making/ (2964)
5 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (38360)
6 sdm.ti,ab. (2402)
7 4 or 5 or 6 (40657)
8 3 and 7 (90)
9 limit 8 to yr="2012 -Current" (86)

MEDLINE: 1946-2018/Aug week 3
Searched: 29.8.18

1 (LVAD or ventricle-assist device or ventricular assist device or heart-assist device or heart-assist pump or artificial ventricle or mechanical circulatory support).ti,ab,ot. (8570)
2 Heart-Assist Devices/ (11856)
3 1 or 2 (13456)
4 exp Decision Making/ (179418)
5 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (23576)
6 sdm.ti,ab. (1485)
7 or/4-6 (196693)
8 3 and 7 (129)
9 limit 8 to yr="2012 -Current" (77)

Ovid MEDLINE(R) Epub Ahead of Print: August 28, 2018
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations: August 28, 2018
Ovid MEDLINE(R) Daily Update: August 28, 2018
Searched: 29.8.18

1 (LVAD or ventricle-assist device or ventricular assist device or heart-assist device or heart-assist pump or artificial ventricle or mechanical circulatory support).ti,ab,ot. (1624)
2 Heart-Assist Devices/ (24)
3 1 or 2 (1631)
4 exp Decision Making/ (312)
5 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (5301)
6 sdm.ti,ab. (459)
7 or/4-6 (5867)

8 3 and 7 (10)
9 limit 8 to yr="2012 -Current" (10)

Cochrane Central Register of Controlled Trials (CENTRAL): Issue 7 of 12, August 2018 Searched: 29.8.18

ID Search Hits
#1 MeSH descriptor: [Heart Failure] explode all trees 7858
#2 (heart OR cardiac) NEAR/2 (failure or decompensation) 22435
#3 (LVAD OR ((ventricle OR ventricle OR ventricular OR heart) NEAR/2 assist NEAR/2 device) OR "artificial ventricle" OR "mechanical circulatory support") 470
#4 MeSH descriptor: [Heart-Assist Devices] explode all trees 150
#5 #1 or #2 or #3 or #4 22676
#6 MeSH descriptor: [Decision Making] this term only 1977
#7 ((share* or sharing* or inform*) near/3 (decision* or deciding* or choice*)):ti,ab,kw 2894
#8 sdm:ti,ab,kw 246
#9 #6 or #7 or #8 4601
#10 #5 and #9 with Cochrane Library publication date between Jan 2012 and Sep 2018 71

CENTRAL = 51