Ministero della Salute

Agenzia Nazionale per i Servizi Sanitari Regionali

HTA REPORT

"Implantable LVAD (Left Ventricular Assist Device) in addition to guideline directed medical therapy (GDMT) in end stage heart failure"

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REGIONE UMBRIA

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FOREWORD

This HTA project was developed as part of a collaboration between Agenas and Ministry of Health - General Directorate of medical devices and pharmaceutical services (VII HTA-agreement). The agreement provides for the production of Health Technology Assessment reports involving the use of the same in the context of our country (Article 1 of the Agreement).

The technology for evaluation followed a notification process that involved reports from the Italian Network of regional HTA units (RIHTA), databases searches of HTA AGENAS group, reports by industry representatives, reports arising from Extra Fee Reimbursement and Replacement National/Regional Rate and reports arising from "Greater budget impact devices " analysis. The reports were prioritized by a committee composed of representatives from some RIHTA regions (Emilia Romagna, Puglia, Liguria, Lombardy and Veneto), the General Directorate of Medical Devices and Pharmaceutical Service of the Ministry of Health and from Agenas.

The manufacturers contributed to deliver technical, scientific and economic information.

The involvement of clinical experts, as external auditors, took place in accordance with the procedure in place taking into account their specific knowledge and with the following requirements:

- No direct working relationship with the institution that conducts the assessment HTA;
- Qualified experience in the field of interest;
- Track record of publications at national and international level on this subject;
- Excellent knowledge of English.

The clinical experts/external reviewers have confirmed their collaboration by reviewing the final texts of the protocol and sometimes collaborating as co-authors for relevant parts.

ABSTRACT

Background: Left ventricular assist device (LVAD) is considered an alternative to transplantation in end stage acute or chronic left ventricular congestive heart failure (HF). Use of LVAD improves the allocation of transplants alleviating the shortage of donors. The target population of the technology is represented by patients with end stage heart failure.

Objectives: To assess the effect of using a LVAD in addition to guideline directed medical therapy (GDMT) (including Cardiac Resynchronization Therapy Defibrillator CRT-P, implantable cardioverter-defibrillator ICD and Cardiac Resynchronization Therapy Defibrillator CRT-D) in adult patients with end stage heart failure who are not eligible or immediately eligible for cardiac transplant in stage D of the ABCD classification of the American College of Cardiology (ACC)/American Heart Association (AHA), and class III–IV of the New York Heart Association (NYHA) functional classification.

Methods: We used the Agenas model (see Appendix 1) and structure derived from the EUnetHTA Core Model® for seven domains: Health problem and current use of technology (CUR), Description and technical characteristics of technology (TEC), Regulatory status (REG), Clinical effectiveness (EFF), Safety (SAF), Organisational aspect (ORG), Costs and economic evaluation (ECO). We included evidence from systematic reviews, manufacturers and from the national project run by Centro Nazionale Trapianti.

Results: In 2012 and 2013 up to 87% of procedures were performed on males aged between 25 and 74. 65% of VAD procedures were performed in Lombardia, Veneto and Lazio Regions. Evidence from two trials (one randomised and one controlled clinical trial) showed a consistent improvement in 1-year overall survival in favour of patients that received LVAD. Both studies were not immune from selection bias and the overall sample size was limited. In the 5 included full economic evaluations, LVAD patients had higher mean costs with higher survival benefits compared to GDMT; however continuous-flow LVAD is not cost-effective. LVAD cost-effectiveness estimates were sensitive to several variables (e.g. technology improvement, length of follow up and cost).

Conclusions: Continuous-flow LVAD represents a promising technology considering the shortage of donor hearts, the increase in survival and quality of life. The technology is the only alternative treatment in patients who are temporarily or definitively not eligible for transplant.

SINTESI

Introduzione

L'insufficienza ventricolare sinistra è la principale causa di insufficienza cardiaca grave. Con l'avvento di supporti circolatori meccanici durevoli e affidabili (MCS), i dispositivi di assistenza ventricolare sinistra (LVAD) sono diventati una vera e propria alternativa al trapianto. Gli outcome in pazienti supportati da LVAD hanno continuato a migliorare costantemente nel tempo grazie ad un miglioramento del design del dispositivo, della selezione dei pazienti, e delle cure post-operatorie.

La popolazione target della tecnologia è rappresentata da pazienti con scompenso cardiaco in fase terminale stadio D della classificazione ABCD della American College of Cardiology (ACC)/ American Heart Association (AHA), e classe III-IV della New York Heart Association (NYHA) classificazione funzionale.

Il crescente utilizzo di LVAD migliora l'assegnazione dei trapianti alleviando la carenza di donatori.

Obiettivo

L'obiettivo di questo report è stato quello di valutare quale sia l'effetto di utilizzare un LVAD in aggiunta alla GDMT (comprese Cardiac Resynchronization Therapy Defibrillator CRT, implantable cardioverter-defibrillator ICD and Cardiac Resynchronization Therapy Defibrillator CRT-D) in pazienti adulti con insufficienza cardiaca in stadio terminale che non sono immediatamente eleggibili per il trapianto cardiaco (bridge to transplantation o destination therapy) a causa di patologie concomitanti (irreversibili o non immediatamente reversibili).

Metodi

Per rispondere alla domanda di ricerca abbiamo utilizzato il modello Agenas (in Appendice 1 derivato da EUnetHTA Core Model®. Per ciascuno dei seguenti domini abbiamo selezionato le domande di ricerca rilevanti (AE) dal modello Agenas che sono state oggetto di ricerca di questo report: problema di salute e uso corrente della tecnologia (CUR), descrizione e caratteristiche tecniche della tecnologia (TEC), efficacia clinica (EFF), sicurezza (SAF), aspetti organizzativi (ORG), costi e valutazione economica (ECO). Le revisioni sistematiche sono state eseguite seguendo le necessità dei domini pertinenti. In aggiunta sono stati utilizzati dati raccolti dai produttori con questionari AGENAS strutturati e dal progetto nazionale Centro Nazionale Trapianti.

Risultati e Discussione

Problema sanitario ed uso corrente della tecnologia (CUR)

I dati relativi alle dimissioni ospedaliere per procedure VAD in Italia mostrano che il 81% e il 87% (anni 2012 e 2013) delle procedure vengono eseguite sui maschi e più del 84% (per il 2012) e il 94% (2013) dei casi hanno riguardato pazienti tra i 25 e i 74 anni. Il numero totale di centri (presenti in 13 su 20 Regioni) che hanno impiantato VAD, è stato rispettivamente di 24 e di 22 per il 2012 e il 2013, con in testa la Regione Lombardia con il più alto volume di impianti VAD seguita dal Veneto e dal Lazio. In queste tre Regioni è stato eseguito il 65% degli impianti VAD nel 2012 e il 71% nel 2013 (tutti classificati con il codice DRG 103).

Descrizione e caratteristiche della tecnologia(TEC)

La nostra valutazione si è concentrata sui dispositivi di seconda e terza generazione e sui dispositivi più utilizzati in Italia. In particolare sui seguenti dispositivi: INCOR® (Berlin Heat GmbH), HVAD (HeartWare Inc), Jarvik 2000 FLOWMAKER® (Jarvik Heart Inc), HeartAssist5® (ReliantHeart Inc), HeartMate II® LVAD (Thoratec Corporation).

Efficacia clinica e sicurezza (EFF-SAF)

In questo rapporto sono stati inclusi e riassunti i risultati di due revisioni sistematiche e due report di HTA sull'efficacia e la sicurezza di utilizzo di LVAD per i pazienti con insufficienza cardiaca. Ulteriori due studi sperimentali (di cui uno solo randomizzato) sono stati inclusi e hanno mostrato un consistente miglioramento nella sopravvivenza generale ad 1 anno e della qualità della vita a favore dei pazienti che hanno ricevuto LVAD. Tuttavia, nessuno dei due studi era privo di bias di selezione e la dimensione complessiva del campione era limitata. Inoltre, il principale limite degli studi sperimentali era la mancanza di controlli. L'effetto positivo di supporto LVAD in stadio terminale dell' insufficienza cardiaca è a favore della sopravvivenza anche se la qualità delle prove è bassa e il verificarsi di eventi avversi importanti deve essere considerato con attenzione nella selezione dei pazienti.

Costi e valutazione economica (ECO)

La valutazione di questa dimensione è stata effettuata mediante revisione sistematica della letteratura scientifica italiana e internazionale pubblicata, al fine di identificare e analizzare gli studi economici sull'utilizzo degli LVAD in aggiunta alla terapia medica (inclusi CRT, ICD e CRT-D) in base alla popolazione target definita nel presente report. Sono state incluse tutte le tipologie di

analisi economica che hanno valutato gli LVAD in aggiunta alla terapia medica comparati con la sola terapia medica. Sono stai inclusi, estratti e analizzati in maniera narrativa sei studi: 5 valutazioni economiche complete e 1 analisi dei costi. Tutti gli studi hanno comparato gli LVAD a flusso continuo con la terapia medica (anche se chiamati in maniera differente all'interno degli studi) e sono: 1 studio di analisi del costi [Mishra et al, 2012], 2 analisi di costo-efficacia [Sutcliffe et al, 2013; Long et al, 2014], 1 analisi di costo-utilità [Neyt et al, 2013] e due studi che hanno condotto sia una analisi di costo utilità che di costo-efficacia [Moreno et al, 2012; Rogers et al, 2012].

In tutte le valutazioni economiche il gruppo di pazienti con impianto di LVAD ha avuto sia benefici che costi medi superiori al gruppo di pazienti con la sola terapia medica, per tutti gli orizzonti temporali considerati. I risultati economici sono stati espressi come tasso incrementale di costo-efficacia (ICER) per anni di vita e QALY in tutte le 5 valutazioni economiche complete incluse. Nei due studi che hanno valutato l'utilizzo degli LVAD come ponte al trapianto il valore dell'ICER varia:

- da £219.705 ($351.528) a £124.066 ($198.506) per anni di vita a sei mesi e 18 mesi rispettivamente e da £258.922 ($414.275) a £133.860 ($214.176) per QALY per gli stessi orizzonti temporali [Moreno et al, 2012];
- da £117.278 (a 3 anni) a £46.322 (50 anni/per tutta la vita) per anni di vita e da £122.730 (a 3 anni) a £55.173 (50 anni/per tutta la vita) per QALY [Sutcliffe et al, 2013].

Le analisi economiche che hanno valutato l'uso degli LVAD nei pazienti ineleggibili al trapianto hanno mostrato che gli ICER per anni di vita guadagnati e per QALY sono pari rispettivamente a:

- $167.208 [Rogers et al, 2012], €94.100 [Neyt et al, 2013] e $131.800 [Long et al, 2014] e
- $198.184 [Rogers et al, 2012], €107.600 [Neyt et al, 2013] e $201.600 [Long et al, 2014],

In base alle nostre conoscenze l'unico lavoro italiano riportante costi per impianto LVAD è stato condotto all'interno del progetto nazionale del Centro Nazionale Trapianti (CNT) – Istituto superiore di Sanità (Grave insufficienza d'organo-Cuore) al quale Agenas ha partecipato conducendo una revisione sistematica degli studi economici sugli LVAD. Il *case-study* all'interno del report "LVAD: tecnologia, efficacia, sicurezza, analisi economica e fabbisogno nazionale" è una analisi di micro-costing condotta nel 2012 e ha previsto la rilevazione dei costi in due ospedali italiani di due Regioni (Veneto e Lombardia).

L'analisi di micro-costing è stata costruita utilizzando il metodo del costo pieno, comprendendo sia i costi della procedura che i costi indiretti. Sono stati considerati i dati relativi alla casistica dei due ospedali; i costi diretti; i costi della diagnosi per i ricoveri attribuiti ai DRG 103, 525, 541 (ICD9-CM 3741, 3762, 3765, 3766). I costi diretti e indiretti sono stati misurati considerando la prospettiva

dell'azienda ospedaliera per la sola procedura di impianto LVAD, escludendo quindi la fase di valutazione pre-impianto e il follow up.

I risultati della revisione sistematica hanno evidenziato che in base alle soglie della disponibilità a pagare (WTP – *willingness to pay*) adottate, gli LVAD a flusso continuo non sono costo efficaci comparati con la terapia medica.

Abbiamo inoltre rilevato che gli LVAD sono sensibili a: aumenti nella qualità della vita (QoL – *Quality of Life*) dovuti al progresso tecnologico e/o alla riduzione della complicanze; una più lunga durata del follow-up; misure di abilità funzionale, riduzione del costo del dispositivo, sopravvivenza dei pazienti a lungo termine; riduzione delle complicanze e degli eventi avversi.

Ciononostante, gli LVAD a flusso continuo rappresentano una tecnologia promettente considerando la sempre più ridotta disponibilità di donatori di cuori; l'aumento della sopravvivenza che raggiunge tassi simili a quelli del trapianto di cuore [Long et al, 2014; Sutcliffe et al, 2013]; il miglioramento della qualità della vita dei pazienti che altrimenti non potrebbero condurre le attività quotidiane; l'innovazione della tecnologia che porta ad una riduzione delle infezioni e delle complicanze (ad esempio un guasto/fallimento del dispositivo). Inoltre, progressi tecnologici dei dispositivi e la curva di apprendimento dei professionisti sanitari sembrerebbero determinare un miglioramento della costo efficacia; Rogers et al, 2012 hanno mostrato che la seconda generazione dei dispositivi aumenta la probabilità che i VAD siano costo efficaci.

L'analisi di micro-costing condotta nei due centri ha mostrato che il primo ospedale ha un costo medio totale per procedura di impianto LVAD pari a €165.350 ed un rimborso medio pari a €59.417 mentre il secondo ospedale ha un costo medio totale di €216.070 con un rimborso medio di €54.427. Pertanto i due centri coinvolti nell'analisi soffrirebbero di una perdita finanziaria per ogni procedura di impianto LVAD poiché il rimborso risulta non essere sufficiente a coprire i costi totali sostenuti per la procedura di impianto di LVAD. Dal 2014 in associazione al codice di intervento ICD9CM 37.66 "Inserzione di sistema di assistenza cardiaca impiantabile", la Regione Lombardia riconosce ad alcune strutture una tariffa sostitutiva pari a €125.900 (DGR2313/2014) mentre la Regione Veneto eroga un rimborso aggiuntivo di €91.000 al DRG 103 "Trapianto di cuore o impianto di sistema di assistenza cardiaca" (DGR 2310/2014).

Aspetti organizzativi (ORG)

La valutazione della dimensione organizzativa ha preso avvio dall'analisi del report italiano "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD" approvato dalla Conferenza Nazionale Stato – Regioni e Province Autonome il 2 Luglio 2015. La

finalità di tale valutazione era di indagare i cambiamenti nei processi di lavoro; le modalità di comunicazione necessarie all'interno e tra le diverse organizzazioni che utilizzano gli LVAD a lungo termine; la formazione del personale coinvolto nell'utilizzo del LVAD a lungo termine. Inoltre, sono state condotte delle ricerche nei siti web dei centri di trapianto di cuore e delle cardiochirurgie non sedi di trapianto che hanno partecipato al progetto nazionale "Grave insufficienza d'organo – Cuore", per raccogliere informazioni sulle procedure organizzative e sui percorsi di cura, definiti ed adottati negli stessi centri, inerenti l'impianto degli LVAD. E' stato elaborato un questionario ad hoc, inviato ai produttori della tecnologia LVAD nel mese di Maggio 2015, con l'intento di raccogliere anche informazioni e dati sulle conseguenze di natura organizzativa della procedura di impianto degli LVAD. Infine, abbiamo analizzato gli studi pubblicati, risultanti dalla ricerca sistematica economica, per selezionare quelli in cui fossero stati indagati gli aspetti organizzativi.

In base a quanto riportato nel "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD", la complessità della tecnologia LVAD è determinata dall'insieme di diversi elementi comprendenti: la gravità dei pazienti trattati; la necessità di sviluppare una competenza specifica; l'interazione con la lista di attesa per il trapianto cardiaco; il rischio di complicanze per l'intera vita del paziente; le difficoltà psicologiche vissute dai pazienti con un LVAD; i costi elevati della procedura e della gestione a lungo termine. Ne consegue che l'attività di impianto degli LVAD deve essere svolta in Centri esperti dotati di un'elevata competenza specifica in quanto centri con programma di trapianto cardiaco o centri con un considerevole volume di attività di impianto degli LVAD. Tali Centri esperti (Centri MCS) – dotati di una previa specifica autorizzazione regionale da rinnovare periodicamente - devono soddisfare i requisiti definiti e riportati nel "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD". In particolare, il Centro MCS deve essere dotato: di un programma integrato medico-chirurgico per il trattamento dell'insufficienza cardiaca avanzata, per garantire un'assistenza integrata al paziente con LVAD; di competenze cardiochirurgiche, cardiologiche, anestesiologiche, interventistiche ed infermieristiche per la gestione appropriate del paziente con LVAD; di un team multidisciplinare idoneo a fornire assistenza integrata e la cui composizione e responsabilità siano chiaramente definite all'interno di protocolli/procedure locali; tecnologie e competenze idonee per la diagnosi ed il trattamento delle diverse complicanze, anche di natura psicologica; un sistema per la consulenza telefonica e per l'assistenza specialistica in ospedale in emergenza, attivo 24 ore; una rete per il referral dei pazienti ed un protocollo di valutazione dell'indicazione, delle controindicazioni e dei fattori di rischio coerentemente con le linee guida internazionali e le disposizioni locali; dati di follow up a tempo indeterminato di tutta la casistica trattata (almeno negli ultimi 5 anni); conferimento dei dati in un registro multicentrico secondo i criteri regionali e nazionali stabiliti. Analogamente, a livello macro, il Centro MSC dovrebbe comunicare ed essere

integrato con le altre organizzazioni/professionisti coinvolti nella gestione del paziente a tutti i diversi livelli di cura. Infatti il "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD" stabilisce che si debba sviluppare sul territorio nazionale una rete di competenze e comunicazioni per il follow up routinario e per il primo approccio alle emergenze. Inoltre il/le protocollo/procedure locali devono definire: la comunicazione delle dimissioni e delle raccomandazioni pertinenti alle ASL, ai servizi di emergenza, ai fornitori di energia elettrica ecc.; le modalità di formazione continua e di verifica di competenza del personale medico ed infermieristico che fornisce l'assistenza, sia all'interno che all'esterno (es. strutture riabilitative esterne, assistenza domiciliare). Sulla base delle informazioni fornite da tre produttori che hanno compilato il questionario, tutti i professionisti, pazienti e care givers sono istruiti, riguardo l'utilizzo della tecnologia, e/o per la gestione e la cura dei pazienti con LVAD, dagli stessi produttori/distributori. Due produttori, inoltre, hanno affermato di fornire un consulente tecnico esperto (del distributore) per l'intera durata del supporto o come supporto ai chirurghi durante l'impianto della tecnologia.

Aspetti regolatori (REG)

In Italia i sistemi LVAD registrati nel Repertorio dei dispositivi medici (RDM), classificati secondo la Classificazione nazionale (CND) nella classe "J010301 – SISTEMI DI ASSISTENZA VENTRICOLARE" sono 5, tutti con marchio CE e 2 con approvazione FDA (Food and Drug Administration - USA).

Conclusioni

La tecnologia sta rapidamente evolvendo e rappresenta oggi l'unica alternativa nei pazienti in cui il trapianto non è temporaneamente o definitivamente possibile.

L'effetto positivo di supporto LVAD nell' insufficienza cardiaca in stadio terminale è a favore della sopravvivenza, anche se la qualità delle evidenze è bassa e il verificarsi di eventi avversi importanti deve essere considerato con attenzione nella selezione dei pazienti.

La valutazione economica e di costo ha valutato tutte le informazioni economiche degli impianti LVAD rispetto a MMT utilizzando una revisione sistematica e una analisi microcosting, eseguita in due ospedali italiani in due regioni (Veneto e Lombardia).

La nostra revisione sistematica ha prodotto informazioni limitate sul rapporto costo-efficacia di LVAD rispetto alla MMT. Studi per raccogliere ulteriori informazioni sulla costo-efficacia di LVAD procedura di impianto e l'iter pre-impianto e la gestione del paziente LVAD durante il follow-up sono necessari.

LVAD è una tecnologia complessa, il cui utilizzo richiede non solo ingenti quantità di risorse umane, tecnologiche, organizzative ed infrastrutturali, ma anche una azione organizzativa coordinata ed impegnativa per assicurare il governo appropriato dell'attività di impianto. Tale attività dovrebbe essere realizzata in Centri esperti, evitandone la parcellizzazione che risulterebbe a detrimento dei risultati.

Nel contesto italiano finora non ci sono dati sufficienti per la valutazione economica sui LVAD rispetto alla MMT. Sono necessari una valutazione economica completa e un'analisi di impatto economico sui LVAD sulla base di dati raccolti da più centri italiani.

Il codice ICD9-CM 37.66 ("Inserimento del cuore impiantabile sistema di assistenza") non è specifico per LVAD impiantabile e pertanto non consente una rilevazione puntuale della sola procedura LVAD.

Raccomandazioni

Sono necessari ulteriori studi con raccolta di dati standardizzata per questa tecnologia in rapida evoluzione in quanto l'evidenza disponibile è di qualità bassa. Inoltre è improbabile che vi possano essere veri studi randomizzati per questa tecnologia. Pertanto registri obbligatori, aggiornati e controllati possono sopperire a questa mancanza. L'effetto positivo dei LVAD nell'insufficienza cardiaca in stadio terminale a favore della sopravvivenza e il verificarsi di eventi avversi importanti devono essere considerati con attenzione nella selezione dei pazienti.

Sono necessari studi che considerino non solo la procedura di impianto, ma anche l'iter di pre-impianto e gestione dei pazienti LVAD durante il follow-up per raccogliere ulteriori informazioni sulla costo-efficacia dei LVAD.

L'attività di impianto degli LVAD dovrebbe essere svolta in Centri esperti in grado di soddisfare requisiti rigorosi secondo quanto stabilito nel "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD"; requisiti descritti nel capitolo relativo alla dimensione organizzativa.

1. INTRODUCTION

The structure of this document is derived from that of the EUnetHTA Core Model (CM)® as adapted by Agenas as we detailed in the protocol. The CM is made up of numerous questions (generally known as Assessment Elements or AEs) which are listed in each chapter and identified by a letter and numbers (for example B0004) in the text for each different domain (perspective). Examples of domains are Current Use or CUR or safety - SAF). See **Appendix 1** for a full description.

The main stages of the production process of the report were the following: identification of the contributions (coordinator, authors, technology experts, reviewers); development of the research protocol with internal/external review; conducting the research and production of the document with internal audit/external review.

All the procedures that led to the production of this HTA followed the provisions in the Agenas' "Handbook on Procedures HTA" (http://www.agenas.it/aree-tematiche/hta-health-technology-assessment/attivita-hta).

2. OBJECTIVES, POLICY AND RESEARCH QUESTIONS

The objectives of this assessment were defined as follows:

Policy question

What is the effect of using a LVAD in addition to GDMT in adult patients with end stage heart failure who are not eligible or immediately eligible for cardiac transplant (bridge to transplantation or destination therapy) because of underlying (irreversible or not immediately reversible) pathologies?

Research questions

To answer the research question we used Agenas' model and structure derived from EUnetHTA Core Model® (see Appendix 1). For each investigated domain, we selected the Assessment Elements (AEs) as listed at the beginning of each domain.

We developed the report in the following domains:

1. Health problem and current use of technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Clinical effectiveness (EFF)
4. Safety (SAF)
5. Costs and economic evaluation (ECO)
6. Organisational aspect (ORG)

3. HEALTH PROBLEM AND CURRENT USE

3.1 METHODS

The following AEs from CUR domain were developed in accordance with the general scope of the project.

Assessment elements/Research questions

Assessment Element ID	Research question
A0001a	For which health condition is the technology proposed?
A0001b	Which group of patients represents the target population for the technology?
A0001c	For what purposes is the technology used?
A0002	What is the health condition in the scope of this assessment?
A0024	How is the health condition identified/diagnosed?
A0003	What are the known risk factors for the health condition?
A0004	What is the natural course of the health condition?
A0018	What are the alternatives to the current management of the health condition?
B0001b	What is(are) the comparator(s)?
A0011	What is the diffusion of the technology?

To assess the diffusion of the technology in Italy (A0011) we used the most recent information contained in the New Health Information System (NSIS) as the official source of the Ministry of Health. Among the broad information contained in NSIS we selected hospital discharges "SDO" database helpful for our investigation.

The sources of data for current use analysis were 2012 and 2013 national hospital discharges database (SDO 2012; SDO 2013).

The International Classification of Diseases (9^{th} Edition) - Clinical Modification (ICD9-CM) does not include specific code only for LVAD. For this reason, we searched discharges records with the ICD9-CM code 37.66 ("Insertion of implantable heart assist system") for VAD implantation

(including: Insertion of Implantable Heart Assist System; Axial Flow Heart Assist System; Diagonal Pump Heart Assist System; Left Ventricular Assist Device (LVAD); Pulsatile Heart Assist System; Right Ventricular Assist Device (RVAD); Rotary Pump Heart Assist System; Ventricular Assist Device (VAD); Not Otherwise Specified including BVAD, in at least one of variables corresponding to principal and other procedures in hospital discharges records.

Descriptive analyses was used on national and regional estimates on the numbers of VAD implantations. Data from SDO 2012 and 2013 were analyzed on the hypothesis that each single procedure had been carried out on a single patient, as the databases we used did not show the patient's code identification. Hospital and demographic characteristics were estimated and tabulated.

Data management and analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

3.2 RESULTS

(A0001a)

Heart failure remains a significant cause of morbidity and mortality in western countries. By 2010, over five million Americans carried a diagnosis of heart failure with another 825,000 patients receiving the diagnosis in that year alone [Alan 2014] and of at least 10 million in Europe [Swedberg 2005] and over 23 million worldwide with an overall prevalence to be about 2–3%[Lloyd-Jones D 2010, McMurray 1998].Roughly, 5% of patients with heart failure have end-stage disease that is refractory to medical therapy (stage D heart failure) [Costanzo 2008] and a prevalence of 0,2% [Khawaja A 2007].This patient population has a 1-year mortality rate of approximately 50% and requires special therapeutic interventions [Cleland 1999].The prevalence of moderate to severe systolic dysfunction (ejection fraction <40%) has prevalence of 2.0% [Redfield 2003]. In the Hillingdon study the incidence of heart failure increased from 0.2/1000 person years in those aged 45–55 years to 12.4/1000 person years in those aged >85 years. In Rotterdam the incidence increased from 2.5/1000 person years (age 55–64 years) to 44/1000 person years (>85 years or older).[Roger 2004, Levy2006]

(A0001b)

The target population for the technology are adults with end stage LV failure (reversible or irreversible conditions), stage D of the ABCD classification of the American College of Cardiology (ACC)/American Heart Association (AHA), class III–IV of the New York Heart Association (NYHA)

functional classification [Yancy 2013] and who are not eligible for transplant because of specific contraindications or donor unavailability. They are characterized by advanced structural heart disease and marked symptoms of heart failure at rest or upon minimal physical exertion despite optimal Guideline Directed Medical Therapy (GDMT) [see table 19 and 20 from Yancy 2013] and require specialized interventions. Left ventricle (LV)failure is the leading cause of severe heart failure.

(A0001c)

The purpose of the technology is to support cardiac output in end stage LV failure.

LVAD implantation has become the standard of care for many patients awaiting transplant (BTT), who develop end-stage organ dysfunction or a life threatening exacerbation of their existing heart failure [Frazier 1995, Farrar 1997, Frazier 2001] and for those who are not candidates for cardiac transplantation it represents a DT. In addition, as devices have improved and experience with LVAD has become more extensive, a subset of patients have been found to recover (bridge to recovery BTR) myocardial function after temporary LVAD support [Birks 2006]. Generally, patients with a high one-year mortality from heart failure, those who are inotrope dependent, or those who are otherwise unable to maintain end-organ function and are not expected to recover without long term MCS should be considered for LVAD placement [Feldman 2013].

Patients may cross from one group to the other as their clinical condition deteriorates or improves, or other medical co-morbidities cause a once transplant-eligible patient to remain on indefinite MCS.

(A0002)

The health condition in the scope of this assessment is: refractory to GDMT low cardiac output syndrome requiring a durable mechanical support.

(A0024)

The health condition is identified/diagnosed by severe impairment of functional class, hemodynamic parameters and LV function imaging. These are patients failing optimal medical management demonstrated by intolerance to drugs and diuretics and poor 6 minute walk test as well as recurrent heart failure readmissions [Pinkermann 2013].

(A0003)

The known risk factors for the health condition are: all cardiovascular risk factors.

(A0004)The natural course of the health condition is death by multiorgan failure and/or malignant arrhythmias.

(A0018)

There are no alternatives to the current management of the health condition

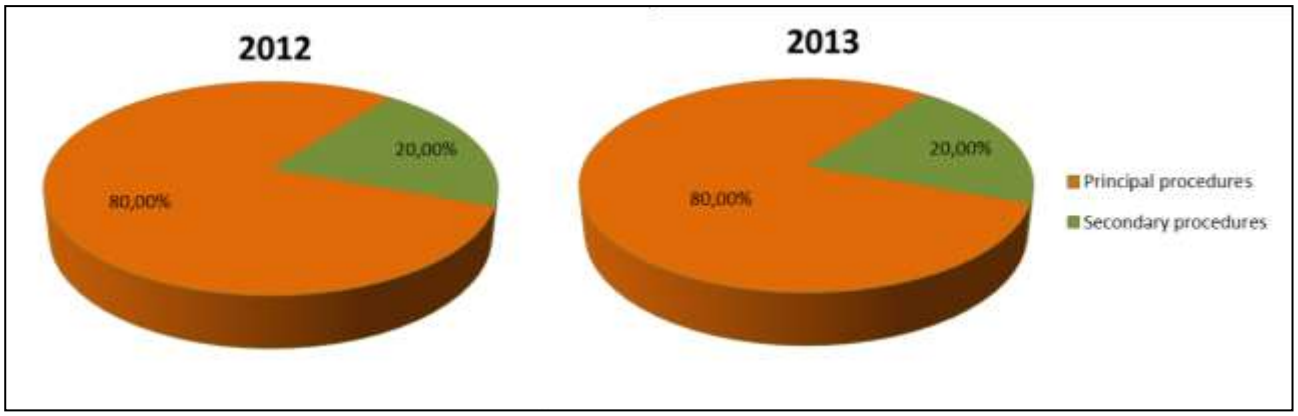
(B0001b)

The comparator is GDMT (including CRT-P, ICD and CRT-D)

(A0011)

The estimate absolute total number of VAD discharges in Italy was 85 in 2012 and 80[1] in 2013, of which the 80% was recorded as principal procedure (see Figure 3.1).

Figure 3.1: VAD implants performed in 2012 and 2013 in Italy.

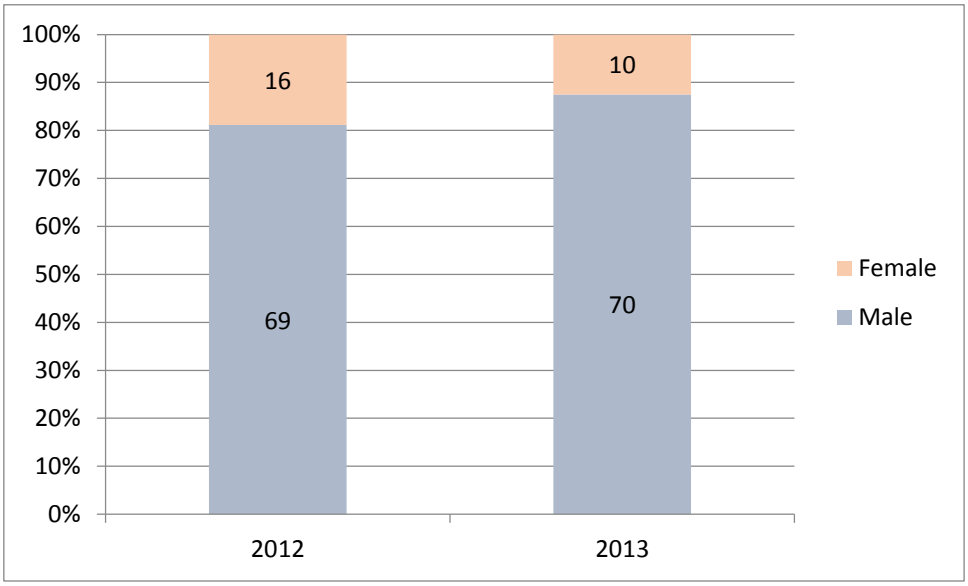


Source: Agenas analysis based on SDO 2012 and SDO 2013.

The data on discharges for VAD procedures show that the 81% and 87% of procedures are performed on males in 2012 and 2013 respectively (Figure 3.2) and more than 84% (for 2012) and 94% (for 2013) of cases were aged between 25 and 74 years (Table 3.1).

[1]This number does not include 1 discharge case because one Region warned us that there has been an error in the code used in the hospital discharge record.

Figure 3.2: Hospital discharges on VAD per gender– years 2012- 2013 (absolute values)



Source: Agenas analysis based on SDO 2012 and SDO 2013.

Table 3.1: Hospital discharges for VAD by age class – years 2012- 2013 (absolute and percentage values)

	2012		2013	
Age class (years)	**Absolute value**	**%**	**Absolute value**	**%**
0-24	**7**	**8.24**	**3**	**3.75**
25-64	**54**	**63.53**	**60**	**75.00**
65-74	**17**	**20.00**	**15**	**18.75**
75-84	**5**	**5.88**	**2**	**2.50**
85+	**2**	**2.35**		
Total	**85**	**100.00**	**80**	**100.00**

Source: Agenas analysis based on SDO 2012 and SDO 2013.

Table 3.2 reports VAD total discharge volumes broken down by Region. No case was found in seven Regions (Valle D'Aosta; P.A. Bolzano; P.A. Trento; Liguria; Marche; Molise; Sardegna). The

total number of centres performed VAD procedures was 24 and 22 for 2012 and 2013 respectively. Lombardia has the highest volume of VAD implantations followed by Veneto and Lazio (the volume ranges from 10 to 27 for 2012 and 11 to 25 for 2013). These Regions account for nearly 65% of the total discharges in 2012 and 71% in 2013. We found that all these discharges were allocated in 103 DRG codes.

Table 3.2: Distribution of VAD total discharge volumes by Region – years 2012-2013.

	2012			2013		
	Number of Centers	**Discharge**		**Number of Centers**	**Discharge**	
		Absolute value	**%**		**Absolute value**	**%**
PIEMONTE	**1**	**1**	**1.18**	**1**	**4**	**5.00**
VALLE D'AOSTA		**-**	**-**		**-**	
LOMBARDIA	**5**	**27**	**31.76**	**7**	**25**	**31.25**
P.A. BOLZANO		**-**	**-**		**-**	
P.A. TRENTO		**-**	**-**		**-**	
VENETO	**2**	**18**	**21.18**	**2**	**21**	**26.25**
FRIULI V. GIULIA	**1**	**1**	**1.18**	**1**	**5**	**6.25**
LIGURIA						
EMILIA ROMAGNA	**1**	**3**	**3.53**	**1**	**2**	**2.50**
TOSCANA	**1**	**4**	**4.71**	**1**	**2**	**2.50**
UMBRIA	**1**	**1**	**1.18**		**-**	
MARCHE		**-**	**-**		**-**	
LAZIO	**4**	**10**	**11.76**	**4**	**11**	**13.75**
ABRUZZO	**1**	**5**	**5.88**	**1**	**1**	**1.25**
MOLISE		**-**	**-**		**-**	
CAMPANIA		**-**	**-**	**1**	**2**	**2.50**
PUGLIA	**2**	**5**	**5.88**	**2**	**3**	**3.75**
BASILICATA	**1**	**1**	**1.18**		**-**	
CALABRIA	**1**	**1**	**1.18**		**-**	
SICILIA	**3**	**8**	**9.41**	**1**	**4**	**5.00**
SARDEGNA		**-**	**-**		**-**	
ITALY	**24**	**85**	**100.00**	**22**	**80**	**100.00**

Source: Agenas analysis based on SDO 2012 and SDO 2013.

4. DESCRIPTION OF THE TECHNOLOGY

4.1 METHODS

We concentrated our analysis on implanted LVADs commercialised and used in Italy. We consulted different sources to identify producers and models, including "Repertorio dei Dispositivi Medici" (RDM) and "Flusso Consumi" owned by Ministry of Health (referred to the VADs consumption in 2014) and a recent HTA report [Sutcliffe P et al., 2013]. The producers and distributors identified were contacted by e-mail and afterwards by questionnaire (Appendix 7. Manufacturer Questionnaire). Subsequently producers and distributors who accepted to participate were invited to discuss the information provided. We used technical information of non-responding producers from their official website. Producers and distributors were asked to identify competitors to ensure coverage of all LVADs used in Italy. Producers and distributors provided technical, regulatory, economical and organizational information.

Assessment Elements/Research questions

Assessment Element ID	**Research question**
B0001	What is this technology and the comparator(s)?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
Additional AE evaluated	
B0004	How is the technology used?
B0005	In which setting and level of care is the technology used?
B0009	What disposables and supplies are needed to use the technology?

4.2 RESULTS

We identified the following producers/Italian distributors:

- Berlin Heart GmbH;
- HeartWare Inc/Aptiva medical s.l.r;
- Jarvik Heart Inc/Artech s.l.r;
- Reliant Heart;

- Terumo Corporation;
- Thoratec Thoratech Corporation.

Subsequently we contacted them by e-mail. Three producers/distributors answered to our invite and provided information using the Agenas questionnaire (Appendix 7. Manufacturer Questionnaire): HeartWare Inc/Aptiva medical s.l.r., Jarvik Heart Inc/Artech s.l.r and Thoratech Corporation.

We identified the following devices: INCOR® (Berlin Heat GmbH), HVAD (HeartWare Inc), Jarvik 2000 FLOWMAKER® (Jarvik Heart Inc), HeartAssist5® (ReliantHeart Inc) andHeartMate II® LVAD (Thoratech Corporation) (B0001).

VADs are mechanical pumps that provide circulatory support to the failing heart by helping the ventricles to pump blood around the body. VAD is implanted with a cardiac surgery procedure and requires staff (e.g. cardio surgeons and biomedical engineer) for patient management (B0005). Many different mechanical devices have been developed to support the failing heart, ranging from total artificial hearts (TAH) to VADs. There are 3 major components of the VAD: the inflow cannula, the outflow cannula, and the pump itself. The inflow cannula is a large tube that drains blood from the heart into the pump; the outflow cannula returns blood to either the aorta (in a left ventricular assist device or LVAD) or pulmonary artery (in a right ventricular assist device).

VADs include left ventricular assist devices (LVAD), right (RVAD) or biventricular assist device (BiVAD). We concentrated on LVAD. LVADs were originally developed to serve as a temporary bridge to heart recovery, and then as a bridge to transplant [Givertz M 2011] or as DT. These devices are used as either short or long term support in patient awaiting Heart Transplantation (HT). They are implanted temporarily to support blood flow to allow the heart to recover from a condition, as post-myocardial infarction or post-cardiotomy shock. This procedure is known as BTR. When recovery is impossible and patient are ineligible for HT, then LVADs are used as DT [Sutcliffe P et al., 2013].

Usually LVADs are identified and classified as first, second and recently as third generation. The differences between generations are in dimensions, efficiency and durability of pump, the reduction of the excessive surgical dissection required for placement of the device, and nerveless reduction of diameter driveline and noisy pump operation. (B0003)

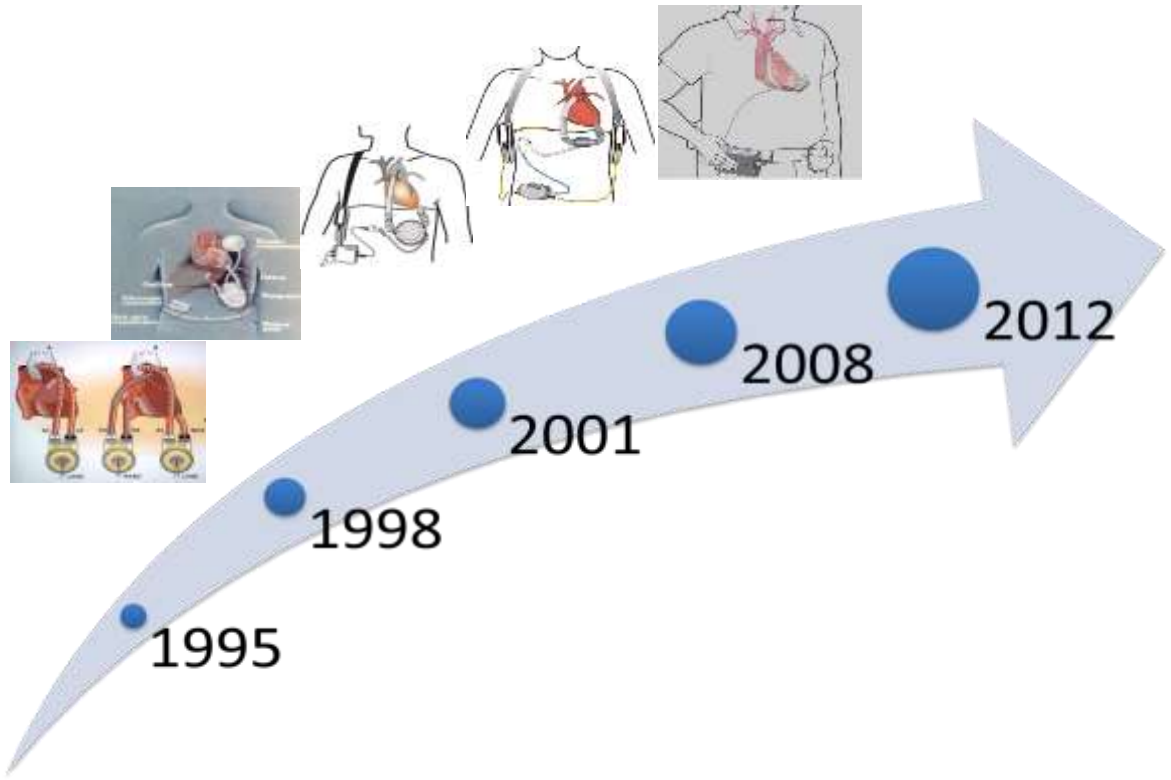


Fig. 4.1 - VAD technology evolution – based on (Zhongjun Jon Wu**,** Thrombogenicity of Mechanical Circulatory Support Devices: Experience and Challenges from Design to Clinical Use. http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM397155.pdf)

First Generation of LVAD Types

The first generation of VADs were pulsatile, volume displacement pumps and were paracorporeal pumps [Sutcliffe P et al., 2013] such as PVAD (Thoratec Inc.; Pleasanton, Calif, US) and the Berlin Heart Excor (Berlin Heart AG, Berlin, Germany), and implantable pumps such as HeartMate XVE (Thoratec Inc.), or Novacor (World Heart Corp., Oakland, Calif) [Garbade J 2011].

The HeartMate LVAD was first used in a clinical trial starting in 1986 as a pneumatically actuated system that required a large cumbersome console that did not allow patients much mobility outside the hospital. The HeartMate VE was used in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial to compare medical and circulatory assist device treatments for end-stage heart failure [Garbade J, 2011]. (B0003)

Second and third Generation of LVAD Types

The engineering of continuous-flow rotary pump technology represents a milestone and novel design concept for LVADs. The second- and third-generation LVADs, now in use, are smaller nonpulsatile continuous-flow blood pumps. Because of their simpler design (no mechanical bearings, no mechanical or biological valves), *these devices showed a potentially longer durability* [Garbade J, 2011]. These devices have now largely replaced the use of the first generation of pulsatile, volume displacement pumps. The second-generation rotary pumps have the advantage

of a smaller design and potential for greater long-term mechanical reliability by eliminating the reservoir chamber and valves needed for first-generation pulsatile pumps [Miller LW,2007]. The second-generation rotary blood pumps are typically with an "axial" blood flow path, which have an internal rotor within the blood flow path that is suspended by contact bearings.

In comparison, third-generation pumps have generally been used to categorize continuous-flow rotary devices with an impeller or rotor suspended in the blood flow path using a "noncontact" bearing design which uses magnetic forces or hydrodynamic levitation [Birks EJ, 2010].

Future generations of LVAD will undergo further reduction in size such as the HeartMate III (Thoratec Corporation) and MVAD (HeartWare Inc), and have integrated the rotor into the intraventricular housing eliminating the need for an inflow cannula as some earlier system as Jarvik 2000. [Giridharan GA, 2012]."(B0003)

Our assessment was on second and third generation on the devices most used in Italy and in particular on the following devices:

Manufacturer	Device name
Berlin Heart GmbH	INCOR®
HeartWare Inc	HVAD
Jarvik Heart Inc	Jarvik 2000 FLOWMAKER®
ReliantHeart Inc	HeartAssist5®
Thoratec Corporation	HeartMate II® LVAD

INCOR® - Berlin Heart GmbH

Berlin Heart GmbH has not provided information; we extract information from the HTA report by Sutcliffe P et al., 2013 and from INCOR® LVAD brochure (http://www.nefromedicas.com/files/Brochure_INCOR.pdf).

The INCOR LVAD is a magnetic bearing, flow pump with axial design which circulates blood from the LV apex to the ascending aorta. At present, the device is not available in the USA. [Sutcliffe P et al., 2013].

System is intended for use in acute or chronic left ventricular failure refractory to optimal medical and interventional therapy (NYHA class IV, INTERMACS Level 2-6).

INCOR® is an implantable left-ventricular assist device (LVAD), which in addition to BTT (bridge to transplantation) and BTR (bridge to recovery) therapy is also approved for use as permanent therapy or alternative to transplantation (ATT) in Europe with the CE mark [INCOR® LVAD brochure].

HeartWare HVAD – HeartWare Inc.

The HeartWare® System consists of a blood pump with an integrated, partially sintered inflow cannula; a 10mm diameter gel impregnated polyester outflow graft, and a percutaneous driveline. A strain relief is used on the outflow graft to prevent kinking and secures the outflow graft to the pump. The driveline cable is wrapped with woven polyester fabric to encourage tissue in-growth at the skin exit site. The small pump has a displaced volume of 50cc and weighs 160 grams. The pump has one moving part, an impeller, which spins blood to generate up to 10 L/min of flow. There are two motors in the pump housing with one motor providing redundancy. A short integrated inflow cannula is inserted into the left ventricle and the outflow graft connects the HVAD® Pump to the aorta. A sewing ring attaches to the myocardium and allows for pump orientation adjustments intraoperatively. The device size and short inflow cannula allow for pericardial placement and can be implanted via thoracotomy.

The others main components are:

- HeartWare® Controller: The controller is a microprocessor unit that controls and manages HeartWare® System operation. It sends power and operating signals to the blood pump and collects information from the pump.
- HeartWare® Monitor: The monitor is a touch screen tablet that uses proprietary software to display system performance and to permit adjustment of selected controller parameters.
- HeartWare® Controller Power Sources: The controller requires two power sources for safe operation: either two batteries, or one battery and an AC adapter or DC adapter.
- A set of surgical tools (B0009).

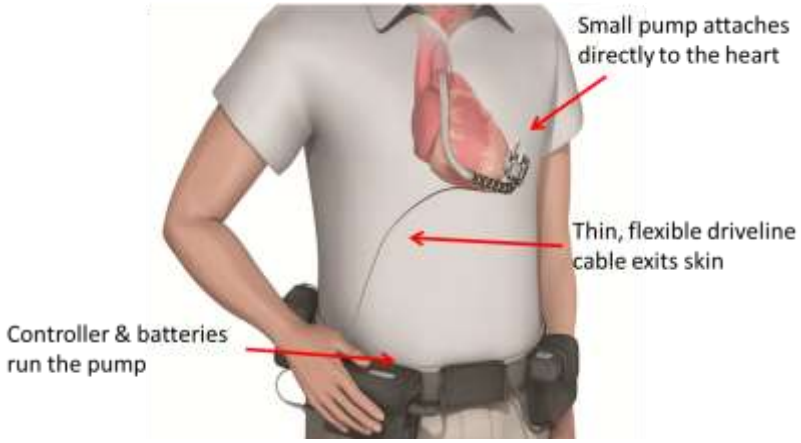


Fig. 2.2 – HeartWare HVAD, Implantable and External Components reproduced with permission from HeartWare.

All technical information about HeartWare HVAD were provided by the Italian distributor Aptiva medical s.l.r.

JARVIK 2000 FLOWMAKER® - Jarvik Heart Inc

Jarvik 2000® Ventricular Assist System (VAS) includes two models; the Model JHI-001 with a drive cable connector at the post-auricular area of the head, and the Model JHI-002 with a drive cable exiting the abdominal wall. The Jarvik 2000® Ventricular Assist Device (the blood pump itself) is identical for both models, only the drive cables and external connectors are different. The two models utilize identical VAD geometry, identical sewing cuff design, the same type of vascular graft, and the same basic drive cable configuration.

The Jarvik 2000® VAS Model JHI-001 with post-auricular connector is typically used for heart failure patients (NYHA Class IIIB and IV) who are ineligible for cardiac transplantation, or may become eligible for transplantation at some future time. This is often referred to as DT or BTR. As declared by producer the model JHI-001 is more suitable for periods of support exceeding six month due to the improved resistance to infection, and to the ability to shower (or swim) without waterproof dressings, provided by the post-auricular drive cable exit.

The Jarvik 2000® VAS Model JHI-002 with abdominal drive cable connector is typically used for heart failure patients (NYHA Class IIIB and IV) who are known to be eligible for cardiac transplantation, and who are waiting for a suitable donor organ, or require stabilization prior to receiving a donor organ. This is usually referred to as BTT. As declared by producer the Model JHI-002 may be more suitable for periods of support expected to be less than six months, due to the slightly improved easy of removal of the drive cable at the time of cardiac transplantation.

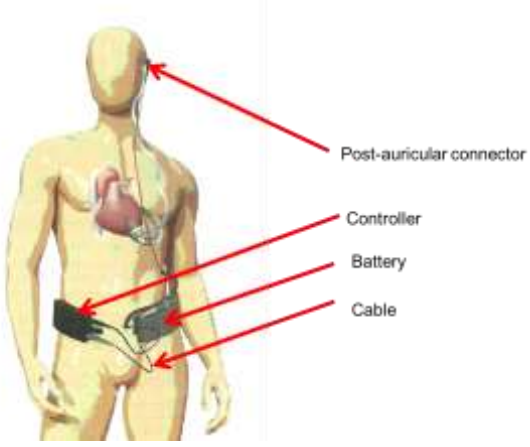


Fig. 4.3- Jarvik 2000®, Implantable and External Components reproduced with permission from Jarvik Heart Inc.

This LVAD has no inflow cannula; it is retained in the apex of the ventricle by means of a polymer ring on the sewing cuff, which engages in a mating groove in the VAD housing. Two umbilical ties located by loops on the sewing cuff, are tied to securely anchor the VAD. The VAD is implanted into the apex of the left ventricle by left thoracotomy, full-sternotomy or by combined minimal access (small left thoracotomy plus upper mid-sternotomy or bilateral mini-thoracotomy, left and right). A woven Dacron vascular graft offloads blood from the VAD, to either the descending or to the ascending thoracic aorta. The pump has provided of an Intermittent Low Speed (ILS) function that decreases every minute for few seconds the pump speed allowing the LV to wash the aortic root out by its own output.

Jarvik system includes many accessories as ILS Flowmaker controllers, batteries and cables. There is also a dedicated kit for the system implant.

All technical information about Jarvik 2000® were provided by the Italian distributor Artech s.l.r.

HeartAssist5® -ReliantHeart Inc

ReliantHeart Inc has not provided information; we extract information from the HTA report by Sutcliffe P et al., 2013 and from HeartAssist5® brochure (http://reliantheart.com/wp-content/uploads/2013/09/HeartAssist5-Technology-English.pdf).

The design of MicroMed DeBakey has been improved over the years and it is now marketed as HeartAssist 5, which has both CE and FDA approval as a BTT. HeartAssist 5 represent the new-generation device that includes new features such as flow accurate diagnostics and heart assist remote, which provide direct online measurement of blood flow. This is an improvement over MicroMed DeBakey in terms of designs, prevention of pump thrombosis and power fluctuation. In 2002, the MicroMed DeBakey was used in the USA as a BTT. Description from [Sutcliffe P et al., 2013].

HeartAssist5® is small Axial Flow Pump. The HeartAssist5® VAD weighs 92 grams. The pumping components have been optimized to reduce shear forces on the blood. Other components are the HeartAssist5® inflow cannula, a controller, a programmer and e remote monitoring. *The HeartAssist5® utilizes a proprietary ultrasonic flow probe to measure and display heart and pump interaction. Real time flow measurement provides accurate VAD flow and helps to simplify patient management during critical clinical situations* [HeartAssist5® brochure].

HeartMate® II - Thoratec Corporate

HeartMate® II LVAS is an axial-flow, rotary ventricular assist system. Designed for long-term implantation, it is capable of pump flows up to 10 liters per minute.

Attached to the apex of the left ventricle and the ascending aorta, by means of an inflow and outflow conduit respectively,the pump diverts blood from the weakened left heart and propels it forward. The System Controller regulates the pump speed and has the ability to adjust blood flow to be responsive to biologic demand.

HeartMate II Left Ventricular Assist System (LVAS) consists of an implanted axial flow blood pump and external main components as:

- System Pocket Controller: is a microprocessor unit that controls pump operation and management. The unit sends power and operating signals to the blood pump and collects and interprets information received from the implanted device. The Controller initiates pre-programmed adjustments in pump operation to maintain the selected level of cardiac support. The System Controller is wearable.
- Power Module: provides power to the HeartMate LVAS during tethered operation (when connected to AC mains electrical power).

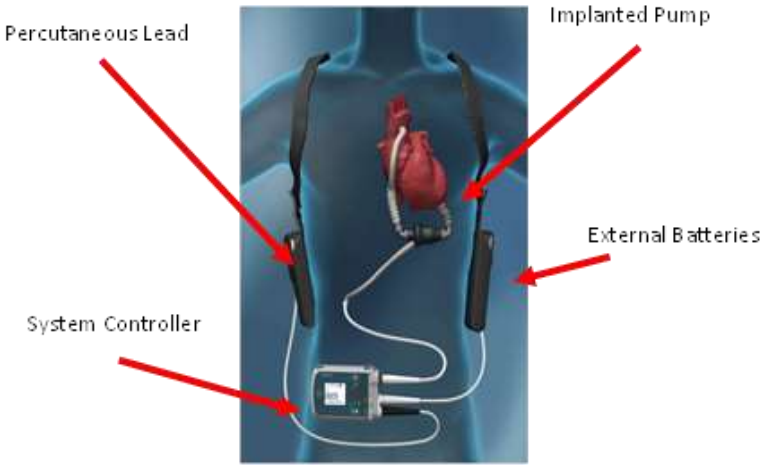


Fig. 4.4 – HeartMate II LVAS, Implantable and External Components reproduced with permission from Thoratec Corporate

All technical information about HeartMate® were provided by Thoratec Corporation.

Other components are a Patient Cable connecting the Power Module (PM) to the System Controller's power leads, Universal Battery Charger AC Cord**,** Advanced Battery Technology for patients' active lifestyles and Universal Battery Charger (UBC).

5. REGULATORY ASPECTS

The following research questions were selected in order to describe the LVADs most used in the Italian market and their regulatory status. As sources we use the RDM and the questionnaire (Appendix 7. Manufacturer Questionnaire) received from producers and distributors involved.

Assessment Element ID	Research question
A0020	What is the marketing authorisation status of the technology?
I0016	Does the technology need to be listed in a national/EU database?

In Italy LVADs were registered on the General Repertory of medical devices (RDM) (as of 4rd September 2015) using the National Classification of Medical Devices (CND) code associated to this kind of devices: "J010301 – SISTEMI DI ASSISTENZA VENTRICOLARE". Using the search results on RDM, integrating data with searches on the internet and with the contribution of manufacturers who provided information we represented the regulatory status of devices assessed. (A0020) (I0016).

Manufacturer	Model	RDM	CE mark	FDA approval for BTT	FDA approval for DT
Berlin Heart GmbH	**INCOR®**	**81899**	**2010**	**-**	**-**
HeartWare Inc	**HVAD**	**306813**	**2009**	**2012**	**-**
Jarvik Heart Inc	**Jarvik 2000 FLOWMAKER®**	**79807 (mod. JHI-001)** **301688 (mod. JHI-002)**	**2005**	**-**	**-**
ReliantHeart Inc	**HeartAssist5®**	**412578**	**2012**	**-**	**-**
Thoratec Corporation	**HeartMate II® LVAD**	**63451**	**2005*** **2010****	**2008**	**2010**

*Declared by Manufacturer. **RDM .

6. CLINICAL EFFECTIVENESS

6.1 METHODS

The following research questions contained in AEs were addressed in this domain, in accordance with the research protocol.

Assessment Element ID	Research question
D0001	What is the effect of the intervention on all-cause mortality?
D0002	What is the effect on the disease-specific mortality?
D0005a	How does the technology affect symptom frequency of the target condition?
D0005b	How does the technology affect symptom severity of the target condition?
D0005c	How does the technology affect symptom duration of the target condition?
D0006a	How does the technology affect the progression of the target condition?
D0006b	How does the technology affect the recurrence of the target condition?
D0012	What is the effect of the technology on generic health-related quality of life?

We looked for HTA reports, systematic reviews, randomized controlled trials, controlled clinical trials, and case series carried out in adults with advanced LV failure and with reversible or irreversible conditions who were not eligible for transplant. The interventions were LVAD with GDMT compared with GDMT (including CRT-P, ICD and CRT-D) and the outcomes of interest were mortality and morbidity, postoperative length of stay and duration of inotropic support.

The literature search strategy is in Appendix 2 and a list of excluded studies in Appendix 3.

The search was carried out on 14 April 2015. Analysis of clinical effectiveness of LVAD and its comparator was carried out using the following approach. Studies of interest were evaluated by researchers independently and a flow chart for the selection of the studies was drawn up. A standardized data extraction sheet was developed and used by two review authors that

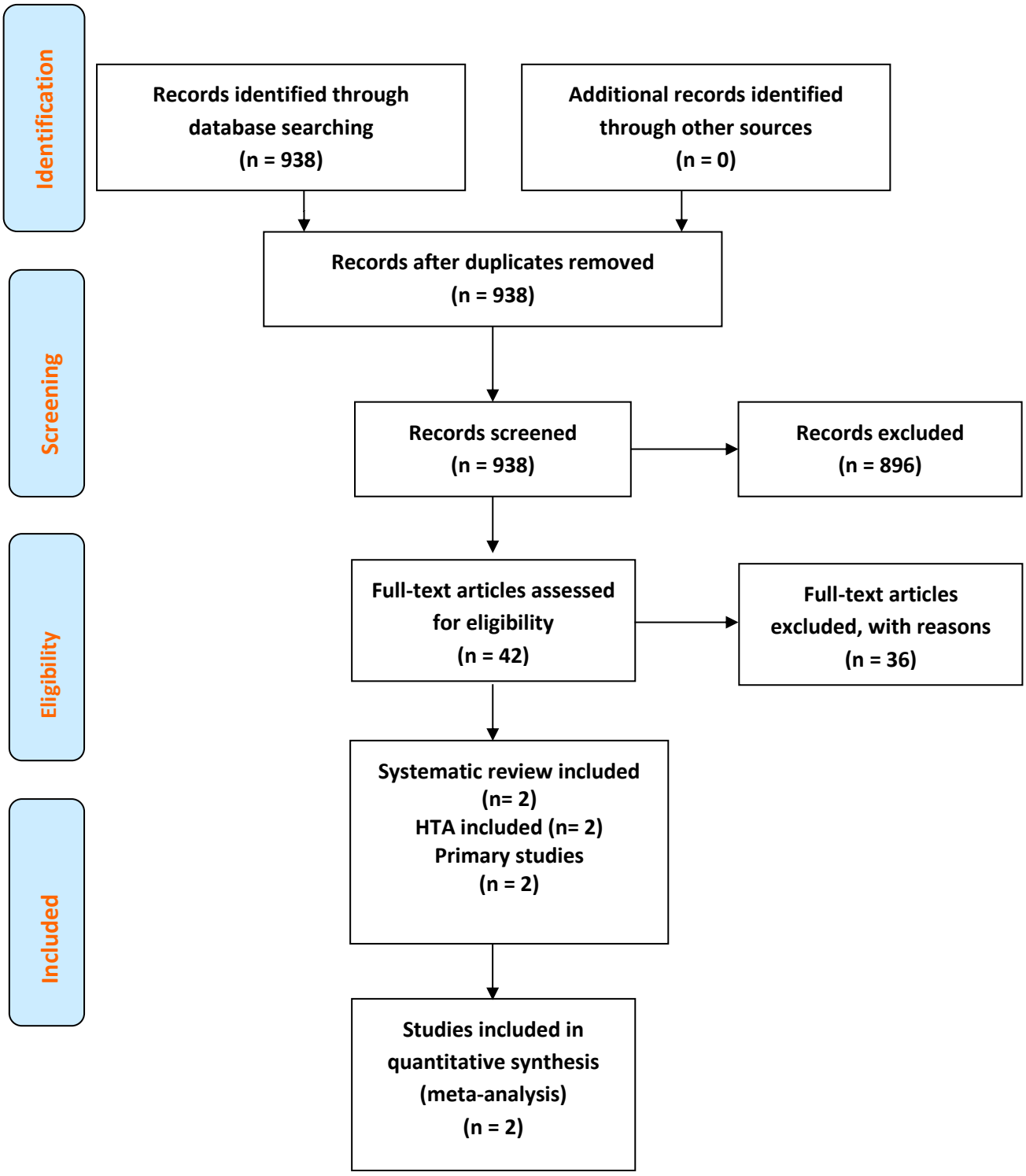
independently extracted data. Agreement among researchers was sought for both included articles and data extraction.

Risk of bias was assessed using the Cochrane tool [Higgins 2011]. Items of risk of bias included: sequence generation, allocation concealment, blinding of patients and participants, blinding of outcome assessor, incomplete outcome data, selective outcome reporting.

6.2 RESULTS

The literature screening process was done considering both domains EFF and SAF and is shown in Figure 6.2.1.

Figure 6.2.1: Flow-chart of the studies according to PRISMA (from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.



Below is an outline of included HTA reports (Table 6.2.1), systematic reviews (Table 6.2.2), and primary studies (one RCT and one CCT).

HTA reports

Table 6.2.1: HTA reports

Article	- **Literature search dates** - **Included Study type** - **Outcomes of interest for this report**	**Conclusions**
Sutcliffe 2013	- 2003 to March 2012 - Publications with control groups, case series with more than 50 patients - Survival, functional capacity (e.g. change in New York Heart Association functional classification), quality of life and adverse events	Authors highlight the limitation of the clinical effectiveness because of lack of randomised controlled trials.
Clegg 2005	- Up to 2003 - Systematic reviews, randomized, controlled trials (RCTs), controlled clinical trials, cohort studies, case series, case studies, economic evaluations and cost studies. - Survival, functional capacity (e.g. New York Heart Association (NYHA) functional classification, activities of daily living) and and quality of life.	Authors concluded that LVADs could be clinically effective as a BTT with ESHF, however, the economic evaluation indicated that they are not cost-effective. Further research is needed to examine the clinical effectiveness of LVADs for people with ESHF, assessing patient survival, functional ability, quality of life and adverse events.

Sutcliffe 2013 reports the clinical effectiveness and cost-effectiveness of second- and third-generation LVAD as either BTT or alternative to transplant for adults (> 16 years) eligible for HT. The authors systematically searched MEDLINE, Embase, the Cochrane Library and 6 databases. The inclusion criteria were publications from the last 5 years with control groups, or case series

with 50 or more patients. Outcomes included were survival, functional capacity (e.g. change in New York Heart Association functional classification), quality of life and adverse events. The authors found 40 publications on clinical effectiveness and one about cost-effectiveness of VAD. No comparative trial of VAD with optimum medical management or heart transplant were identified. Some publications reported outcomes (e.g. on clinical functioning or functional assessment/ quality of life) using patients as their own controls (before–after designs) or within-study comparison on the basis of baseline characteristics such as age > 70 years. According to the authors, approximately 15-25% of the patients receiving a device had died by 12 months. Studies reported the following wide ranges for adverse events: 4-27% bleeding requiring transfusion; 1.5-40% stroke; 3.3-48% infection; 1-14% device failure; 3-30% HF; 11-32% reoperation; and 3-53% renal failure. Quality of life and functional status were reported as improved in studies of two devices [HeartMate II (HMII; Thoratec Inc., Pleasanton, CA, USA) and HeartWare (HW; HeartWare Inc., Framingham, MA, USA)]. The authors concluded highlighting the limitation of the evidence due to lack of randomized trials.

Clegg AJ 2005 assessed the clinical and cost effectiveness of LVADs as a BTT, as a BTR or as a long-term chronic support (LTCS) for people with end-stage heart failure (ESHF) in people aged 16 or older. Primary outcomes considered were: survival, functional capacity (e.g. New York Heart Association (NYHA) functional classification, activities of daily living) and quality of life. The authors found sixteen studies assessing the clinical effectiveness of *LVADs as a BTT* (11 first generation and 5 second generation). Evidence of the clinical effectiveness of *LVADs as a BTR* was limited to seven non-comparative observational studies (first generation only) that appeared to show that the LVADs were beneficial in providing support until myocardial recovery. Six studies assessed the clinical effectiveness of *LVADs as an LTCS* (4 first generation and 2 second generation). The authors concluded that for LVADs as BTT despite the poor methodological quality of the evidence, LVADs appeared beneficial compared to other treatment options (i.e. inotropic agents or usual care) or to no care (i.e. the natural history of ESHF) improving the survival of people with ESHF during the period of support and following heart transplantation and patients supported by a LVAD appeared to have an improved functional status compared with those on usual care and experienced an improvement in their quality of life from before device implantation to the period during support; for LVADs as a BTR it was not possible to assess whether the LVAD was more effective than other alternatives or specific devices. No evidence was found on the quality of life or functional status of patients and limited information on adverse events was reported; for LVADs as LTCS, although the nature and methodological quality of the evidence varied between the different

devices, it was evident that LVADs provided benefits in terms of improved survival, functional status and quality of life. The final conclusion reported that although the review showed that LVADs are clinically effective as a BTT in ESHF, the economic evaluation indicated that they were not cost-effective.

Systematic reviews

Table 6.2.2: Systematic reviews

Article	**-Literature search dates** **-Included Study type** **-Outcomes of interest for this report**	**Conclusions**
McIlvennan 2014	- January 2007 to December 2013 -All studies for all indications including DT and BBT - Estimated actuarial survival, functional class and quality of life and adverse events.	Authors conclude that there are consistent improvements in survival and quality of life in favour of L-VAD devices that are however counterbalanced by a range of adverse events. They also highlight the need for high-quality patient-centered data collected with standard definitions.
Boothroyd 2013	- January 2008-June 2012 -NA -Survival, Recovery, Transplantation; NYHA class I or II; Mean/median 6 min walk distance; Neurocognition; Renal/hepatic function.(All divided by transplant eligibility and type of device)	The authors concluded that evidence is sufficient to support LVAD use regardless of transplantation eligibility status, as long as patients are carefully selected and program infrastructure and budget are adequate

McIlvennan 2014 performed a systematic search on PubMed and Cochrane Library from January 2007 to December 2013 to summarize the current evidence on outcomes of continuous-flow left ventricular assist devices. The authors considered studies of any design and with all indications including DT and BTT. The studies included were 10 industry-funded trials and registries, 10 multicenter reports, and the remainder single-center observational experiences. Estimated actuarial survival after continuous-LVADs ranged from 56% to 87% at 1 year, 43% to 84% at 2 years, and 47% at 4 years. Improvements in functional class and quality of life were reported, but missing data complicated interpretation. Adverse events were experienced by the majority of patients, but estimates for bleeding, stroke, infection, right heart failure, arrhythmias, and rehospitalizations varied greatly. The authors conclude that there are consistent improvements in survival and quality of life in favour of LVAD devices that are however counterbalanced by a range of adverse events. They also highlight the need for high-quality patient-centered data collected with standard definitions.

Boothroyd LJ 2013 reviewed the evidence on clinical effects and cost-effectiveness of 2 types of continuous-flow LVADs (HeartMate II [HM II] and HeartWare), for BTT and DT patients. They systematically searched the scientific literature from January 2008 to June 2012. They included 14 clinical studies (approximately 2900 HM II and approximately 200 HeartWare patients. They reported 1-year survival reaching 86% for BTT and 78% for DT (compared with 25% for medical therapy), as expected survival was higher for transplant-eligible patients than for transplant-ineligible patients. For patients who could be tested an improvement of activities of daily living after LVAD therapy was shown, at least 80% of those of either patient type or with either device implant were able to accomplish with minor or no symptoms, based on NYHA class, at 6 months of LVAD support. Also at 6 months of support, patients could walk an average of > 270 m in 6 minutes; an average of > 300 m was sustained at 2 years for HM II transplant-ineligible patients. Common adverse events were bleeding (as expected for major surgery), infections, and arrhythmias. When comparing transplant-eligible and transplant-ineligible patients who received an HM II implant, the rates of adverse events were quite similar. Quality of life at 6 months, according to the Kansas City Cardiomyopathy Questionnaire, improved to a clinically significant extent (more than 5 points) across patient type and device, when compared with baseline. For patients not eligible for transplantation, the improvement persisted at 2 years of support. Similar improvements for transplant-eligible patients were found using the Minnesota Living With Heart Failure instrument at 6 months (HM II), and using the generic European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale at 6 months (HW)and at 1 year (HM II). Only 1 quality of life study did not find significant improvement in overall score using the generic Short Form 36 (SF-36) questionnaire at 6 months of support for 36 transplant-eligible HM II patients, compared

with assessment at approximately 6 weeks after implantation (rather than a baseline measure before implantation in other studies). The authors conclude that evidence is sufficient to support LVAD use, regardless of transplantation eligibility status, as long as patients are carefully selected and program infrastructure and budget are adequate. Data were however limited to 2-3 studies per outcome with gaps in information across the various time points.

Primary studies (see also extraction at Table 6.2.3)

We identified only two prospective comparative studies which could contribute to the evidence base of safety and efficacy of LVAD. One trial was randomized and the other was a non-randomized controlled clinical trial.

Table 6.2.3: L-VAD Characteristics of included primary studies

ID Study [ref.]	Country	Study Design	Procedure	Patients	Groups (number of patients)	Device assessed (Manufacturer)	Comparator	Outcomes reported	Funding	Conflict of interest
Rose 2001	USA	Randomized trial	LVAD	129 patients with end-stage heart failure (NYHA class IV) and ineligible for cardiac transplantation	LVAD: 68; optimal medical management: 61.	Thoratec	optimal medical management	Overall survival serious adverse events Days of hospitalization Quality of life Depression Functional status.	Mixed funding (National Heart, Lung, and Blood Institute and Thoratec Corporation.)	Yes (one author full employee of Thoratec Corporation
Rogers 2007	USA	Cohort prospective comparative	LVAD	55 patients with NYHA IV symptoms who failed weaning from inotropic support	LVAD: (n=37); Comparator group (n=18)	Novacor LVAD	Optimal medical therapy	Functional capacity (assessed with NYHA functional class assessment)	Funded by for profit agency (WorldHeart, Oakland, California)	Yes (Authors reported payment for conducting the study or were member of WorldHeart

Rose 2001 was a randomized trial investigating the efficacy of LVAD compared to optimal medical therapy. Included patients were adults with chronic end-stage heart failure NYHA class IV heart failure for at least 90 days, contraindications to transplantation in addition to a peak oxygen consumption of no more than 12 ml per kilogram of body weight per minute or a continued need for intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion. The primary end point was death from any cause whereas the secondary end points included the incidence of serious adverse events, the number of days of hospitalization, the quality of life, symptoms of depression, and functional status.

The authors stated that the study was randomized but failed to report how the random numbers were generated and how allocation was concealed. The assignment was based on blocks but numbers were not reported. The outcome assessors were blinded. Analysis was by intention-to-treat and only two patients were lost to follow-up. The two groups did not have any statistical difference in terms of prognostic factors.

The study was funded by the National Heart, Lung, and Blood Institute and the Thoratec Corporation that was the manufacturer of the device. One of the authors was employed by the manufacturer.

Rogers 2007 prospectively enrolled 55 patients in 13 centers in the US and Canada. Eligible patients were adults with an ejection fraction <25%, and NYHA functional class IV symptoms for ≥ 3 months before enrollment, inotrope-dependent stage D heart failure, and were not candidates for cardiac transplantation. Patients were excluded from the study if their body surface area was ≤ 1.5 m^2 or there was a contraindication to chronic anticoagulation. Eighteen of the included patients did not receive an LVAD either because of patient preference (n=14) or unavailability of the device (n=4) but consented to follow-up and represented the control group. All-cause mortality at 6 months was the primary end point whereas all-cause mortality at 12 months, adverse events, functional capacity, and health related quality of life were secondary end points.

Methodologically the study was not randomized and was thus liable to selection bias, however, there was no statistically difference among the groups in terms of predictors of adverse outcomes in heart failure except for plasma sodium level that resulted higher in L-VAD group (134 mmol/dl ± 4.3) than in the control group (128 mmol/dl ± 8.0). Both groups had elevated liver function tests, elevated blood urea nitrogen and creatinine, and hyponatremia indicating an end-organ hypoperfusion. The study reported relevant outcomes and apparently all participants were included in the final analysis.

The study was funded by the L-VAD manufacturer for-profit agency (WorldHeart) and authors declared the presence of conflict of interest with WorldHeart.

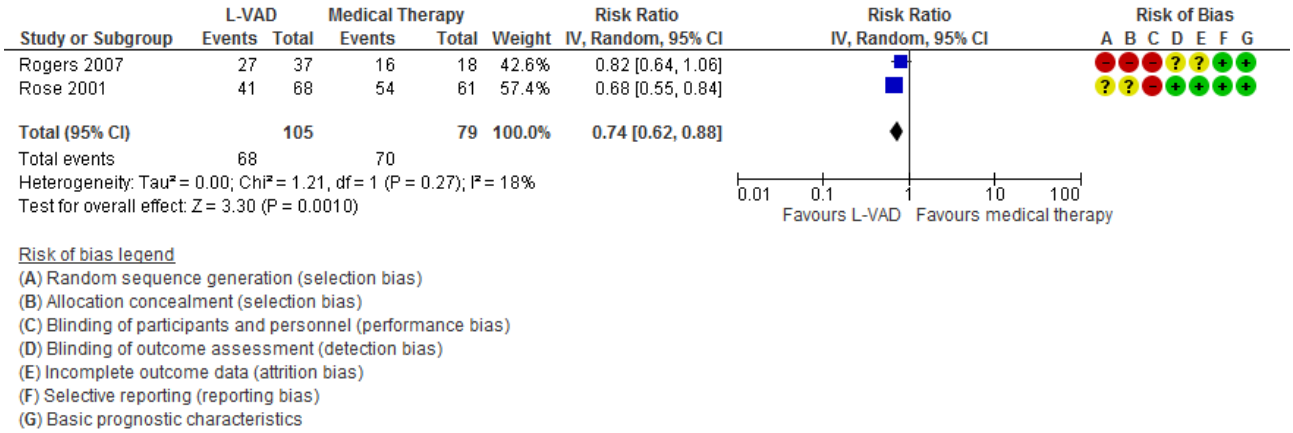
Meta-analysis of primary studies (Rose 2001 and Rogers 2007)

Overall mortality (D001)

Both studies reported overall mortality and data in terms of patients population and the device used were comparable [Rose 2001; Rogers 2007]. In Rose 2001 41/68 subjects in the LVAD group and 54/61 in the OMT group died during follow-up whereas in Rogers 27/37 in the LVAD group and 16/18 control group died. The pooled overall mortality showed a reduction of mortality at 12 months by 26% [RR 0.74(95% CI 0.62, 0.88] without important heterogeneity.

The following figure shows the meta-analysis for overall mortality with risk of bias table.

Figure 6.2.2 : Meta-analysis for overall mortality with risk of bias table



Health-related quality of life (D0012)

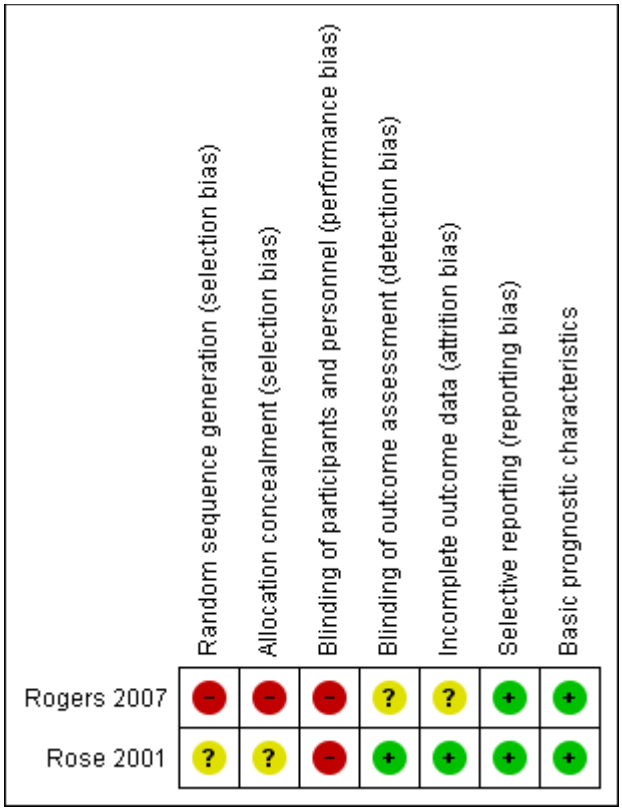
In the randomized trial [Rose 2001] quality of life and functional status were assessed with the use of the Minnesota Living with Heart Failure questionnaire, two prespecified subscales — physical function and emotional role — of the 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36), and the NYHA classification. In the device group all but 1 of the 24 patients who were alive at one year completed the questionnaires; 5 of the 11 patients in the control group did not complete the questionnaires.

Scores on the physical-function and emotional role subscales of the SF-36, the Beck Depression Inventory and the NYHA class were significantly higher in the device group whereas no significant difference were observed in the Minnesota Living with Heart Failure scale.

Rogers 2007 et al [Rogers 2007] reported that the Minnesota Living With Heart Failure Questionnaire scores and SF-36 Health Survey physical and mental functioning scores improved throughout the observation period in the LVAD group but data were not reported. In addition, they reported that the small number of patients in the medical group did not allow a meaningful comparison of the quality of-life measures.

Our assessment of the Risk of Bias in Rogers 2007 and Rose 2001 is at Fig. 6.2.3

Fig. 6.2.3: Risk of Bias in Rogers 2007 and Rose 2001



Our search strategy failed to identify sufficient evidence to answer AEs D0002, D0005c, D0006a and D0006b.

7. SAFETY

7.1 METHODS

The following research questions were addressed in this domain, in accordance with the research protocol.

Assessment elements/Research questions

Assessment Element ID	Research question
C0001	What harms are associated with the use of the technology?
C0002	Are the harms related to the exposure to the technology?
C0005	Are there susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are there applications or maintenance procedures of the technology which may increase the risk of harmful events?
C0061	Can different organizational settings increase or decrease harms?
C0062	How can the safety risks for patients be reduced?
C0063	How can the safety risks for professionals be reduced?

Our search flow is reported in Fig 6.2.1. (see search strategy in Appendix 2 and excluded studies in Appendix 3). Data on the *safety* of the use of the technology were summarized in a descriptive summary.

7.2 RESULTS

Adverse events (C001)

Adverse events were more consistently reported across 2 studies.

Rose 2001 reported that the rate of adverse events was more than two times higher in the LVAD group than in the control group (rate ratio, 2.35; 95% CI, 1.86 to 2.95). The most relevant events were represented by non-neurological bleeds and neurological dysfunction. Device-related adverse events comprised infection of the left ventricular assist device (with a probability of occurrence of 28 percent (95% CI , 15 to 38 percent), bleeding (with a frequency of 42 percent at 6 months). Though no device failed by 12 months, the probability of device failure was 35% at 24 months. In 10 patients the device was replaced.

Rogers 2007 reported that bleeding was the most reported adverse event and its rate was higher in the LVAD group than in the control group. Cardiovascular dysfunction and stroke were also significantly associated with device use. The rate of infections was higher in the LVAD group but no statistical difference was observed compared to the control group. Conversely, renal failure was significantly higher in the control group than in the device group.

Food and Drugs Administration (FDA) is alerting health care providers, patients, and caregivers about serious adverse events associated with LVADs. These adverse events include an increased rate of pump thrombosis (blood clots inside the pump) with Thoratec's HeartMate II and a high rate of stroke with the HeartWare HVAD since approval of the devices. FDA is also aware of bleeding complications associated with both devices (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm457327.htm August 2015). Although the HVAD is not currently approved for DT, it is the same device approved for the BTT indication. The FDA is aware of bleeding complications related to both the Thoratec HeartMate II and HeartWare HVAD, through adverse event reports and information from a variety of sources. The cause of bleeding complications is not fully understood, but is likely due to many different factors. One possible factor may be modification to blood thinning (anticoagulation) therapy in an attempt to lower the risks of pump thrombosis and embolic stroke.

FDA concludes however that "a careful review of all available data suggests the benefits of the device, when used in appropriately selected patients, continue to outweigh the risks for the currently approved indications."

Our search strategy failed to identify sufficient evidence to answer AEs C0002, C0007, C0060, C0061, C0062 and C0063.

7.3 DISCUSSION CLINICAL EFFECTIVENESS AND SAFETY

We summarized previous systematic reviews and HTA reports on the effectiveness and safety of LVAD use for patients with end-stage heart failure. We also identified and assessed primary studies with controls focusing on specific outcomes including overall mortality, disease specific mortality, the impact of the technology on symptom frequency, severity and duration, the progression and recurrence of the target disease and its effect on health related quality of life.

Two studies included in our assessment showed a consistent improvement in 1-year overall survival in favour of patients that received LVAD. However, none of the two studies was free from selection bias and the overall sample size was limited. Also the main limitation of experimental studies was the lack of controls.

The following data were not reported or were incompletely reported in the studies examined: disease specific mortality, the impact of the technology on symptom frequency, severity and duration, the progression and recurrence of the target disease.

Thus a standardized data collection should be mandated for hospitals.

Furthermore it is unlikely that true randomized trials in this therapeutic space will ever exist. Thus properly maintained and audited mandatory registries may be the only solution. Such registries such as INTERMACS in the USA and IMACS in Europe have started toward this goal.

Food and Drugs Administration (FDA) although alerting (August 2015) health care providers, patients, and caregivers about serious adverse events associated with LVADs concludes that "a careful review of all available data suggests the benefits of the device, when used in appropriately selected patients, continue to outweigh the risks for the currently approved indications."

8. COST AND ECONOMIC ANALYSIS

8.1 METHODS

We have focused on continuous-flow LVADs since pulsatile-flow LVADs seems to be no longer implanted in adults as long term support system in Italy, as indeed confirmed by manufacturers. The studies on pulsatile-flow LVAD were not extracted and analyzed in this review. Anyway the main findings of the 2 referenced reports by Clegg [Clegg et al, 2005] and Sharples [Sharples et al, 2006] were briefly reported.

Assessment Element ID	Research question
E0001	Can you identify what types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?
E0002	Can you quantify what amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?
E0009	What were the measured and/or estimated unit costs of the resources used by the assessed technology and its comparator(s)?
E0005	What is (are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?
E0006	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?
E0010	What are the uncertainties surrounding the inputs and economic evaluation(s) of the technology and its comparator(s)?
E0012	To what extent can the model estimates of inputs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)?
G0007	What are the likely budget impacts of implementing the technologies being compared?

We carried out a systematic review to answer cost and economic Assessment Elements. Italian and international scientific literature was searched to identify and analyze the economic studies on LVAD in addition to GDMT in patients with end stage heart failure who are not eligible or immediately eligible for cardiac transplant (bridge to transplantation or destination therapy) because of underlying (irreversible or not immediately reversible) pathologies.

Three electronic databases including Pubmed, Embase, Cochrane library (EED database - HTA database) were searched for published studies from January 2002 to May 2015. The search strategy is described in Appendix 4. We included all types of economic analysis: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-consequences analysis (CCA) and cost-minimization analysis (CMA) comparing the use of LVAD plus MMT with MMT alone. Cost analyses which reported insufficient details or full economic evaluations which did not provide an estimate of cost-effectiveness were excluded. When more papers referred to the same economic analysis or model, only the papers with more recent data and the most complete reports were included.

Two reviewers (MC and SP) independently screened the title or abstract (if available) of studies yielded from literature searches. Disagreements were resolved through discussion. The full texts of potential eligible studies were investigated to select studies to be included in the analysis, according to the inclusion criteria stated above. Differences in reviewers' judgments were resolved by discussion. We used EndNote X7.2 to manage retrieved studies. Economic data from included studies were extracted by one reviewer using a predefined extraction sheet, and were checked by a second reviewer. Resolution of the differences in the extraction was reached by mutual agreement. The quality of the included study was investigated by a single reviewer using the guidelines for authors and peer reviewers of economic submissions to the BMJ [Drummond M, 1996]. Economic assessment was performed through a narrative review based on tabulation of economic data and results of all included studies. The interpretation of the studies' results was done in terms of numerousness, quality and consistency.

To our knowledge the only case study reporting Italian costs for LVAD implantation was carried out for a national project run by Centro Nazionale Trapianti (CNT) – Istituto superiore di Sanità (Grave insufficienza d'organo – Cuore). Agenas was involved in that project conducting a systematic review of the economic evaluations on LVAD. The case-study named "LVAD: tecnologia, efficacia, sicurezza, analisi economica e fabbisogno nazionale" in 2012 was a micro-costing analysis performed in two Italian hospitals in two Regions (Veneto and Lombardia). The cost analysis was constructed using full cost method, that includes procedure costs (general costs) plus indirect costs. The data were collected by management control systems and checked with cardiac surgery units to identify the consumption of the most relevant resources.

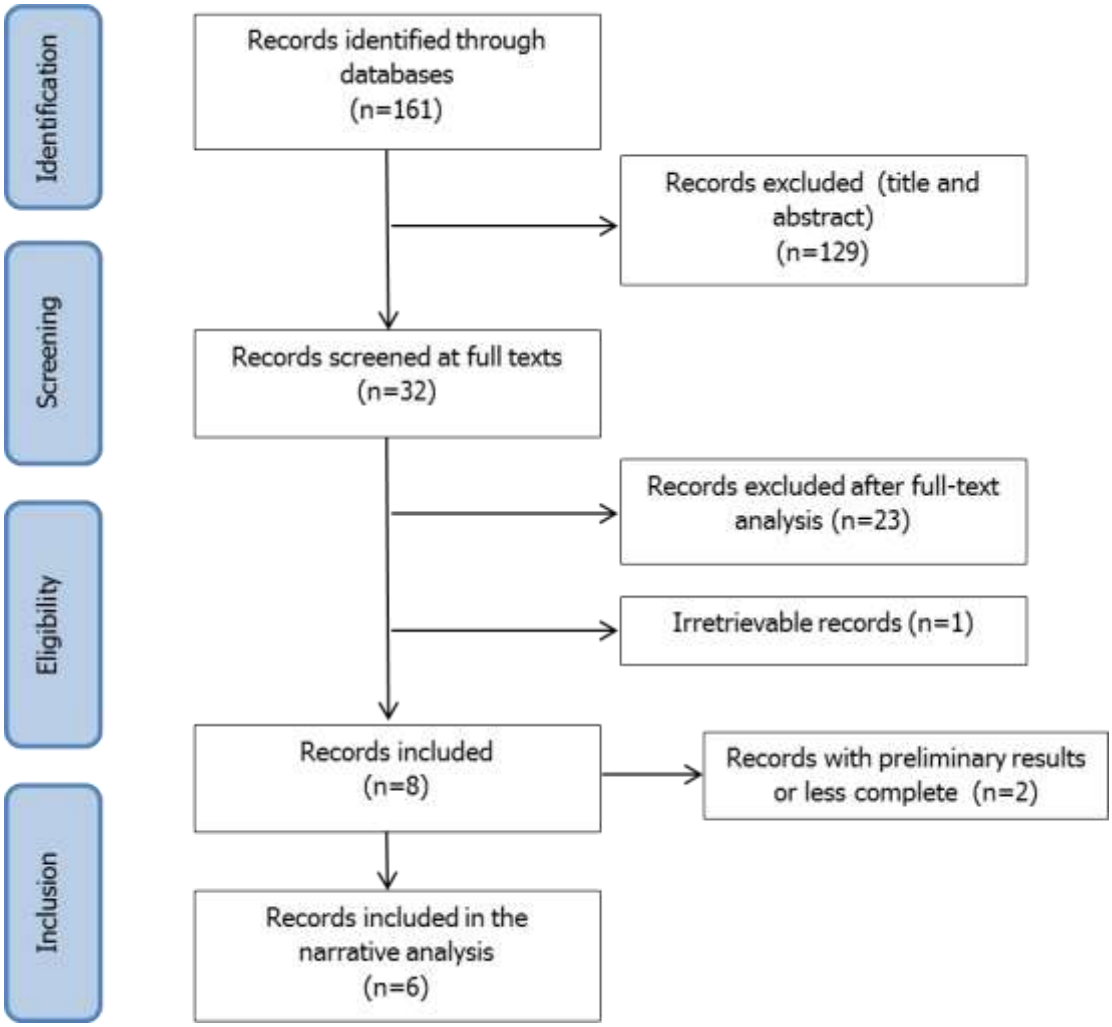
Cost analysis considered the structure records, the direct costs for the service and the diagnosis costs of hospital discharges attributed to DRGs 103-525-541 (ICD9-CM 3741, 3762, 3765, 3766). The cost analysis considered direct and indirect costs of LVAD implantation in 2012 using hospital perspective. Only costs related to LVAD procedure were considered, excluding the pre-implantation workup and the follow up.

8.2 RESULTS

Systematic review results

The electronic database searches yielded 161 records. After reading the title and/or the abstract, the full text of 32 papers were retrieved for further assessment. According to our predefined inclusion criteria 8 papers were included; 6 full economic evaluations and 2 cost analyses. Two studies [Mishra et al, 2010; Clarke et al, 2014], reporting preliminary results of a more recent cost analysis [Mishra et al, 2012] or referring to a more complete report [Sutcliffe et al, 2013] respectively, were not extracted and analyzed in the narrative assessment. The PRISMA flow-chart describing the inclusion process of the economic studies is shown in figure 8.2.1. The included and excluded papers along with the reason for exclusion are reported in Appendix 5 and Appendix 6 respectively.

Figure 8.2.1: Flow-chart of the studies according to PRISMA [Moher 2009].



An overview of the 6 evaluations included in our economic systematic review is reported in Table 8.2.1. All the studies compared continuous-flow LVAD versus medical treatment (although differently named); specifically 4 studies [Moreno et al, 2012; Neyt et al, 2013; Rogers et al, 2012; Long et al, 2014] analyzed effectiveness and economic data related to HeartMateII, while Mishra [Mishra et al, 2012] and Sutcliffe [Sutcliffe et al, 2013] have evaluated a miscellaneous of LVAD (2^{nd} and 3^{rd} generation). The six studies include one cost analysis [Mishra et al, 2012], 2 cost-effectiveness analyses [Sutcliffe et al, 2013; Long et al, 2014], one cost-utility analysis [Neyt et al, 2013] and the last two studies by Moreno and Rogers [Moreno et al, 2012; Rogers et al, 2012] carried out both cost-effectiveness and cost-utility analysis on LVAD. The target population consisted of patients with end stage heart failure who were candidates to heart transplant included in the waiting list, or who were not because of the age (>65 years) or their comorbidities. In particular 3 studies [Mishra et al, 2012; Moreno et al, 2012; Sutcliffe et al, 2013] assessed the

LVADs in patients on waiting list to cardiac transplantation and used as "bridge to transplantation" (BTT) with MMT. One study [Sutcliffe et al, 2013] assessed LVAD comparing them as BTT versus medical management and LVAD as "alternative to transplant" (ATT) versus LVAD as BTT. However in our analysis we considered only the first comparison since it is the only that meets our inclusion criteria. Two studies [Neyt et al, 2013; Rogers et al, 2012] analyzed the implantation of LVAD as "destination therapy" (DT) in patients ineligible to HT compared to MMT. The last study by Long [Long et al, 2014] focused on both the indications of use for LVAD (e.g. BTT and DT). Among transplant-ineligible patients, LVAD as destination therapy was compared with inotrope-dependent medical therapy (IDMT). For transplant-eligible patients, the study evaluated 4 treatment options available so far: IDMT, orthotopic heart transplantation (OHT), LVAD as bridge to transplant (BTT-LVAD) and also as destination therapy (DT-LVAD) since conditions could exist where it may be preferable to receive DT-LVAD in lieu of BTT-LVAD or OHT [Long et al, 2014]. However the economic analysis carried out among transplant-eligible patients is quite unclear and seems not to meet our inclusion criteria so we did omit it. Both of the included studies [Moreno et al, 2012; Sutcliffe et al, 2013] which assessed LVAD as BTT used the model developed by Sharples [Sharples et al, 2006] which was adapted for the decision problem and updated with new data. In particular data of continuous flow LVAD instead of pulsatile flow LVAD were used to populate the model, besides the costs have been inflated to 2011 prices by applying the projected health service cost index (HSCI) [Moreno et al, 2012; Sutcliffe et al, 2013]. Rogers et al used and adapted the economic model developed from the Blue Cross Blue Shield Technology Evaluation Center assessment.

The evaluations were conducted in UK (1), in the Netherlands (1), in Norway (1) in the United States (2) and one country was not clear. Taking into account only the 5 full economic analyses, all of them apart from the study of Long [Long et al, 2014] developed a Markov-model with a time horizon ranging from 3 years to lifetime and with different perspectives.

Authors' disclosure of conflict of interest is reported in all the included studies while the majority of the studies (4/6) did not declare the source of funding. Two studies were publicly funded and the last received funds from one manufacturer (Table 8.2.1).

Table 8.2.1: Summary of findings of the included economic studies - General information.

Study	Country	Objective	Economic analysis and Modelling	Model outputs	Time horizon/Perspective	Intervention	Comparator	Patients	Funding
Mishra, 2012	Norway	"*To investigate how total hospital costs per patient developed as the number of LVAD procedures increased and clinical experience was accumulated*".	Cost analysis/NA	Mean total costs (analysis output).	NA	3th generation LVAD (VentrAssist™; HeartWare™)	NA	Patients with HF evaluated for HTx.	Not reported
Moreno, 2012	NC	*"To estimate the cost- effectiveness of the HeartMate II using the most robust and recently published evidence about its comparative performance vs conventional therapy for patients listed for HT".*	CEA/Markov Model	Survival and post HT survival; LYG; QALY; ICER (for both LYGs and QALYs).	Lifetime/NHS perspective	LVAD as BTT (Heartmate-II)	Conventional therapy (CT)	Hypothetic cohort of patients with end-stage HF listed for HTx.	Not reported
Neyt, 2013	Netherlands	*"To calculate the cost-effectiveness of continuous flow LVADs".*	CUA/Markov Model	Incremental costs (discounted incremental costs) and effects (discounted LYG/QALY, ICER).	Lifetime/ societal perspective	Continuous flow LVAD as DT (HeartMateII)	OMT	Adults with chronic end-stage HF who are not candidates for cardiac transplantation.	Dutch Health Care Insurance Board
Rogers, 2012	USA	*"To perform a CEA of continuous-flow LVADs for DT versus OMM based on the latest clinical and cost data available and to compare these data to previous estimates of the ICER for pulsatile LVADs".*	CEA,CUA/Markov Model	Costs, QALYs and LYGs.	5 years/third party payer	Continuous flow LVAD as DT (HeartMateII)	OMM	Patients with chronic end-stage HF who are not candidates for cardiac transplantation.	Thoratec, Inc.
Sutcliffe, 2013	UK	*"Investigate the cost- effectiveness of 2nd and 3rd generation LVADs as a BTT, compared to MM with inotrope support in the British NHS bridge to heart transplant program".*	CEA/ Semi-Markov multistate model*** (deterministic and probabilistic)	Mean costs and benefits (LYG and QALYs), mean ICERs as Cost/QALY and Cost/LYG.	3 years; 10 years and 50 years (lifetime)/NHS perspective	2nd or 3th generation LVAD as BTT or as ATT (HeartWare HLVAD; Thoratec HeartMate II; Jarvik 2000 FlowMaker; Micromed HeartAssist)	MM; VADs as a BTT.	Participants (aged > 16 years) with advanced HF and considered suitable for receipt of a left ventricular assist device (LVAD), right ventricular assist device (RVAD) or biventricular assist device (BiVAD) as BTT or as potential long-term alternative to HTx.	National Institute for Health Research HTA Program, Great Britain. Project number 12/02/01.
Long, 2014	USA	"*Evaluation of the health benefits, survival, costs, and comparative cost- effectiveness of treatment strategies for patients with inotrope-dependent stage D heart failure".*	CEA - Novel decision-analytic model to estimate survival and costs among patients with inotrope-dependent stage D heart failure under different treatment strategies.	Average life expectancy; QALYs; lifetime costs; and ICERs.	Life time/ societal perspective	Continuous-flow LVAD as DT (HT ineligible patients) Continuous-flow LVAD as BTT and as DT (HT eligible patients) (Heartmate-II)	IDMT (HT ineligible patients); IDMT; OHT (HT eligible patients).	Patients with HF ineligible to transplant or eligible to transplant. (50 y old for base case scenario).	Not reported

KEY: LVADs, left ventricular assist devices; NA, not applicable; HF, heart failure; HTx/OHT heart transplant; NC, not clear; CEA, Cost-effectiveness analysis; CUA, Cost-utility analysis; DT, destination therapy; OMT, optical medical therapy; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; LYG, life year gained; OMM, optimal medical management; NHS, national health system; MM, medical management; ATT, alternative to transplant; BTT, bridge to transplant; IDMT, Inotrope-Dependent Medinal Therapy.

Type (E0001), measurement (E0002) and valuation (E0009) of resource

Type of resources used was reported in all studies. Types included were specific (e.g. personnel, theatre time) or general (e.g. LVAD implantation, rehospitalization, follow up), while measurement was not reported in all studies. Sutcliffe et al 2013 reported values for Pre-VAD implant assessment by medical staff (cardiac MDT, Consultant surgeon, specialist registrar and anaesthetist), VAD surgical procedure (Theatre nursing team; Theatre–average consumables; Pump, Perfusionist, Consumables, Surgeon, Anaesthetist) and drugs. All studies considered only direct costs for both intervention and comparator reporting the mean costs of the resources used and specified currency for both intervention and comparator. Details on type of resources used are listed in table 8.2.2. BTT studies [Sutcliffe et al, 2013; Moreno et al, 2012] also considered heart transplantation costs. They used data from published studies or using real data detected from hospital and administrative databases. Two studies [Sutcliffe et al, 2013; Moreno et al, 2012] obtained data from the same study [Sharple et al, 2006].

Table 8.2.2: Summary of finding of included economic studies – Resource use information.

Study	Resource use identification E0001	Resource-use measurement [Source] E0002	Resource-use valuation [Source] E0009			Currency/year
			Type	Mean cost (±SD) LVAD	Mean cost (comparator)	
Mishra, 2012	- Pre-LVAD phase (personnel, ECMO procedure, blood, drugs, laboratory/radiology) - LVAD phase (personnel, device, operating room, blood, drugs, laboratory/radiology) - Post-LVAD phase (day hospital stays <5h, in-hospital stays, external consultations, internal consultations) - Overheads costs	Not reported	Pre-LVAD phase: VentrAssist™ HeartWare™ LVAD phase: VentrAssist™ HeartWare™ Post-LVAD phase: VentrAssist™ HeartWare™	 186,467 (6,000-586,421) 63,963 (9,738-187,097) 378,450 (41,957-696,483) 346,403 (273,498-425,843) 18,093 (8,729-59,345) 2,819 (11,310-9,724)	NA NA NA NA NA NA	US$/2011
			[Oslo University Hospital data]			
Moreno, 2012	Surgical procedures; intensive care stay unit; cardiac ward; HT assessment; HT procedure and associated ICU and ward stay, follow-up readmissions to the ICU or ward, outpatient visits, investigations, blood tests, and drugs. Resource use data were also collected for all adverse events.	Not reported	**Type**	**Mean cost LVAD**	**Mean cost (CT)**	2011 (£) and $ Key cost results were converted to US $ using an exchange rate of £1 = $1.60
			HeartMate II device	94,200		
			LVAD implant procedure	19,628		
			Post-LVAD implant			
			Month 1	25,601		
			Month 2	13,348		
			Month 3	5,075		
			Month 4	3,810		
			Month 5	3,226		
			Month 6	2,310		
			Month 7+	1,880		
			Conventional therapy			
			HT assessment		1,621	
			Treated Month 1		12,133	
			Treated Month 2		6,350	
			Treated Month 3+		5,925	
			HT surgery (both groups)			
			Peri-op/post-op	16,933	16,933	
			Theater for HT			
			LVAD patient	16,550	16,550	
			Conventional therapy patient		11,317	
			Post-HT patients			
			LVAD Month 1	15,471	15,471	
			Conventional therapy Month 1		13,120	
			Post-HT, both groups			
			Month 2	4,301	4,301	
			Month 3	2,591	2,591	
			Month 4	2,808	2,808	
			Month 5	2,164	2,164	
			Month 6	1,634	1,634	
			Month 7+	1,401	1,401	
			Source (except for the Heartmate II device cost): Sharples , 2006.			

Study	Resource-use identification E0001	Resource-use measurement [Source] E0002	Resource-use valuation [Source] E0009			Currency/year
			Type	Mean cost € (±SD) LVAD	Mean cost (±50%) OMT	
Neyt, 2013	LVAD device (LVAD implantation); surgery room and PSL (LVAD implantation); patient days (LVAD implantation and rehospitalisation); imaging (LVAD implantation and rehospitalisation); laboratory (LVAD implantation and rehospitalisation); blood products (LVAD implantation and rehospitalisation); function examinations (LVAD implantation, rehospitalisation and follow-up); rent PBU (follow up); LVAD accessories (follow up); physiotherapy (follow up); dietetics (follow up); medication (follow up); social work.	Not reported	LVAD device surgery room and PLS patient days imaging laboratory blood products function examinations social work **LVAD implantation (TOT)** patient days imaging laboratory blood products function examinations **Rehospitalisation (TOT)** Rent PBU LVAD accessories Physiotherapy Dietetics Medication Examinations (1st year) Examinations (>1 year) **Monthly follow-up (TOT)**	70,000 4,385 (SD:±50%) 42,378 (SD:30,590) 1,015 (SD:744) 2,319 (SD:1,440) 4,797 (SD:4,935) 411 (SD:434) 1,200 (SD:±50%) **126,505** 7,028 (SD:8,209) 172 (SD:263) 449 (SD:511) 351 (SD:1,108) 119 (SD:225) **8,118** 400 267 81 11 288 145 69 **1,261**	 - - 81 11 687 205 63 **1,047**	Euros/Not reported
			[Real world cost data from UMC Utrecht; 'Farmacotherapeutisch Kompas' database; 'Medicijnkosten' database; hospital data and standard costs from the Dutch guidelines for cost analyses]			
Rogers, 2012	- LVAD implantation (device, intensive care days, medical/surgical days, operating room, diagnostics, laboratory test, blood products, drugs, miscellaneous services, professional services, device replacement) - Rehospitalisation services - Outpatient care (professional services, laboratory tests and drugs)	Not reported	**Type**	**Mean cost US $ (±SD) LVAD**	**Mean cost OMM**	US$/2009
			- LVAD implantation hospital [Slaughter, 2011]	193,812 (122,785-264,839)	NA	
			- Professional service [Centers for Medicare and Medicaid Services, 2008]	8,841 (NA)	NA	
			- LVAD replacement [Medicare Program, 2008]	131,430 (NA)	NA	
			- Rehospitalisation (per event) [Oz, 2003; Anand, 2009]	6,850 (6,850-30,627)	6,850 (6,850-30,627)	
			- Outpatient (monthly) [Moskowitz, 2001; Gelijns, 1997]	2,331 (NA)	2,331 (NA)	
			- End-of-life [Russo, 2008]	44,211 (NA)	44,211 (NA)	

<table>
<tr><th>Study</th><th>Resource-use identification E0001</th><th>Resource-use measurement [Source] E0002</th><th colspan="3">Resource-use valuation [Source] E0009</th><th>Currency/year</th></tr>
<tr><td rowspan="2">Sutcliffe, 2013</td><td rowspan="2">LVAD implant procedure including: device cost, theatre cost and cost of immediate post-operative hospital stay; Post-LVAD implant support including: outpatients visits, adverse events and rehospitalisation (monthly cost); Support on MM (inotrope) including: medications and follow-up assessment as inpatient or outpatient visits (monthly cost); Heart transplantation (HT) theatre cost; HT assessment cost; post-HT hospital stay and follow-up including: outpatient visits, investigation, blood test and drugs (monthly cost).</td><td rowspan="2">Pre-VAD implant assessment by medical staff:
- Cardiac MDT= 0.85h*
- Consultant surgeon= 0.21h*
- SPR= 0.21h*
- Consultant anaesthetist= 0.42h*

VAD surgical procedure:
- Theatre nursing team= 5h*
- Theatre–average consumables= 1h*
- Pump= 1 Unit*
- Perfusionist= 7.5h*
- Consumables average= 1.00 Unit*
- Surgeon= 6.5h*
- Anaesthetist= 6.5h*
- Drugs costs= 1.00 Unit*</td><td>Type</td><td>Mean cost £ (±SD) LVAD</td><td>ù</td><td rowspan="2">GB £/2010-2011 UK prices</td></tr>
<tr><td>VAD device

VAD implant procedure

Post-VAD hospital stay and follow-up:
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Month 7+

Support on MM (inotrope)
Month 1
Month 2
Month 3+

HT theatre cost

HT assessment cost

Post-HT hospital stay and follow-up
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Month 7+</td><td>80,569 (N/A)

3,728 (N/A)

25,777 (2,518)
13,440 (1,306)
5,110 (764)
3,836 (607)
3,248 (460)
2,326 (356)
1,893 (907)

16,663 (N/A)

0 (N/A)

15,577 (1,117)
4,331 (802)
2,609 (470)
2,828 (260)
2,179 (432)
1,646 (138)
1,410 (177)</td><td>

12,216 (1,156)
6,393 (604)
5,965 (193)

11,395 (N/A)

1,633 (N/A)

13,211 (961)
4,331 (802)
2,609 (470)
2,828 (260)
2,179 (432)
1,646 (138)
1,410 (177)</td></tr>
<tr><td colspan="4">Sharples et al (costs were obtained from five UK centers providing long-term VAD support**) inflated to 2010/2011 prices apart from: VAD device cost based on current cost of devices recorded at UK centres and VAD implant procedure cost based on Glasgow Golden Jubilee National Hospital (GJNH) finance department].</td><td></td></tr>
<tr><td>Long, 2014</td><td>Monthly IDMT care; LVAD index hospitalization; Monthly post-LVAD care; End-of-life care; Acute stroke; Monthly poststroke care; Gastrointestinal bleed; Driveline infection; CAV; Monthly post-CAV care; Renal dysfunction initial care; Monthly renal dysfunction care; Skin malignancy; Monthly post–skin malignancy care; Lymphoma/other malignancies.</td><td>Not reported</td><td colspan="2">Type of resource</td><td>Cost (2012 $)</td><td>2012/US dollars</td></tr>
<tr><td colspan="2">Monthly IDMT care

LVAD index hospitalization

Monthly post-LVAD care

End of life care
Acute stroke
Monthly poststroke care
Gastrointestinal bleed
Driveline infection
Cardiac allograft vasculopathy (CAV)
Monthly post-CAV care
Renal dysfunction initial care
Monthly renal dysfunction care
Skin malignancy
Monthly post–skin malignancy care
Lymphoma/other malignancies
[Direct medical costs: Heartmate-II DT trial and the Nationwide Inpatient Sample; Professional fees: prior analysis of Medicare; Direct costs for repeat hospitalizations and outpatient care: Yale-New Haven Hospital],</td><td colspan="2">12 m before death: 9,072
12-24 m before death: 4,404
24+ m death: 2,039
23,9160

Months 1-12: 10,984
Months 12+: 3,121
49,838
20,155
3,076
12,165
41,504
10,674
1,067
10,674
6,674
3,963
132
m 1-32: 1,651
m 24+: 528</td><td></td></tr>
</table>

* Hour(s) per average patient.
** Royal Brompton & Harefield NHS Foundation Trust (RB); Papworth Hospital NHS Foundation Trust; Newcastle upon Tyne Hospital NHS Foundation Trust (NUT); University Hospital of Birmingham NHS Foundation Trust (UNB); University Hospital of South Manchester NHS Foundation Trust (UHSM).

KEY: MDT, multidisciplinary team; SPR, specialist registrar; SD, standard deviation; LVADs, left ventricular assist devices; OMT, optical medical therapy; HF, heart failure; PLS, permanent life support; TOT, total; PBU, power base unit.

Efficacy data and results (E0005)

The efficacy data used in the 5 economic models were derived from indirect comparisons between continuous-flow LVAD and MMT, since no randomized trial has been performed comparing the two treatments head-to-head.

The survival rates in medically treated patients who were ineligible for heart transplant derived from the REMATCH Trial[2] [Rose et al, 2001] were used in all the 3 evaluations assessing the continuous-flow LVAD as DT versus MMT [Neyt et al, 2013; Rogers et al, 2012; Long et al, 2014]. The REMATCH trial demonstrated survival rates of 25% at 1 year and 8% at 2 years in the medical-therapy group [Rose et al, 2001]. Otherwise the survival data for the patients implanted with continuous-flow LVADs were derived from HeartMate II Destination Therapy Trial[3] in two studies [Neyt et al, 2013; Rogers et al, 2012] and from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), which enrolled 6,885 LVAD patients between 2006 and 2012 [Long et al, 2014]. LVAD survival was equal to 68% and 58% at 1 and 2 years in the HeartMate II Destination Therapy Trial [Slaughter et al, 2009] and 88%, 82%, and 74% at 6, 12, and 24 months respectively in the INTERMACS registry [Kirklin et al, 2012; Kirklin et al, 2013]. Long et al assumed 5% lower survival at 1 year for DT patients ineligible for HT. They also assumed a higher mortality rate in the first month post-implantation and increased rates of serious complications which contributed to higher mortality for the first 12 months post-implantation.

Survival estimates for HT-eligible patients conventionally treated (medical therapy) used to populate the economic model developed by Moreno et al, were derived from the American registry SRTR (Scientific Registry of Transplant Recipients)[4] and were 63% after 18 months [Lietz et al, 2007]. Survival rate for LVAD implanted patients eligible to HT obtained from one study [Pagani et al, 2009] conducted on 281 patients undergoing LVAD was 72% after 18 months.

Sutcliffe et al used observed survival data from the Blood and Transplant Database (BTDB) for each group of patients (patients who received a continuous-flow VAD as a BTT or patients who received MM support to transplant) to populate their economic model [Sutcliffe et al, 2013].

Efficacy results were measured in life years gained (LYGs), quality adjusted life years (QALYs) and/or life expectancy within the 5 economic evaluations included (see Table 7.2.3).

The analysis of efficacy findings from the 2 included economic evaluations comparing LVAD as BTT to conventional/medical treatment showed that patients with LVAD gained more life years (LYs) as well as higher QALYs. LYG ranged from 9.19 to 8.87 and from 8.54 to 7.95, at 6 and 18 months,

[2]REMATCH Trial is a randomized trial where 129 patients with end-stage heart failure who were ineligible for cardiac transplantation were randomly assigned to receive a pulsatile-flow LVAD (68 patients) or optimal medical management (OMM) [Rose et al, 2001].

[3]HeartMate II Destination Therapy Trial (NCT00121485) is a randomized trial in which patients with advanced heart failure ineligible for transplantation were enrolled to undergo implantation of a continuous-flow LVAD (134 patients) or pulsatile-flow LVAD (66 patients) [Slaughter et al, 2009].

[4]The SRTR is a USA U.S. government-sponsored registry of 7,376 patients in theHT waiting list (UNOS status 1A and 1B) from 2000-2005.

for LVAD patients and for patients treated conventionally respectively [Moreno et al, 2012]. The other economic evaluation, based on the same economic model adapted and with prolonged time horizons, showed similar gains in LYs of 1.95, 3.81 and 5.40 for LVAD patients at 3 years, 10 years and lifetime compared to 1.13, 1.72 and 2.47 for MMT patients [Sutcliffe et al, 2013]. Taking into account the quality of life (QoL), QALYs of patients with LVAD while in HT waiting list were higher than QALYs of patients treated medically regardless of the time horizon of the analysis - in all the 2 economic evaluations [Moreno et al, 2012; Sutcliffe et al, 2013]. LVAD patients QALYs ranged from 6.93 (at 6 months) to 6.62 (at 18 months) [Moreno et al, 2012] and from 1.48 (at 3 years) to 4.26 (lifetime horizon) [Sutcliffe et al, 2013]. QALYs for MMT patients ranged from 6.38 (at 6 months) to 5.76 (at 18 months) [Moreno et al, 2012] and from 0.69 (3 years) to 1.80 (lifetime horizon) [Sutcliffe et al, 2013].

Although the absolute values of QALYs and LYGs lowered over time in both groups of patients, the trends of incremental effects were increasing both in terms of LYs gained and QALYs demonstrating the beneficial effects of LVAD in bridging the patients to cardiac transplantation. Similarly the other 3 economic evaluations which studied the effects of LVAD in patients ineligible to HT compared to medical/conventional therapies resulted in more LYGs, QALYs and life expectancy for LVAD patients. The incremental effect of LVAD versus medical treatment in terms of LYs gained and QALYs was 3.23 and 2.83 respectively [Neyt et al, 2013]. The analysis by Rogers et al [Rogers et al, 2013] showed LYs and QALYs to be 2.42 and 1.87 in LVAD compared to 0.6 and 0.37 in patients medically managed. The most recent study reported 2.79 and 0.41 QALY for LVAD and MMT patients respectively [Long et al, 2014]. Lastly life expectancy was 4.33 years [Neyt et al, 2013] and 4.42 years [Long et al, 2014] in LVAD-implanted patients and 0.82 [Neyt et al, 2013] and 0.78 years [Long et al, 2014] among patients on medical treatment.

Table 8.2.3: Summary of finding of the included economic studies - Effectiveness, cost and cost-effectiveness results.

Study	Cost results [source]		Efficacy results [source]	Discount rate	Differences in costs and results	Sensitivity analysis	
Mishra, 2012	Mean Total costs ($) VentrAssist™: 585,513 HeartWare™: 413,185		NA	NA	NA	Multivariate regression analyses	
Moreno, 2012		**Base case (6 month interval) Mean (95% CI) / £**	**6 month interval mean (95% CI)** *Survival (LYs)* LVAD: 9.19 (8.48–9.91) Conventional therapy : 8.54 (NR) Difference survival (LYG): 0.65 (–0.06 to 1.36) *QALYs* LVAD: 6.93 (5.94–7.93) Conventional therapy : 6.38 (5.61–7.16) Difference QALY: 0.55 (-0.01–1.11) **12 month interval (mean 95% CI)** *Survival (LYs)* LVAD: 8.99 (8.34–9.65) Conventional therapy : 8.19 Difference survival (LYG): 0.80 (0.15–1.46) *QALYs* LVAD: 6.76 (5.84–7.69) Conventional therapy : 6.04 (5.31–6.78) Difference QALY: 0.72 (0.16–1.28) **18 month interval (mean 95% CI)** *Survival (LYs)* LVAD: 8.87 (7.84–9.91) Conventional therapy : 7.95 Difference survival (LYG): 0.92 (–0.11 to 1.96) *QALYs* LVAD: 6.62 (5.54–7.69) Conventional therapy : 5.76 (5.04–6.48) Difference QALY: 0.86 (0.02–1.69) **[Source:** For survival while listed for HT: Pagani, 2009; For Conventional therapy vs LVAD as BTT the comparative survival data for the conventionally treated patients were taken from the USA U.S. government-sponsored Scientific Registry of Transplant Recipients (www.srtr.org). For post-HT survival: John, 2010.]	3,5%	**Base case (6 month) Mean**	**12-month Mean**	**18 month Mean**
	Costs (£) LVAD CT Difference costs	350,939 (311,726–390,151) 208,444 (178,835–238,053) 142,495 (116,413–168,578)			ICER for a LYG: £219,705 ($351,528) ICER for a QALY: £258,922 ($414,275)	**Costs (95% CI) / £** LVAD: 347,216 (313,018–381,414) CT: 218,630 (190,796–246,464) Difference: 128,586 (108,801–148,371) **Mean ICER** For a LYG: £160,388 ($256,621) For a QALY: £178,829 ($286,126)	**Costs (95% CI) / £** LVAD: 344,170 (303,118–385,222) CT: 229,638 (198,472–260,804) Difference : 114,532 (80,689–148,376) **Mean ICER** For a LYG: £124,066 ($198,506) For a QALY: £133,860 ($214,176)
Rogers, 2012	Total cost ($) LVAD: 360,407 OMM: 62,856 [Model]		**Total QALYs (y)** LVAD: 1.87 OMM: 0.37 **Total LYs (y)** LVAD: 2.42 OMM: 0.64 [**Source:**Clinical outcomes for OMT: REMATCH trial [Rose et al, 2001]; clinical outcomes of continuous-flow LVADs: HeartMate II Destination Therapy Trial [Slaughter et al, 2009]]	3% (costs after 1 year and health outcomes)	ICER: $167,208 per LYG ICER: $198,184 per QALY	Sensitive analyses applied to: cost of LVAD implantation; variations of utility for NYHA classes; rehospitalization costs and long-term survival for the LVAD group	
Neyt, 2013	Incremental cost (€): 299,100 (95% CI, 190,500-521,000) [Model]		**Undiscounted Life expectancy(mean 95% CI)** LVAD: 4.33 (3.17-5.71) OMT: 0.82 (0.66-0.99) **Discounted Incremental effect (mean 95% CI)**	4% (costs) 1.5% (effects)	ICER: €94,100 per LYG (95% CI, 59,100-160,100) ICER: €107,600 per QALY (95% CI, 66,700-181,100)	One-way analyses of the most uncertain parameters: discount rate, extrapolation scenarios, monthly mortality risk, hospitalization per patient-year in OMM group, service life, QoL, LVAD cost. Probabilistic sensitivity analyses: beta distribution (transition probabilities and utilities), gamma distribution	

		3.23 LYG (2.18-4.49) 2.83 QALYs (1.91-3.90) [**Source:** Survival for MMT patients: REMATCH trial [Rose et al, 2001]; survival related to continuous-flow LVADs: HeartMate II Destination Therapy Trial [Slaughter et al, 2009]]]			(cost variables) and uniforms distributions.

Study	Cost results [source]	Efficacy results [source]			Discount rate	Differences in costs and results		Sensitivity analysis
Sutcliffe, 2013	**Deterministic**	**Probabilistic (95% CI)**	**Deterministic**	**Probabilistic (95% CI)**	3.5% (costs and health outcomes)	**Deterministic**	**Probabilistic (95% CI)**	Several types of sensitivity analysis were explored encompassing changes to: 1. TPs between health states 2. inputs for costs 3. utility inputs for health states.
	Lifetime Mean Cost LVAD: £239,832 MM: £104,106 Δ: £135,726 ***10 years*** Mean Cost LVAD: £212,648 MM: £91,450 Δ: £121,198 ***3 years*** Mean Cost LVAD: £176,594 MM: £79,637 Δ: £96,958	***Lifetime*** Mean Cost LVAD: £240,193 (196,411-306,883) MM: £112,802 (65,086-197,666) Δ: £127,391 (36,782-179,736) ***10 years*** Mean Cost LVAD: £212,000 (175,724-264,432) MM: £99,240 (57,026-169,449) Δ: £112,760 (33,076-179,395) ***3 years*** Mean Cost LVAD: £177,009 (154,922-210,495) MM: £83,010 (49,888-124,933) Δ: £93,998 (45,307-139,435)	***Lifetime*** Mean LYG LVAD: 5.40 MM: 2.47 Δ: 2.93 Mean QALY LVAD: 4.26 MM: 1.80 Δ: 2.46 ***10 years*** Mean LYG LVAD: 3.81 MM: 1.72 Δ: 2.09 Mean QALY LVAD: 2.95 MM: 1.17 Δ: 1.78 ***3 years*** Mean LYG LVAD: 1.95 MM: 1.13 Δ: 0.82 Mean QALY LVAD: 1.48 MM: 0.69 Δ: 0.79 [**Sources:** survival data: the Blood and Transplant Database (BTDB) for each group of patients]	***Lifetime*** Mean LYG LVAD: 5.46 (4.29-6.56) MM: 2.67 (1.49-4.59) Δ: 2.79 (0.61-4.33) Mean QALY LVAD: 4.32 (3.31-5.31) MM: 1.94 (1.07-3.33) Δ: 2.38 (0.78-3.59) ***10 years*** Mean LYG LVAD: 3.83 (3.07-4.41) MM: 1.87 (1.05-3.19) Δ: 1.96 (0.55-2.97) Mean QALY LVAD: 2.95 (2.26-3.55) MM: 1.27 (0.73-2.15) Δ: 1.68 (0.63-2.51) ***3 years*** Mean LYG LVAD: 1.96 (1.60-2.22) MM: 1.18 (0.68-1.81) Δ: 0.78 (0.09-1.36) Mean QALY LVAD: 1.49 (1.14-1.80) MM: 0.72 (0.42-1.12) Δ: 0.77 (0.26-1.21)		***Lifetime*** ICER (£/LYG): 46,322 ICER (£/QALY): 55,173 ***10 years*** ICER (£/LYG): 57,989 ICER (£/QALY): 68,088 ***3 years*** ICER (£/LYG): 117,278 ICER (£/QALY): 122,730	***Lifetime*** ICER (£/LYG): 45,659 (30,159-86,586) ICER (£/QALY): 53,527 (31,802-94,853) ***10 years*** ICER (£/LYG): 57,530 (35,881-99,572) ICER (£/QALY): 67,119 (38,756-116,681) ***3 years*** ICER (£/LYG): 114,631 (78,800-374,982) ICER (£/QALY): 120,510 (79,560-251,285)	

Study	Cost results [source]	Efficacy results [source]		Discount rate	Differences in costs and results	Sensitivity analysis
Long, 2014	**Heart transplant ineligible** Inotrope-dependent MT LVAD destination therapy	**Lifetime cost ($)** 112,600 593,000	**5-y survival (life expectancy) [QALY]** 0% (0.78y) [0.41] 32% (4.42y) [2.79] **[Source:** Survival probability: Rose 2001; Rogers 2012; Kirklin, 2013; Kirklin, 2012. QALY: Post 2001; Liem 2008; Earle 2000; Pickard 2007; expert opinion and Yale-New Haven Hospital data]	3%	ICER ($/LYG): 131,800 ICER ($/QALY): 201,600	Sensitivity analysis for key model parameters: patient's age, median wait time for heart transplantation and the monthly probability of death with inotrope-dependent medical therapy. Graphic results only.

KEY:CI, confidence interval; LYG/LY, life year gained; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio; OMM, optical medical management; QoL, quality of life; LVAD, left ventricular assist device; DT, destination therapy; Δ: difference; MT, medical therapy; y, year; mo, month; NA, not applicable; NR, not reported.

Economic results (E0006) (E0010)

In all economic evaluations, LVAD patients had higher mean costs with higher survival benefits compared to MMT patients for all time horizons considered. The economic results are expressed as incremental cost-effectiveness ratio (ICER) for LY and/or QALY in the 5 full economic evaluations included in our systematic review (Table 8.2.3). In the 2 studies assessing the use of VAD as a bridging approach in patients eligible to cardiac transplant compared to medical/conventional therapy, ICERs:

- ranged from £219,705 ($351,528) to £124,066 ($198,506) per LY at 6 months and 18 months respectively and from £258,922 ($414,275) to £133,860 ($214,176) per QALY at the same time horizons [Moreno et al, 2012];
- ranged from £117,278 (at 3 years) to £46,322 (50 years/lifetime) per LY and from £122,730 (at 3 years) to £55,173 (at 50 years/lifetime) per QALY [Sutcliffe et al, 2013].

The available economic evidence shows that the incremental cost per LYG/QALY associated with the use of LVAD decreases by increasing the time horizons. However the ICERs per QALY are always above the currently established willingness to pay (WTP) threshold of £30,000 in UK even for a lifetime horizon (50 years) showing that LVAD is not cost-effective.

Deterministic and probabilistic analyses were performed in both studies to test the robustness and generalizability of the model results. In particular survival estimates, utilities and cost inputs used by Sutcliffe et al to populate the economic model were varied showing that the choice of the comparator population (MMT patients), the probability of receiving a donor heart, the cost of VAD and the cost of lifetime treatment with BTT-LVAD were the most influential model inputs in affecting the estimated ICER of BTT-LVAD compared to MMT [Sutcliffe et al, 2013]. These results were aligned with the findings of the sensitivity analyses carried out by Moreno et al. in which the extension in the waiting time for a HT from 6 to 12 and 18 months was investigated as well as shorter time horizons and lower cost of the LVAD. LVAD implantation was cost-effective compared to MMT (ICER<£30,000) only when the device is implanted for at least 18 months before HT and is given free of charge, whereas the average waiting time to receive a HT was 6 months at present. The purchase price of the device in the UK is £94,200 ($150,720) [Moreno et al, 2012].

The available economic evidence on the use of LVAD in HT ineligible patients shows that ICER for LYG and for QALY were:

- $167,208 [Rogers et al, 2012], €94,100 [Neyt et al, 2013] and $131,800 [Long et al, 2014] and
- $198,184 [Rogers et al, 2012], €107,600 [Neyt et al, 2013] and $201,600 [Long et al, 2014], respectively.

The use of LVAD for the treatment of end stage HF patients who are ineligible for cardiac transplantation appeared not to be cost-effective since it exceeds the threshold of $50,000 per QALY (below the which the use of the technologies is considered to be cost effective in US). It is even higher than the acceptability threshold of $100,000 per QALY (below which the use of technology is considered acceptable in US) [Rogers et al, 2012; Long et al, 2014]. The EU study by Neyt et al found out that ICER for QALY (€107,600) is above the range of WTP (€25,000-40,000) implicitly or explicitly used in health systems similar to Italian NHS [Gruppo di lavoro Aies, 2009].

The sensitive analyses conducted by Rogers et al on the model's parameters and inputs highlighted that ICER was most sensitive to variations in long-term survival probabilities associated with the LVAD, cost of LVAD implantation, utility for NYHA classes I and II, and cost per rehospitalization [Rogers et al, 2012]. One-way and probabilistic sensitivity analyses incorporated methodological uncertainty and checked the robustness of results in the last two studies (see Table 8.2.3). Neyt et al observed that there was no chance for LVAD as DT to be cost effective under a WTP €56,000 per QALY. Besides a decrease in the cost of LVAD implantation and/or extension of the LVAD's service life was necessary to lower the ICER, considering that the high ICERs were not only due to the implantation cost but also to the costs for re-hospitalizations and follow-up costs [Neyt et al, 2013]. Sensitivity analyses for key model parameters (patient's age, median wait time for heart transplantation and the monthly probability of death with inotrope-dependent medical therapy) led Long et al to conclude that LVAD as destination therapy significantly improves life expectancy in HT-ineligible patients. Further reductions in adverse events or improved quality of life are needed for destination therapy-LVAD to be cost effective [Long et al, 2014].

Authors' conclusions

For BTT studies [Sutcliffe et al, 2013; Moreno et al, 2012] the authors cannot conclude that continuous flow LVADs are cost-effective compared with medical management and require more analysis in terms of patient selection and cost of inputs. The absence of randomised or controlled evidence comparing continuous flow LVAD versus MMT, the lack of cost data and their inflation using current price, shortness follow up considered were the limitations of the included studies.

In DT studies [Long et al, 2014; Rogers et al, 2013; Neyt 2013] authors concluded that despite LVAD implantation being an expensive intervention it improves survival and QoL in comparison with medical management for patients ineligible to transplant and encourages improvement in management strategies.

The only cost analysis study included [Mishra et al, 2012] concluded that reductions in hospital costs per patients were a consequence of LVAD implants increasing due to the improvement in patients management by the department. Table 8.2.4 reports conclusions, conflict of interest and quality assessment of the included studies.

Table 8.2.4: Summary of finding of the included economic studies – Authors conclusions and notes.

Study	Conclusion	Notes
Mishra, 2012	*"The hospital costs per patients were falling as the numbers of LVADs were increasing. The higher cost among the first patients can be explained by longer LOS and more invasive treatment in the pre-LVAD phase. As the number of patients increased the department experienced learning effect from better logistics, selection and management of patients. This reduced total costs excluding device costs by approximately $14, 000 or 3.6% per each additionally treated patient".*	Conflicts of interest were declared.
Moreno, 2012	*"LVAD implantation as a BTT does not offer better value for money than conventional medical management. The implication from this analysis is that the recommendation for HeartMate II LVAD implantation to transplant candidates lacks justification in terms of cost-effectiveness".*	The authors declared the absence of conflicts of interest.
Neyt, 2013	*"In conclusion, previous studies indicate that treatment with continuous-flow HeartMate II results in a significantly better survival and QoL in comparison with OMM. Despite these significant improvements, LVAD implantation as DT remains a relatively expensive intervention."*	The treatment effect used in the Markov model was based on an indirect comparison based on two trials (REMATCH and HeartMate II) Conflicts of interest were declared.
Rogers, 2012	*"We have demonstrated a significant improvement in the ICER for LVADs used to treat advanced HF in patients who are not eligible for HT. On the basis of this assessment, it is anticipated that continued refinement of patient selection criteria, technological advances, and improvements in management strategies will converge and result in the demonstration of LVADs as an economically effective treatment option for patients with advanced HF."*	Conflicts of interest were declared.
Sutcliffe, 2013	*"Reimbursement decisions vary through time and by country according to the weight given to economic considerations and to the innovativeness of the technology. The LVAD base case lifetime ICER begins to approach that for at least one intervention recently recommended in the UK by NICE as an end of life treatment for advanced prostate cancer at a cost per QALY of between £46,000 ($73,016) and £50,000 ($79,365) [24]. If the costs of LVADs were reduced by 15% then the technology might be eligible under this consideration by NICE. This finding is complex for the policy arena and will need to be considered carefully in the light of the burden of disease, available funding, and future supply of donor hearts".*	Amount of resource not disaggregated by type. Results not disaggregated by type of device.
Long, 2014	*" study demonstrates that heart transplantation results in improved survival and is a cost-effective strategy for most transplant-eligible patients with inotrope- dependent stage D heart failure, compared with medical therapy alone. However, if the anticipated wait-list time exceeds 1 month, BTT-LVAD results in greater life expectancy for patients awaiting OHT than medical therapy alone. Given national average transplant wait times for status 1A and 1B patients, the cost-effectiveness of BTT-LVAD exceeds $225 000 per QALY gained, but improves substantially with longer expected transplant wait times. In patients ineligible for transplantation, DT-LVAD substantially improves survival compared with medical therapy, although advances in medical complication rates or implantation costs must improve to render it as cost effective as other medical technologies."*	One author had received fee from Thoratec Corporation.

Quality assessment (E0012)

We evaluated the quality of the included studies using the checklist for economic evaluations of health programmes [Drummond M, 1996]. The checklist was divided in ten sections under three headings:

1. study design (7 items),
2. data collection (14 items)
3. analysis and interpretation of results (14 items).

for a total of 35 items (questions). Each item considered four answered option: yes, no, not clear, not appropriate. We evaluated the quality for five of the six study included in the systematic review as one (Mishra, 2012) was not a full economic evaluation.

Study design considers the following sections:

1. study question
2. selection of alternatives
3. form of evaluation

Data collection's sections are:

4. effectiveness data
5. benefit measurement and valuation
6. costing
7. modelling

Analysis and interpretation of results' section are:

8. adjustments for timing of costs and benefits
9. allowance for uncertainty
10. presentation of results

In the summary of findings table we reported the number of answers for each option considered. Sutcliffe 2013 was the study with high positive answers (26/35), probably due to the fact that it was a full HTA report. The lowest positive answers were for Rogers 2012 (16/35). In details the studies with the highest positive answers for the study design headings were Rogers 2012 and Sutcliffe 2013 (6/7 items) while Sutcliffe 2013 had the highest quality for data collection and analysis and interpretation of results (11/14 items).

Table 8.2.5 shows in details the quality assessment for each study included in the systematic review.

Table 8.2.5: Summary of the quality assessment

Study ID	Overall	Study design	Data collection	Analysis and interpretation of results
Rogers, 2012	Y: 16/35 N: 8/35 NC: 6/35 NA: 5/35	Y: 6/7; N:0/7 NC: 1/7; NA: 0/7	Y: 5/14; N:3/14 NC: 3/14;NA:3/14	Y: 5/14; N:5/14 NC: 2/14; NA: 2/14
Moreno, 2012	Y: 20/35 N: 5/35 NC: 4/35 NA: 6/35	Y: 3/7; N:1/7 NC:3/7; NA:0/7	Y: 7/14; N:2/14 NC:0/14; NA:5/14	Y:10/14; N: 2/14 NC: 1/14; NA: 1/14
Sutcliffe, 2013	Y: 26/35 N: 1/35 NC: 3/35 NA: 5/35	Y: 6/7; N:0/7 NC:1/7; NA:0/7	Y: 9/14; N: 0/14 NC:1/14; NA:4/14	Y: 11/14; N: 1/14 NC: 1/14; NA: 1/14
Neyt, 2013	Y: 22/35 N: 9/35 NC: 2/35 NA: 2/35	Y: 5/7; N: 1/7 NC: 1/7; NA: 0/7	Y:7/14; N: 6/14 NC:0/14; NA:1/14	Y:10/14; N: 2/14 NC: 1/14; NA: 1/14
Long, 2014	Y: 21/35 N: 11/35 NC: 0/35 NA: 3/35	Y: 4/7; N: 1/7 NC: 0/7; NA: 2/7	Y: 8/14; N: 6/14 NC: 0/14; NA: 0/14	Y: 9/14; N: 4/14 NC: 0/14; NA: 1/14
Mishra, 2012	NOT APPROPRIATE			

KEY: Y, Yes; N, No; NC, Not clear; NA, Not appropriate.

Italian Cost analysis results

Type of resource for LVAD considered in the analysis were (E0001):

1 - Hospital stay (variable and fixed costs).

2 - Intensive Care (variable and fixed costs).

3 – Transplant Unit (variable and fixed costs).

4 – Health personnel.

5 – General operating theatre (not related to LVAD).

6 – Operating theatre (LVAD cost excluded) including drugs and materials.

7 – Anesthesiologist.

8 – LVAD Cost (mean).

Regarding length of stay (LOS) the difference between the two hospitals (Hospital 1 (H1) and Hospital 2 (H2)) was 7 days divided as following (table 8.2.6):

Table 8.2.6: LVAD - Length of stay

	LOS (day) (E0002)	
Type of Unit care (E0001)	**H1**	**H2**
Ward	45	50
Intensive care unit (ICU)	15	8
Transplant unit	5	na *
Total	**65**	**58**

*Not applicable as LOS for Transplant Unit is comprised in ward and ICU (H2 doesn't have transplant Unit).

The mean LOS is 65 days for H1 and 58 for H2. However, despite the difference in LOS (7 days) total cost related to LOS is quite similar: around 30,000 euros (See table 8.2.7).

Table 8.2.7: LVAD - LOS costs

	Costs (variable + fixed) € (E0009)	
	H1	**H2**
Ward	15,373	25,400
Intensive care unit (ICU)	13,389	6,880
Transplant unit	2,580	na*
Total	**31,342**	**32,280**

*Not applicable as LOS for Transplant Unit is comprised in ward and ICU (H2 doesn't have transplant Unit).

Regarding health personnel costs used for LVAD procedure, the two hospitals used different measures to estimate those costs. H1 considered anesthesiologist cost for the length of the

surgery only (8 hours mean) while H2 considered it for 8 days (for all the length of stay in ICU) (E0001).

Table 8.2.8 reported the personnel costs for the two hospitals. The analysis showed that the total amount for personnel costs were €14,284 for H1 and €26,182 for H2. The difference was due to difference in salaries.

Table 8.2.8: Personnel costs (E0001, E0002, E0009)

	Unit Cost (€)		Time (h/day)		Total (€)	
	H1	H2	H1	H2	H1	H2
Health personnel	211/day	451/day	65 day	50 day	13,724	22,550
Anesthesiologist	70/h	454/day	8 h	8 day	560	3,632

For operating theatre costs the case study reported a total cost of €6,486 for H1 and €1,345 for H2 while general costs were estimated to be 38% (€45,531) and 50% (72,023) of direct total costs. Hence the full total costs for LVAD implantation resulted to be equal to €165,350 and €216,070 for H1 and H2 respectively.

The LVAD procedure code is 37.66 (ICD9-CM) "Insertion of implantable heart assist system", the DRG number is 103 "Heart transplant or implant of heart assist system". The reimbursement for DRG 103 was €62,602 for H1 and €45,976.93 for H2 while the Tariffa Unica Convenzionale (TUC), agreed reimbursement between Italian Regions, was €62,602 at 2012.

The analysis reported that the two hospitals have also used further ICD9-CM codes: 37.41 "Implantation of prosthetic cardiac support device around the heart", 37.62 "Insertion of temporary non-implantable extracorporeal circulatory assist device" and 37.65 "Implant of single ventricular (extracorporeal) external heart assist system" driving to the following DRG codes: DRG 525 "Other heart assist system implant" (€34,179 for H1 and €21,232 for H2) and DRG 541 "Ecmo or Tracheostomy with MV 96+ Hours or PDx Except Face, Mouth and Neck with Major O.R. Procedure" (€37,123 for H1 and €37,123 or €74,247, depending on hospital stay, for H2). Considering the mean of hospital stay, the LOS threshold and payment for additional LOS beyond the threshold reported by the two hospitals, the mean value of reimbursement was €62,601 (H1) and €59,552 (H2) for DRG 103; €46,738 (H2 only) for DRG 525 and €37,123 (H1 only) for DRG 541. Considering the total number of procedures and the use of different ICD9-CM codes H1 had a reimbursement (mean) of €59,417 per LVAD implant with a mean total cost of €165,350 while for H2 the reimbursement (mean) was €54,427 with a mean total cost of €216,070 per LVAD implant. Therefore, for each LVAD implant, the two centers involved in the analysis would suffer a financial loss since the reimbursement (based on DRG system) results to be not sufficient to cover the total costs incurred for the LVAD implantation procedure. Since 2014 Lombardia Region provides some

selected centers with a tariff equal to €125,900 (DGR 2313/2014) while Veneto region gives an additional tariff of €91,000 to DRG 103 (DGR 2310/2014) related to ICD9-CM procedural code 37.66.

8.3 DISCUSSION

In the cost and economic analysis domain we carried out a systematic review of published economic literature and we reported the results of a micro-costing analysis included in "LVAD: tecnologia, efficacia, sicurezza, analisi economica e fabbisogno nazionale, 2012".

The results of our systematic review show that continuous-flow LVAD is not cost-effective compared to MMT therapy considering the WTP thresholds adopted. Assessing the available evidence we found that LVAD cost-effectiveness is mainly sensitive to: increase in QoL due to technology improvement and/or reduction in complications; longer length of follow up; functional ability measures; reduction in LVAD cost; long term patient survival; reduction in complications and adverse events. However, based on the available evidence, it is not yet possible to determine if costs can be modified by reducing adverse events or if they are depending by the nature of the therapy. So the correlation between LVAD therapy costs and reduction in adverse events has to be investigated. However continuous flow LVAD represents a promising technology considering the shortage and decreasing availability of donor hearts; the increase in survival compared to MMT which is approaching rates similar to HT [Long et al, 2014; Sutcliffe et al, 2013]; QoL improvements in patients who otherwise couldn't carried out daily routine activities; the innovation of the technology which resulted in a reduction of infections and complications (e.g device failure). The technological improvements of devices and the learning curve of health professionals seem to determine an improved cost effectiveness; Rogers et al, 2012 showed that the 2nd generation of devices increased the likelihood of the VAD to be cost effective.

Finally since economic evidence from published literature showed that continuous flow LVAD is still an expensive therapeutic option and it cannot be considered cost-effective, the patients selection and patients management are also crucial for a cost effectiveness evaluation and they should be carefully assessed when implementing a LVAD implantation program and for its governance.

9. ORGANIZATIONAL ANALYSIS

9.1 METHODS

Assessment Element ID	Research questions
G0001	How does the technology affect the current work processes?
G0004	What co-operation and communication of activities have to be mobilised?
G0005	How do de-centralisation or centralisation requirements influence the implementation of the technology?
G0003a	Is there the need of training for the staff members?
G0003b	Is there the need of training for the patient?
G0003c	Is there the need of training for the care givers?
G0003d	What training is required for the patient?
G0003e	What training is required for care givers?
G0003f	What training is required for staff members?
G0003g	How much does the training for staff members cost?
G0003h	How much does the training for patients cost?
G0003i	How much does the training for care givers cost?
G0003j	who will fund the training for staff members?
G0003k	who will fund the training for patients?
G0003l	who will fund the training for care givers?
G0012	How is the quality assurance and monitoring system of the new technology organised?
D0023	How does the technology modify the use of resources?

To answer organizational AEs we started from the analysis of the Italian report "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD" approved by the Conferenza Nazionale Stato – Regioni e Province Autonome on the 2nd of July 2015. The document was the main result of a national project run by Centro Nazionale Trapianti – Istituto Superiore di Sanità (CNT-ISS) named "Grave insufficienza d'organo – Cuore". The document was drafted by the working group comprised by the Italian Heart Transplantation Centers and the National Cardiac Surgeries - not performing heart transplant - that carry out the LVAD implantation. Besides further activities were performed to assess the organizational impact of LVAD:

- Searches on Italian transplant/cardiac-surgery Centers' website that took part in the national project "Grave insufficienza d'organo – Cuore". The purpose was to collect information about the organizational procedure and the care pathways of patients undergoing LVAD implantation, established within those Centers. The searches were

perfomed from July to September 2015 entering the keywords (protocollo OR procedura OR percorso) AND (LVAD OR "assistenza ventricolare").

- A structured questionnaire was sent to manufacturers (May 2015) to gather information and data also about the organizational consequences of performing LVAD implantation.
- We have also scanned published literature resulting from the systematic search on economic aspects focusing on organisational aspects.

The analysis was aimed at investigating the following organizational issues concerning LVAD utilization:

- Changing in the work processes;
- Types of intra and inter-setting communication required;
- Education and training of the staff involved.

9.2 RESULTS

The organizational analysis basically lays on the Italian Report "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD". It represents a "National Guideline" for the governance and uniformity of the LVAD implantation activities realized within the Italian National Health System (SSN) in terms of access, performance and control of the device. The Italian National Health System was recognized to be in charge of ensuring the uniformity and harmonization at national level of the eligibility criteria for a healthcare organization to be a LVAD implantation center and of the general principles that should govern and control LVAD implantation activities. Besides it should be promoted the creation of a national registry to be connected to international registries with an audit system able to check the quality of data entered such as the quality control system already established for the National Transplant Registry.

One of the main aspects investigated in the Italian report are the organizational consequences related to the implantation of long term MCS (including LVAD) and total artificial heart. In our analysis we refer only to long term LVAD. The complexity of using LVAD is recognized to be caused by several factors: the severity of patients eligible to LVAD implantation; the need of developing and ensuring a high level specific expertise to guarantee the correct indications of patients and best outcomes; the interaction with the waiting list for heart transplantation; the exposure to the risk of complications not only in the post-procedural period but for the lifetime; the psychological difficulties/challenges faced by patients with LVAD; the costs for both LVAD procedure and long term management.

Therefore the authors pointed out that LVAD implantation should be performed, within the Italian SSN, in skilled centers with high level of expertise in the management of end stage HF (e.g.

centers with an established heart transplant program) and with a high volume of LVAD implantations performed allowing to develop and maintain a specific expertise in the overall management of LVAD patients (starting from the assessment of patient eligibility for LVAD to follow up, including all kinds of complications). Hence atomizing and disseminating the LVAD implantation's activity should be avoided since it would lead to a worsening of results. Conversely LVAD implantation should be performed in skilled centers - with an ad hoc authorization from Italian Regions (to be periodically renewed) - that show to meet requirements defined and listed in the "National guideline", called "MCS centers" hereinafter. An integrated medical-surgical program on the treatment of advanced HF needs to be implemented in the "MCS centers" that should also hold the following requirements: high expertise in cardiology, cardiac-surgery, anesthesia, intensive care and nursing for the proper management of LVAD patients during the pre and post-surgical phases and the follow up as well; a multidisciplinary team jointly coordinated by a cardiologist and a cardiac-surgeon which comprises several specialists (e.g. psychologist, psychiatrist, specialist in pain management and palliative care, infectivologist, physiotherapist, dietician, pharmacist, social consultant, etc.) able to provide an integrated care during the follow up; skills and technologies able to cope with the diagnosis and the treatment of complications; a telephone advice system or a specialist care in hospital 24h for the emergency; a network of patients' referrals and an evaluation protocol about indications, contraindications and risk factors consistent with the international guidelines and local regulations; indefinitely collection of follow-up data of all patients in the last 5 five years at least; provision of data to a multicenter registry according to the national or regional criteria (G0005).

The management of patients requires the involvement of several professionals in the pre-procedural, peri-procedural and post-procedural phase so each "MCS center" is required to have an integrated medical-surgical program for the governance of an integrated care to be provided to the LVAD patient. A multidisciplinary team should be in charge of LVAD patients management whose composition and responsibilities should be defined in local protocol/procedure that "MCS centers" are recommended to produce. The protocol/procedure should also clearly identify every specialist of reference. Similarly, at macro level, the "MCS centers" should communicate and be integrated with all other health care organizations/professionals involved in the patient's management at all health care levels. Hence in the "National Guideline" it is stated the need to develop a national system of communications and tasks to manage the routine follow up and the first emergency. In particular, the "MCS centers" are recommended to define procedure/protocol concerning: the ways to communicate the discharge and the relevant recommendations to the ASL, emergency services, electricity suppliers, etc.; the modalities of everlasting training and control of medical and nursing staff expertise providing care both in-home and external (e.g. rehabilitation centers, home care, etc.). In addition "MCS centers" not authorized to perform HT,

should communicated and interact with HT Centers in order to manage patients with LVAD that could receive a HT. The purposes of defining the interactions between "MCS centers" and "Transplant centers" are: to ensure that patient can access the various treatment options without conditions related to the availability of resources in a single center; to integrate transplant and LVAD therapy aimed at implementing structured and shared pathways for the care end stage HF (G0004).

The network of Transplant centers assumes the role and responsibility of reference for the LVAD program that will involve (as stated above) "Transplant centers" and other skilled centers ("MCS centers") which have developed a lasting interest in LVAD activity with a clear commitment of material, intellectual and human resources. Those last centers should have performed at least 15 MCS implantations in the last 3 years, maintain the volume of MCS activity of 5 MCS/year and identify the "Transplant center" to refer to. The "Transplant center" which has the responsibility to judge if patient could be transplanted should be in charge of LVAD activities as "bridge to transplant" (BTT) or "bridge to transplant candidacy" (BTC); hence the other "MSC centers" should perform only LVAD implantation as DT.

However the searches on the websites of the health care centers involved in the above mentioned project did not yield any organizational protocol related to LVAD implantation procedure or LVAD patient pathway approved locally.

We did not find any detailed information about the training of staff member, care-givers and patients in relation to LVAD within the available economic evidence, the "National Guideline" or on the already mentioned websites. However two manufacturers gave us the information about the training of all the professionals involved in the management of the LVAD patient. In particular the LVAD patient management (including indication, implantation and follow up) required a multidisciplinary approach, as already mentioned. The working team usually comprises:

- cardiologist skilled about timing and indications for LVAD implantation, skilled echocardiografist, etc. (pre-implantation phase);
- cardiac surgeons, anesthesiologists, instrumentation nurse, perfusionist, etc. (implantation phase);
- ICU personnel (intensivists and intensive nurses); ward personnel (physicians, nurses, etc.) (post-implantation phase);
- other professionals could be involved in the LVAD patient management (e.g. infectivologist, hematologist, psychologist, rehabilitation cardiologists, physiotherapist and consultants in further medical specialties).

Both manufacturers stated to provide an expert technical consultant (from the device distributors) *"for checking and controlling correct operation on the pump for the entire duration support*" or to support surgeons *"in or during the first implantation of the device"*. All professionals are trained for

using LVAD, and/or for managing and taking care of LVAD patients. As regards HeartWare HVAD *"training about the indications, surgical implant and post implantation management are held in experienced centers. Training regarding the use of peripherals, alarm understating and in general every-day-care for physicians, nurses, patients and their care givers are done by Technical Consultants of Aptiva medical, trained and certified by HeartWare Inc.*". Concerning Jarvik 2000 FLOWMAKER® the distributor [Artech Srl] "*provides full training on Jarvik 2000® VAS management to all Hospital professionals at Hospital facilities for Surgeons, Intensive Care personnel, Cardiology and General Ward personnel. Artech supports the Hospital in the patient discharge home process by providing training to the patient, out-of-hospital care givers and patient's relatives, Emergency service on the territory and general practitioners all under Hospital supervision and indications (…)".* As stated by Thoratec "*some senior staff will require specific training on the device. The training is typically provided by, or in collaboration with Thoratec and certified physicians".* (G0003a-G000f)

As stated by the manufacturers: HeartWare HVAD training costs *"about 10.000,00 Euro per training, covered at today by the manufacturer [HeartWare Inc.] and the distributor [Aptiva Medical Srl.]"* ; *"the cost of all training sessions (related to Jarvik 2000 FLOWMAKER®) are included in the purchasing price of the device: as of today no extra charge is applied to the Hospital for the full training package"* and, as regards Thoratec, "*no charge is made for the training although Thoratec reserves the right to charge if needed".* (G0003g-G0003l)

LVAD implantation increases the consumption of resources compared with the MMT. As stated by one manufacturer [HeartWare Inc.] *"LVAD implantation is a complex surgical and multidisciplinary procedure (…) that begins with the correct patient indications, goes on a high specialized surgical procedure and keep on with a every day patient care".* Hence huge amounts of human, technological, organizational and infrastructural resources and facilities are needed for performing the procedure of LVAD implantation. (D0023). This finding is consistent with the results of our systematic review of economic evaluations; in fact it showed that although difference in type, quantification, mesauring of resources used for LVAD implantation as well as differences in time horizon, currency, discount rate etc, among the included studies, the incremental cost of using LVAD procedure versus MMT resulted to be always high.

Apart from the requirements defined in the "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD" no evidence was found to answer the AE G0012 among the economic studies resulted from our systematic search. In US the Joint Commission defined mandatory international quality standards to award an advanced-level of certification in nine clinical or procedural areas, including VAD as DT. These programs must meet the requirements for Disease-Specific Care (DSC) Certification (meeting standards included in the DSC Certification Manual, conformity with clinical practice guidelines or evidence-based practice, complying with

requirements for performance measures) plus additional, clinically-specific requirements and expectations [http://www.jointcommission.org/certification/ventricular_assist_device.aspx].

In particular, programs seeking VAD certification must also:

- Be providing VAD as DT to an adult population.
- Have facilities with the infrastructure to support VAD placements as evidenced by adequate staffing and facilities to perform and to recover patients after cardiac surgery.
- Be an active continuous member of a national, audited registry for MCS devices that requires submission of health data on ventricular assist device destination therapy patients from the date of implantation throughout the remainder of their lives.
- Include a cardiac surgeon who placed 10 ventricular assist devices in the past 36 months with current activity in the past 12 months (or if a surgeon did not, the volume requirements can be met by including artificial heart placements for no more than 50% of the total volume).

[http://www.jointcommission.org/certification/ventricular_assist_device.aspx].

9.3 DISCUSSION

Ventricular Assisted Device is a complex technology requiring not only huge amounts of human, technological, organizational and infrastructural resources to be mobilized but also a coordinated and demanding organizational commitment to assure a proper governance for its utilization. The Italian Report "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD" as well as US Joint Commission's "Requirements for Certification in Ventricular Assist Device" pointed out that health care organizations performing LVAD implantation should/must meet strict requirements described in details in the previous section and related to the staff skills and expertise; the facilities and infrastructures for performing the LVAD procedure and for recovering LVAD patients; the coordination and communications within the health care organisation and among health care organisations; the provision of data to a registry for MCS devices; etc.

In conclusion LVAD implantation should be performed in skilled centers avoiding the spread and diffusion of LVAD implantation activity since it would lead to a worsening of performances and clinical results. Besides, at health care organization level, an integrated medical-surgical program (with clear identification of roles, responsibilities and specialists of reference) is necessary for the governance of an integrated care to be provided to the LVAD patient as well as, at macro level, all health care organizations/professionals involved in the patient's management at all health care levels should communicate and be integrated with each other.

10. CONCLUSIONS

With the advent of durable and reliable mechanical circulatory support (MCS), left ventricular assist device (LVAD) has become a real alternative to transplantation in end stage left ventricular congestive heart failure when patients are temporarily or definitively not eligible for transplant. Outcomes in patients supported by LVADs have continued to improve consistently over time with improvement in device design, patient selection, and post-operative care. The increasing use of LVAD improves the allocation of transplants alleviating the shortage of donors.

The positive effect of LVAD support in end-stage heart-failure are in favour of overall survival, although the quality of the evidence was low and the occurrence of important adverse events must be considered carefully when selecting patients.

The cost and economic evaluation assessed all economic information on LVAD implant compared to MMT using a systematic review and a micro-costing analysis, performed in two Italian hospitals in two Regions (Veneto and Lombardia).

Our systematic review produced limited information on the cost-effectiveness of continuous flow LVAD compared to MMT. Studies to gather further information on cost-effectiveness of LVAD implantation procedure and the pre-implantation workup and LVAD patient management during the follow up are needed.

In the Italian context so far there are insufficient data on the economic evaluation on LVAD compared to MMT. A comprehensive economic evaluation and a budget impact analysis on LVAD based on data collected from more NHS Italian centers are required.

The ICD9- CM code 37.66 ("Insertion of implantable heart assist system") is not specific for implantable LVAD, which does not enable a punctual detection of LVAD procedure only.

According to the "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD", LVAD implantation should be performed in skilled centers avoiding the spread and diffusion of LVAD implantation activity since it would lead to a worsening of performances and clinical results. Besides, at health care organization level, an integrated medical-surgical program (with clear identification of roles, responsibilities and specialists of reference) is necessary for the governance of an integrated care to be provided to the LVAD patient as well as, at macro level, all health care organizations/professionals involved in the patient's management at all health care levels should communicate and be integrated with each other.

11. RECOMENDATIONS

Further robust studies with standardized data collection are needed for this fast evolving technology as the available evidence was low. Furthermore it is unlikely that true randomized trials in this therapeutic space will ever exist. Thus properly maintained and audited mandatory registries may be the only solution. The positive effect of LVAD support in endstage heartfailure are in favour of overall survival and the occurrence of important adverse events must be considered carefully when selecting patients.

Studies to gather further information on cost-effectiveness of LVAD are needed considering not only the implantation procedure but also the pre-implantation workup and LVAD patient management during the follow up.

According to the "Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo – LVAD", LVAD implantation should be performed in skilled centers avoiding the spread and diffusion of LVAD implantation activity. Besides MCS centers are recommended to define procedure/protocol concerning: the ways to communicate the discharge and the relevant recommendations to the ASL, emergency services, electricity suppliers, etc.; the modalities of everlasting training and control of medical and nursing staff expertise providing care both in-home and external (e.g. rehabilitation centers, home care, etc.). In addition MCS centers not authorized to perform HT, should communicate and interact with HT Centers in order to manage patients with LVAD who may became candidates to HT.

A specific coding for implantable LVAD only, would be appropriate within the national hospital discharges database.

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13. COMPETING INTERESTS DECLARATION

The Authors declare that they will not receive either benefits or harms from the publication of this report. None of the Authors has or has held shares, consultancies or personal relationships with any of the manufacturers of the devices assessed in this report.

BIBLIOGRAPHY

Alan S. Go, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014;129:399-410 [PubMed]

Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med 2006;355:1873-84 [PubMed]

Birks EJ. Left ventricular assist devices. Heart 2010;96 :63– 71

Boothroyd LJ, Lambert LJ, Sas G et al. Should eligibility for heart transplantation be a requirement for left ventricular assist device use? Recommendations based on a systematic review. Can Cardiol 2013

Centers for Medicare and Medicaid Services. Standard Analytic File,2008. Centers for Medicare and Medicaid Services, Baltimore, MD.

Clarke A, Pulikottil-Jacob R, Connock M, Suri G, Kandala NB, Maheswaran H, et al. Cost-effectiveness of left ventricular assist devices (LVADs) for patients with advanced heart failure: analysis of the British NHS bridge to transplant (BTT) program. Int J Cardiol. 2014;171(3):338-45.

Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, et al. The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. Health Technol Assess. 2005;9(45):1-132, iii-iv.

Cleland JG, Gemmell I,Khand A, et al. Is the prognosis of heart failure improving? Eur J Heart Fail 1999;1:229–41.

Costanzo MR, Mills RM, Wynne J. Characteristics of "stage D" heart failure: insights from the Acute Decompensated Heart Failure National Registry Longitudinal Module (ADHERE LM). Am Heart J. 2008;155: 339–347.

Documento di Indirizzo del Gruppo Nazionale sulle Gravi Insufficienze d'Organo-Cuore, 2014. available at:http://www.statoregioni.it/Documenti/DOC_047907_100%20csr%20%28p.%2010%20odg%29.pdf

Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissionsto the BMJ. BMJ 1996;313:275–83.

Earle CC, Chapman RH, Baker CS, Bell CM, Stone PW, Sandberg EA, Neumann PJ. Systematic overview of cost-utility assessments in oncology. J Clin Oncol. 2000;18:3302–3317.

Farrar DJ, Hill JD, Pennington DG, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the thoratec ventricular assist device as a bridge to cardiac transplantation. J ThoracCardiovascSurg 1997;113:202-9

Frazier OH, Rose EA, McCarthy P, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. Ann Surg 1995;222:327-36; discussion 336-8 [PMC free article] [PubMed]

Frazier OH, Rose EA, Oz MC, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. J ThoracCardiovascSurg 2001;122:1186-95 [PubMed]

Garbade J, Bittner HB, Barten MJ. Current Trends in Implantable Left Ventricular Assist Devices. Volume 2011. Cardiology Research and Practice.

Gelijns AC, Richards AF, Williams DL, Oz MC, Oliveira J, Moskowitz AJ. Evolving costs of long-term left ventricular assist device implantation. Ann Thorac Surg. 1997;64:1312–1319.

Giridharan GA, Lee TJ, Ising M et al. Thoughts and Progress: Miniaturization of Mechanical Circulatory Support Systems. Artif Organs. 2012 August ; 36(8)

Givertz M. Ventricular Assist Devices. Circulation. 2011;124:e305-e311.

Grave insufficienza d'organo – Cuore: "LVAD:tecnologia, efficacia, sicurezza, analisi economica e fabbisogno nazionale" , 2012.

Gruppo di lavoro Aies: LG per la valutazione economica dell'HTA, 2009.

Haj-Yahia S, Birks EJ, Rogers P et al. Midterm experience with the Jarvik 2000 axial flow left ventricular assist device. Journal of Thoracic and Cardiovascular Surgery, vol. 134, no. 1, pp. 199–203, 2007.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 2011.

http://www.jointcommission.org/certification/ventricular_assist_device.aspx (last access: October 16, 2015)

http://www.statoregioni.it/Documenti/DOC_047907_100%20csr%20%28p.%2010%20odg%29.pdf

John R, Pagani FD, Naka Y, Boyle A, et al. Post-cardiac transplant survival after support with a continuous-flow left ventricular assist device: impact of duration of left ventricular assist device support and other variables. J Thorac Cardiovasc Surg 2010;140:174-81.

Khawaja A A, Steven JJ, Douglas W M, et al.. Prevalence and Prognostic Significance of Heart Failure Stages. Application of the American College of Cardiology/American Heart Association Heart Failure Staging Criteria in the Community. Circulation. 2007; 115: 1563-1570

Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, Baldwin JT, Young JB. The Fourth INTERMACS Annual Report: 4,000 implants and counting. J Heart Lung Transplant. 2012;31:117–126.

Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, Timothy Baldwin J, Young JB. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant. 2013;32:141–156.

Levy W C, Mozaffarian D, Linker D T. et al The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006; 113:1424–1433.

Liem YS, Bosch JL, Hunink MG. Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta analysis. Value Health. 2008;11:733–741.

Lietz K, Miller LW. Improved survival of patients with end-stage heart failure listed for heart transplantation: analysis of organ procurement and transplantation network/U.S. United Network of Organ Sharing data, 1990 to 2005. J Am Coll Cardiol 2007;50:1282–90.

Lloyd-Jones D, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation 2010;121:e46–e215. [PubMed: 20019324]

Long EF, Swain GW, Mangi AA. Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure. Circ Heart Fail. 2014;7(3):470-8.

McIlvennan C. K., Magid K.H., Ambardekar A. V., et al. Clinical Outcomes After Continuous-Flow Left Ventricular Assist Device: A Systematic Review. Circ Heart Fail. 2014;7:1003-1013.

McMurray JJ, Petrie MC, Murdoch DR, et al.. Clinical epidemiology of heart failure: public and private health burden. Eur Heart J 1998;19 (Suppl P):P9–P16. [PubMed: 9886707]

Medicare Program; changes to the hospital inpatient prospective payment systems and fiscal year 2009 rates; payments for graduate medical education in certain emergency situations; changes to disclosure of physician ownership in hospitals and physician self-referral rules; updates to the long-term care prospective payment system; updates to certain IPPSexcluded hospitals; and collection of information regarding financial relationships between hospitals; final rule. Federal Register. 73; 8-19-2008.

Miller LW, Pagani FD, Russell SD et al. Use of a continuous-flow device in patients awaiting heart transplantation. The New England Journal of Medicine, vol. 357, no. 9, pp. 885–896, 2007.

Mishra V, Fiane AE, Geiran O, Sorensen G, Khushi I, Hagen TP. Hospital costs fell as numbers of LVADs were increasing: experiences from Oslo University Hospital. J Cardiothorac Surg. 2012;7:76.

Mishra V, Geiran O, Fiane AE, Sorensen G, Andresen S, Olsen EK, et al. Costs and reimbursement gaps after implementation of third-generation left ventricular assist devices. J Heart Lung Transplant. 2010;29(1):72-8.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

Moreno SG, Novielli N, Cooper NJ. Cost-effectiveness of the implantable HeartMate II left ventricular assist device for patients awaiting heart transplantation. J Heart Lung Transplant. 2012;31(5):450-8.

Moskowitz AJ, Rose EA, Gelijns AC. The cost of long-term LVAD implantation. Ann Thorac Surg. 2001;71:S195–S198.

Neyt M, Van den Bruel A, Smit Y, De Jonge N, Erasmus M, Van Dijk D, et al. Cost-effectiveness of continuous-flow left ventricular assist devices. Int J Technol Assess Health Care. 2013;29(3):254-60.

Oz MC, Gelijns AC, Miller L, Wang C, Nickens P, Arons R, Aaronson K, Richenbacher W, van Meter C, Nelson K, Weinberg A, Watson J, Rose EA, Moskowitz AJ. Left ventricular assist devices as permanent heart failure therapy: the price of progress. Ann Surg. 2003;238:577–583.

Pagani FD, Miller LW, Russell SD, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol 2009;54:312-21.

Pickard AS, Wilke CT, Lin HW, Lloyd A. Health utilities using the EQ 5D in studies of cancer. Pharmacoeconomics. 2007;25:365–384.

Redfield MM, Jacobsen SJ, Burnett JC Jr, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003 Jan 8; 289(2):194-202.

Roger V L, Weston S A, Redfield M M. et al Trends in heart failure incidence and survival in a community-based population. JAMA 2004 Vol292, 344–350.

Rogers G J, Butler J, et al. Journal of the American College of Cardiology Vol. 50, No. 8, 2007

Rogers JG, Bostic RR, Tong KB, Adamson R, Russo M, Slaughter MS. Cost-effectiveness analysis of continuous-flow left ventricular assist devices as destination therapy. Circ Heart Fail. 2012;5:10–16.

Rose E A, Gelijns A C et al. (2001). 'Long-term mechanical left ventricular assistance for end-stage heart failure.' New England Journal of Medicine, 345 (20), 1435-1443.

Russo MJ, Gelijns AC, Stevenson LW, Sampat B, Aaronson KD, Renlund DG, Ascheim DD, Hong KN, Oz MC, Moskowitz AJ, Rose EA, Miller LW. The cost of medical management in advanced heart failure during the final two years of life. J Card Fail. 2008;14:651– 658.

Sharples LD, Dyer M, Cafferty F, Demiris N, Freeman C, Banner NR, et al. Cost-effectiveness of ventricular assist device use in the United Kingdom: results from the evaluation of ventricular assist device programme in the UK (EVAD-UK). J Heart Lung Transplant. 2006;25(11):1336-43.

Siegenthaler MP, Frazier OH, Beyersdorf F et al. Mechanical reliability of the Jarvik 2000 Heart. Annals of Thoracic Surgery, vol. 81, no. 5, pp. 1752–1759, 2006.

Singh TP, Almond CS, Taylor DO, Graham DA. Decline in heart transplant wait list mortality in the United States following broader regional sharing of donor hearts. Circ Heart Fail. 2012;5:249–258.

Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM III, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361:2241–2251.

Sutcliffe P, Connock M, Pulikottil-Jacob R et al. Clinical effectiveness and cost-effectiveness of second- and third-generation left ventricular assist devices as either bridge to transplant or alternative to transplant for adults eligible for heart transplantation: systematic review and cost-effectiveness model. Health Technol Assess 2013;17 (53).

Sutcliffe P, Connock M, Pulikottil-Jacob R, Kandala N-B, Suri G, Gurung T, et al. Clinical effectiveness and cost-effectiveness of second- and third-generation left ventricular assist devices as either bridge to transplant or alternative to transplant for adults eligible for heart transplantation: systematic review and cost-effectiveness model. Health Technol Assess 2013;17(53).

Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European

GLOSSARY

AC Adapter: A power adapter that plugs into a wall electrical outlet

BT bridge to transplantation

BTC Bridge to candidacy

BTR Bridge to recovery: for patients in whom the native heart function may possibly be recovered

BTT Bridge to transplant: for patients who are transplant candidates but who will not survive waiting until an organ is available

CE Conformité Européenne

CEA Cost-Effectiveness Analysis

CBA Cost-Benefit Analysis

CCA Cost-Consequences Analysis

CMA Cost-Minimization Analysis

CRT cardiac resynchronisation treatment

CRT-D Cardiac Resynchronization Therapy Defibrillator

CUA Cost-Utility Analysis

DC Adapter: A power adapter that uses power from an automobile electrical outlet to run the controller and VAD

DT Destination Therapy: for patients who are not transplant candidates

ESHF end-stage heart failure

FDA US Food and Drug Administration

GDMT guideline directed medical therapy

HT Heart Transplantation

ICER Incremental Cost Effectiveness Ratio

ICD implantable cardioverter-defibrillator

LOS Length Of Stay

LTCS long-term chronic support

LV Left ventricle

LVAD left ventricular assist device

LY Life Year

LYG Life Year Gained

MCS mechanical circulatory support

MMT: Medical Management Therapy

NYHA New York Heart Association

OHT Orthotopic Heart Transplantation

OMT optimal medical therapy

QALY Quality Adjusted Life Year

QoL Quality of Life

APPENDIX 1

The Agenas adaptation of the EUnetHTA Core Model ®

Health Technology Assessment (HTA) is the multidisciplinary evaluation of one or more health interventions in their context of use. Since 2006 Agenas has been involved in the European HTA network EUnetHTA (http://www.eunethta.eu/contactus/all/356/all). EUnetHTA's main aim is to increase collaboration and avoid inefficiencies and duplications by using shared, standardised and agreed methods. These in a continuous development cycle. One of the methods produced and used is the HTA Core Model ® (http://meka.thl.fi/htacore/BrowseModel.aspx). The idea behind the Model is the provision of a standard method for HTA evidence synthesis, structuring and presenting in a standard format to facilitate its use by network agencies and others.
The Core Model is divided into domains which represent the various aspects of the assessment of health technologies' research. Each domain contains a series of research questions or Assessment Elements (AEs). Ver 2.0 of the EUnetHTA Core Model is divided into domains:

1. Health problem and current use of technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Safety (SAF)
4. Clinical effectiveness (EFF)
5. Costs and economic evaluation (ECO)
6. Ethical analysis (ETH)
7. Organisational aspects (ORG)
8. Social aspects (SOC)
9. Legal aspects (LEG)

While using the Core Model in both Joint Actions 1 and 2 with the European Commission, Agenas identified some recurring common problems with the Core Model requiring further development work if the Model were to be used in the production of Health Technology Assessment reports in Italy.

The problems are mainly AEs repetition, partial or complete overlap of AE content and likely answers, as well as lack of definition and clarity.

As a consequence Agenas undertook its own review of the Model to streamline its use and increase its relevance to everyday work of both HTA doers and HTA users. The Model basis for the review was version 2.0, medical and surgical intervention application.

The review process included a visual inspection of the 104 AEs with linked clarifications to identify any likely overlaps. The second phase consisted in grouping all AEs related to a unique concept (such as informed consent, technology and comparator(s) descriptions, regulatory information, mortality as a burden of illness measure, mortality as an outcome measure) into the likeliest domain of relevance. Agenas also attempted to link some of the text of each AE's clarification note

more closely with the AE and corrected any English syntax problems. In addition a single AE containing multiple questions was divided into sub questions. All original AE identifiers were maintained to denote the origin of the AE. To make identification of the information quicker and unpack some domains, Agenas also introduced two new domains REG or Regulatory Information and HAZ or Environmental Hazard for the assessment of possible harms not directly caused to the technology's recipient.

Agenas started using its Core Model adaptation for the 2014-2015 crop of Agenas HTA reports. Although some Agenas HTA reports are adaptations to Italy of up to date reports produced elsewhere or updates of previous Agenas work. In these cases the Agenas Core Model adaptation use will be partial.
Agenas plans to evaluate and develop the Model further.

APPENDIX 2. Search Strategy Safety and Clinical Effectiveness

The following literature search was used on 14 April 2015 to answer the pertinent Assessment Elements (see Appendix 2) with the addition of specific outcomes for Safety and Effectiveness domains (All-cause mortality, Post-operative mortality, Cardiovascular mortality, Heart failure-related hospitalizations, Change in New York Heart Association (NYHA) functional class, Length of stay, Duration of inotropic support, Left ventricular ejection fraction (LVEF), Left ventricular end-diastolic volume, Exercise capacity: peak oxygen consumption (peak VO2), distance on the 6-minute walk test (6MWT), Quality of life (measured by a validated scale questionnaire), Adverse events (major stroke, bleeding complication, peri-procedural myocardial infarction, acute renal injury, major vascular complication, infections, right ventricular failure), LVAD replacement rate).

MEDLINE

MESH descriptor:"Heart-Assist Devices"[Mesh] OR **“ left ventricular assist device*” OR** **LVAD OR LVADS OR** **HeartMate II HeartMate II® OR** **HeartWare OR** **HLVAD pump OR** **Jarvik heart OR** **Jarvik 2000 FlowMaker OR** **BerlinHeart OR** **Incor EXCOR® OR** **MicromedCardiovascular HeartAssist 5®** **OR** **(“mechanical circulatory” AND “support devices”) OR** **MSCD OR “continuous flow”**	**AND**	**MESH descriptor: Safety OR** **MESH descriptor:** **Comparative Effectiveness Research OR** **MESH descriptor: “quality of life” OR** **MESH descriptor: “Return to work” OR** **MESH descriptor: “Patient Satisfaction” OR** **MESH descriptor: “Hospitalization” OR** **MESH descriptor:”Patient discharge” OR** **MESH descriptor: “Survival Rate” OR** **MESH descriptor: “Treatment Outcome” OR** **MESH descriptor: “Postoperative Complications” OR** **MESH descriptor: “Follow-Up Studies” OR** **MESH descriptor:"Ventricular Function, Left” OR** **MESH descriptor: “Heart Failure” OR** **MESH descriptor:"Ventricular Function, Left” OR** **MESH descriptor:" Ventricular Dysfunction”** **Ricerca in [Title/Abstract]** **“Length of stay” OR** **“Duration of inotropic support” OR**

		“Exercise capacity” OR Safety OR Mortality OR Effectiveness OR “return-to-work” OR “Back-to-Work” OR Complication* OR pain OR “Adverse events” OR “side effects” OR morbility OR “Right Ventricular failure”OR “Heart Failure” OR “LVAD replacement rate” OR Left ventricular ejection fraction (LVEF) OR “Left ventricular end-diastolic volume” OR stroke OR” bleeding complication” OR “peri-procedural myocardial infarction” OR “acute renal injury” OR infections
	AND	**“"optimal medical therapy" OR “guidelines-directed medical therapy”**
“Heart-Assist Devices/adverse effects"[Mesh]		

EMBASE

'left ventricular assist device'/exp OR LVAD OR LVADS OR 'continuous flow left ventricular assist device'/exp OR "continuous flow" OR HeartMate II HeartMate II® OR HeartWare OR HLVAD pump OR Jarvik heart OR Jarvik 2000 FlowMaker OR BerlinHeart OR Incor EXCOR® OR MicromedCardiovascular HeartAssist 5®	AND	EMTREE TERM: 'quality of life'/exp OR EMTREE TERM:"clinical effectiveness" OR EMTREE TERM: "comparative effectiveness" OR EMTREE TERM: 'device safety'/exp OR EMTREE TERM: 'program effectiveness'/exp OR EMTREE TERM: 'program evaluation'/exp OR EMTREE TERM: 'risk assessment'/exp OR EMTREE TERM: Mortality/exp OR EMTREE TERM: "return-to-work"/exp OR EMTREE TERM: "Back-to-Work"/exp OR EMTREE TERM: 'program acceptability'/exp OR EMTREE TERM: Safety/exp OR EMTREE TERM: 'heart failure'/exp EMTREE TERM: Ventricular Function, Left" OR EMTREE TERM:" Ventricular Dysfunction" OR "Length of stay" OR " Duration of inotropic support" OR "Exercise capacity" OR Complications OR pain OR 'device failure analysis'/exp OR Effectiveness OR "Comparative Effectiveness Research" Survival Rate OR Treatment Outcome OR "Postoperative Complications" OR infections OR "Adverse events" OR "side effects" OR "quality of life" OR QoL OR "Right Ventricular failure"OR "LVAD replacement rate" OR Left ventricular ejection fraction (LVEF) OR Left ventricular end-diastolic volume OR stroke OR "bleeding complication" OR "peri-procedural myocardial infarction" OR "acute renal injury"
	AND	""optimal medical therapy" OR "guidelines-directed medical therapy"

COCHRANE

MESH descriptor:"Heart-Assist Devices"[Mesh] OR (left ventricular assist device) : ti,ab,kw OR (left ventricular assist devices) : ti,ab,kw	AND	MESH descriptor: Safety OR MESH descriptor: "Comparative Effectiveness Research" OR MESH descriptor: "quality of life" OR MESH descriptor: "Return to work" OR MESH descriptor: "Patient Satisfaction" OR

OR **LVAD: ti,ab,kw OR** **LVADS: ti,ab,kw OR** **(HeartMate II) OR** **(HeartMate II®) OR** **HeartWare OR** **(HLVAD pump) OR** **(Jarvik heart) OR** **Jarvik 2000 OR** **FlowMaker OR** **BerlinHeart OR** **(Incor EXCOR®) OR** **(MicromedCardiovascular HeartAssist 5) OR** **((mechanical circulatory) AND "support devices") : ti,ab,kw OR** **MSCD OR** **(ventricular assist device) : ti,ab,kw OR** **(ventricular assist devices) : ti,ab,kw OR** **(continuous flow):ti,ab,kw**		**MESH descriptor: "Hospitalization OR MESH descriptor:"Patient discharge" OR MESH descriptor: Survival Rate OR MESH descriptor: Treatment Outcome OR MESH descriptor: "Postoperative Complications" OR MESH descriptor: "Follow-Up Studies" OR MESH descriptor: "Heart Failure" OR MESH descriptor:"Ventricular Function, Left" OR MESH descriptor:" Ventricular Dysfunction"** **Ricerca in [Title/Abstract] per** **(Length of stay) OR** **Infections OR** **(Duration of inotropic support) OR** **(Exercise capacity) OR** **Safety: ti,ab,kw OR Mortality: ti,ab,kw OR** **Effectiveness: ti,ab,kw OR (return-to-work) OR** **(Back-to-Work) OR Complication: ti,ab,kw OR** **Complications: ti,ab,kw OR** **pain: ti,ab,kw OR (Adverse events) : ti,ab,kw OR** **(side effects) : ti,ab,kw OR** **morbility OR** **(Right Ventricular failure) OR** **(LVAD replacement rate) OR** **(Left ventricular ejection fraction) OR** **(Left ventricular end-diastolic volume) OR stroke OR (bleeding omplications) OR (peri-procedural myocardial infarction) OR (acute renal injury)**

APPENDIX 3. List of excluded studies Safety and Clinical Effectiveness

Excluded Articles (reasons: not RCT /CCT /not relevant/not found)

Backes D, van den Bergh WM, van Duijn AL, Lahpor JR, van Dijk D, Slooter AJ. Cerebrovascular complications of left ventricular assist devices. Eur J Cardiothorac Surg 2012

Brouwers C, Denollet J, de Jonge N, Caliskan K, Kealy J, Pedersen SS. Patient-reported outcomes in left ventricular assist device therapy: a systematic review and recommendations for clinical research and practice. Circ Heart Fail 2011

Cheng JM, den Uil CA, Hoeks SE et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J 2009

Clegg AJ, Scott DA, Loveman E, Colquitt J, Royle P, Bryant J. Clinical and cost-effectiveness of left ventricular assist devices as destination therapy for people with end-stage heart failure: a systematic review and economic evaluation. Int J Technol Assess Health Care 2007

Cowger J, Sundareswaran K, Rogers JG et al. Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. J Am Coll Cardiol 2013

Daneshmand MA, Rajagopal K, Lima B et al. Left ventricular assist device destination therapy versus extended criteria cardiac transplant. Ann Thorac Surg 2010

Deng MC, Weyand M, Hammel D et al. Selection and management of ventricular assist device patients: the Muenster experience. J Heart Lung Transplant 2000

Deng MC, Weyand M, Hammel D et al. Selection and outcome of ventricular assist device patients: the Muenster experience. J Heart Lung Transplant 1998

Deo SV, Sharma V, Cho YH, Shah IK, Park SJ. De novo aortic insufficiency during long-term support on a left ventricular assist device: a systematic review and meta-analysis. ASAIO J 2014

Esmore D, Kaye D, Spratt P et al. A prospective, multicenter trial of the VentrAssist left ventricular assist device for bridge to transplant: safety and efficacy. J Heart Lung Transplant 2008Gazzoli F, Vigano M, Pagani F et al. Initial results of clinical trial with a new left ventricular assist device (LVAD) providing synchronous pulsatile flow. Int J Artif Organs 2009

Jaski BE, Kim J, Maly RS et al. Effects of exercise during long-term support with a left ventricular assist device. Results of the experience with left ventricular assist device with exercise (EVADE) pilot trial. Circulation 1997

Jaski BE, Lingle RJ, Kim J et al. Comparison of functional capacity in patients with end-stage heart failure following implantation of a left ventricular assist device versus heart transplantation: results

of the experience with left ventricular assist device with exercise trial. J Heart Lung Transplant 1999

John R, Naka Y, Smedira NG et al. Continuous flow left ventricular assist device outcomes in commercial use compared with the prior clinical trial. Ann Thorac Surg 2011

Kugler C, Malehsa D, Tegtbur U et al. Health-related quality of life and exercise tolerance in recipients of heart transplants and left ventricular assist devices: a prospective, comparative study. J Heart Lung Transplant 2011

Mancini D, Goldsmith R, Levin H et al. Comparison of exercise performance in patients with chronic severe heart failure versus left ventricular assist devices. Circulation 1998

Morgan JA, Park Y, Kherani AR et al. Does bridging to transplantation with a left ventricular assist device adversely affect posttransplantation survival? A comparative analysis of mechanical versus inotropic support. J Thorac Cardiovasc Surg 2003

Pamboukian SV, Tallaj JA, Brown RN et al. Comparison of observed survival after ventricular assist device placement versus predicted survival without assist device using the Seattle heart failure model. ASAIO J 2012

Rogers JG, Boyle AJ, O'Connell JB et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: design and rationale of the ROADMAP clinical trial. Am Heart J 2015

Sorabella R.A., Yerebakan H., Walters R. et al. Comparison of outcomes after heart replacement therapy in patients over 65 years old. Ann. Thorac. Surg. 2015

Morgan J.A., Nemeh H.W., Paone G. Should left ventricular assist devices be implanted in patients seventy years of age and older: A comparative analysis. Heart Surg. Forum 2014

Mulloy DP, Bhamidipati CM, Stone ML, Ailawadi G, Kron IL, Kern JA. Orthotopic heart transplant versus left ventricular assist device: a national comparison of cost and survival. J Thorac Cardiovasc Surg 2013

Pinkerman C, Sander P, Breeding JE, et al. Institute for Clinical Systems Improvement. Heart Failure in Adults. Updated July 2013.Mayo Clin Proc. 2010 Feb; 85(2): 180–195. doi: 10.4065/mcp.2009.0494

Trivedi JR, Cheng A, Singh R, Williams ML, Slaughter MS. Survival on the heart transplant waiting list: impact of continuous flow left ventricular assist device as bridge to transplant. Ann Thorac Surg 2014

Wozniak C.J., Stehlik J., Baird B.C. et al. Ventricular assist devices or inotropic agents in status 1A patients? Survival analysis of the united network of organ sharing database. Ann. Thorac. Surg. 2014

Sharples L, Buxton M, Caine N et al. Evaluation of the ventricular assist device programme in the UK. Health Technol Assess 2006

Sharples LD, Cafferty F, Demitis N et al. Evaluation of the clinical effectiveness of the Ventricular Assist Device Program in the United Kingdom (EVAD UK). J Heart Lung Transplant 2007

Neyt M, Van den Bruel A, Smit Y et al. Cost-effectiveness of continuous-flow left ventricular assist devices. Int J Technol Assess Health Care 2013

Rogers JG, Bostic RR, Tong KB, Adamson R, Russo M, Slaughter MS. Cost-effectiveness analysis of continuous-flow left ventricular assist devices as destination therapy. Circ Heart Fail 2012

Owens AT, Jessup M. Should left ventricular assist device be standard of care for patients with refractory heart failure who are not transplantation candidates?: left ventricular assist devices should not be standard of care for transplantation-ineligible patients. Circulation 2012

Williams ML, Trivedi JR, McCants KC et al. Heart transplant vs left ventricular assist device in heart transplant-eligible patients. Ann Thorac Surg 2011

Reedy JE, Pennington DG, Miller LW et al. Status I heart transplant patients: conventional versus ventricular assist device support. J Heart Lung Transplant 1992

Pennington DG, Oaks TE, Lohmann DP. Permanent ventricular assist device support versus cardiac transplantation. Ann Thorac Surg 1999

Urban M, Pirk J, Dorazilova Z, Netuka I. How does successful bridging with ventricular assist device affect cardiac transplantation outcome? Interact Cardiovasc Thorac Surg 2011

Park SJ, Milano CA, Tatooles AJ et al. Outcomes in advanced heart failure patients with left ventricular assist devices for destination therapy. Circ Heart Fail 2012

Saeed D., Arusoglu L., Gazzoli F. et al. Results of the European Clinical Trial of Arrow CorAide Left Ventricular Assist System. Artif. Organs 2013

Stevenson LW, Miller LW, Desvigne-Nickens P et al. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). Circulation 2004

Schechter MA, Daneshmand MA, Patel CB, Blue LJ, Rogers JG, Milano CA. Outcomes after implantable left ventricular assist device replacement procedures. ASAIO J 2014

APPENDIX 4. Search strategy of economic evidence

MEDLINE

MESH descriptor:"Heart-Assist Devices"[Mesh] OR " left ventricular assist device*" OR LVAD OR LVADS OR HeartMate II HeartMate II® OR HeartWare OR HLVAD pump OR Jarvik heart OR Jarvik 2000 FlowMaker OR BerlinHeart OR Incor EXCOR® OR MicromedCardiovascular HeartAssist 5® OR ("mechanical circulatory" AND "support devices") OR MSCD OR "ventricular assist device*	AND	Mesh descriptor ""Costs and Cost Analysis" OR Mesh descriptor "Economics" OR Mesh descriptor "Cost Allocation" OR Mesh descriptor "Cost-Benefit Analysis" OR Mesh descriptor "Cost of Illness" OR Mesh descriptor "Cost Control" OR Mesh descriptor "Cost Savings" OR Mesh descriptor "Health Care Costs" OR Mesh descriptor "Direct Service Costs" OR Mesh descriptor "Hospital Costs" OR Mesh descriptor "Efficiency, Organizational/economics Cost-effectiveness [Title/Abstract] OR Cost-utility [Title/Abstract] OR Cost – effectiveness [Title/Abstract] OR Cost – utility [Title/Abstract] OR "resource used" [Title/Abstract] OR "Cost effectiveness analysis" *[Title/Abstract] OR CMA (title/abstract) OR "cost effectiveness" (title/abstract) OR CEA (title/abstract) OR "cost utility" (title/abstract) OR CUA (title/abstract) OR CEA [Title/Abstract] "Cost utility analysis " [Title/Abstract] OR "Cost benefit analysis" [Title/Abstract] OR "Cost consequences analysis "*[Title/Abstract] OR " Cost minimization analysis" *[Title/Abstract] OR (economic AND (evaluation OR analysis OR aspect OR assessment)) [Title/Abstract] OR "Budget Impact Analysis" [title/abstract]

EMBASE

'left ventricular assist device'/exp OR LVAD OR LVADS OR 'continuous flow left ventricular assist device'/exp OR HeartMate II HeartMate II® OR HeartWare OR HLVAD pump OR Jarvik heart OR Jarvik 2000 FlowMaker OR BerlinHeart OR Incor EXCOR® OR MicromedCardiovascular HeartAssist 5®	AND	"Economic aspect"/exp OR 'cost analysis'/exp OR 'cost of illness'/exp OR " economic evaluation"/exp OR 'cost minimization analysis'/exp OR CMA:ab,ti 'cost effectiveness analysis'/exp OR CEA:ab,ti OR OR 'cost benefit analysis'/exp OR 'cost utility':ab,ti OR CUA:ab,ti OR 'hospitalization cost'/exp 'health care cost'/exp OR (economic AND ('evaluation'/exp OR 'analysis'/exp OR aspect OR assessment)) OR ('budget impact analysis':ab,ti OR BIA:ab,ti)" OR Cost Analysis/:ab,ti OR "Economics"/:ab,ti OR "Cost Allocation"/:ab,ti OR "Cost-Benefit/:ab,ti OR "Cost Control"/exp OR "Cost Saving"/:ab,ti OR "Cost-effectiveness"/:ab,ti OR "Cost-utility"/:ab,ti

COCHRANE

MESH descriptor:"Heart-Assist Devices"[Mesh] OR (left ventricular assist device)" : ti,ab,kw OR (left ventricular assist devices)" : ti,ab,kw LVAD: ti,ab,kw OR LVADS: ti,ab,kw OR HeartMate II HeartMate II® OR HeartWare OR HLVAD pump OR Jarvik heart OR Jarvik 2000 FlowMaker OR BerlinHeart OR Incor EXCOR® OR MicromedCardiovascular HeartAssist 5® OR ((mechanical circulatory) AND "support devices") : ti,ab,kw OR MSCD OR (ventricular assist device) : ti,ab,kw OR (ventricular assist devices) : ti,ab,kw	AND	Mesh descriptor ""Costs and Cost Analysis" OR Mesh descriptor "Economics" OR Mesh descriptor "Cost Allocation" OR Mesh descriptor "Cost-Benefit Analysis" OR Mesh descriptor "Cost of Illness" OR Mesh descriptor "Cost Control" OR Mesh descriptor "Cost Savings" OR Mesh descriptor "Health Care Costs" OR Mesh descriptor "Direct Service Costs" OR Mesh descriptor "Hospital Costs" OR Mesh descriptor "Efficiency, Organizational/economics Cost-effectiveness OR Cost-utility OR Cost – effectiveness OR Cost – utility OR "resource used" OR "Cost effectiveness analysis" OR CMA OR "cost effectiveness"OR CEA OR "cost utility" OR CUA "Cost utility analysis " OR "Cost benefit analysis" OR "Cost consequences analysis " OR " Cost minimization analysis" OR (economic AND (evaluation OR analysis OR aspect OR assessment)) OR "Budget Impact Analysis"

APPENDIX 5. Economic studies included

Full economic evaluations (n=5)

Long EF, Swain GW, Mangi AA. Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure. Circ Heart Fail. 2014;7(3):470-8.

Moreno SG, Novielli N, Cooper NJ. Cost-effectiveness of the implantable HeartMate II left ventricular assist device for patients awaiting heart transplantation. J Heart Lung Transplant. 2012;31(5):450-8.

Neyt M, Van den Bruel A, Smit Y, De Jonge N, Erasmus M, Van Dijk D, et al. Cost-effectiveness of continuous-flow left ventricular assist devices. Int J Technol Assess Health Care. 2013;29(3):254-60.

Rogers JG, Bostic RR, Tong KB, Adamson R, Russo M, Slaughter MS. Cost-effectiveness analysis of continuous-flow left ventricular assist devices as destination therapy. Circ Heart Fail. 2012;5(1):10-6.

Sutcliffe P, Connock M, Pulikottil-Jacob R, Kandala NB, Suri G, Gurung T, et al. Clinical effectiveness and cost-effectiveness of second- and third-generation left ventricular assist devices as either bridge to transplant or alternative to transplant for adults eligible for heart transplantation: systematic review and cost-effectiveness model. Health Technol Assess. 2013;17(53):1-499, v-vi.

Cost analyses (n=1)

Mishra V, Fiane AE, Geiran O, Sorensen G, Khushi I, Hagen TP. Hospital costs fell as numbers of LVADs were increasing: experiences from Oslo University Hospital. J Cardiothorac Surg. 2012;7:76.

APPENDIX 6. Economic studies excluded

List of excluded studies with reasons for exclusion

Not available (n=1):

Hutchinson J, Scott DA, Clegg AJ, Loveman E, Royle P, Bryant J, et al. Cost-effectiveness of left ventricular-assist devices in end-stage heart failure. Expert Rev Cardiovasc Ther. 2008;6(2):175-85.

No technology (n=10):

Bieniarz MC, Delgado R. The financial burden of destination left ventricular assist device therapy: who and when? Curr Cardiol Rep. 2007;9(3):194-9.

Borisenko, O. , G. Wylie, J. Payne, S. Bjessmo, J. Smith, R. Firmin and N. Yonan. "The Cost Impact of Short-Term Ventricular Assist Devices and Extracorporeal Life Support Systems Therapies on the National Health Service in the Uk." Interact Cardiovasc Thorac Surg 19, no. 1 (2014): 41-8.

Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, et al. The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. Health Technol Assess. 2005;9(45):1-132, iii-iv.

Clegg AJ, Scott DA, Loveman E, Colquitt JL, Royle P, Bryant J. Clinical and cost-effectiveness of left ventricular assist devices as a bridge to heart transplantation for people with end-stage heart failure: a systematic review and economic evaluation. Eur Heart J. 2006;27(24):2929-38.

Clegg AJ, Scott DA, Loveman E, Colquitt J, Royle P, Bryant J. Clinical and cost-effectiveness of left ventricular assist devices as destination therapy for people with end-stage heart failure: a systematic review and economic evaluation. Int J Technol Assess Health Care. 2007;23(2):261-8.

Girling, A. J. , G. Freeman, J. P. Gordon, P. Poole-Wilson, D. A. Scott and R. J. Lilford. "Modeling Payback from Research into the Efficacy of Left-Ventricular Assist Devices as Destination Therapy." Int J Technol Assess Health Care 23, no. 2 (2007): 269-77.

P.L. D, M.S. R, B. T, E. B, Y. N, M.C. O. Heart transplant and left ventricular assist device costs. J Heart Lung Transplant. 2005;24(2):200-4.

Sharples LD, Dyer M, Cafferty F, Demiris N, Freeman C, Banner NR, et al. Cost-effectiveness of ventricular assist device use in the United Kingdom: results from the evaluation of ventricular assist device programme in the UK (EVAD-UK). J Heart Lung Transplant. 2006;25(11):1336-43.

SAMSON cost-effectiveness of left-ventricular assist devices as destination therapy for end-stage heart failure. Technol Eval Cent Assess Program Exec Summ. 2004;19(2):1.

"Special Report: Left Ventricular Assist Devices as Destination Therapy for End-Stage Heart Failure--Cost-Effectiveness Analysis." TEC Bull (Online) 20, no. 3 (2003): 33-4.

No comparator (n=3):

Alba AC, Alba LF, Delgado DH, Rao V, Ross HJ, Goeree R. Cost-effectiveness of ventricular assist device therapy as a bridge to transplantation compared with nonbridged cardiac recipients. Circulation. 2013;127(24):2424-35.

Pulikottil-Jacob R, Suri G, Connock M, Kandala NB, Sutcliffe P, Maheswaran H, et al. Comparative cost-effectiveness of the HeartWare versus HeartMate II left ventricular assist devices used in the United Kingdom National Health Service bridge-to-transplant program for patients with heart failure. J Heart Lung Transplant. 2014;33(4):350-8.

Slaughter, M.S. , R. Bostic, K. Tong, M. Russo and J. G. Rogers. "Temporal Changes in Hospital Costs for Left Ventricular Assist Device Implantation." J Card Surg 26, no. 5 (2011): 535-41.

No study design (n=6):

Boothroyd LJ, Lambert LJ, Sas G, Guertin JR, Ducharme A, Charbonneau E, et al. Should eligibility for heart transplantation be a requirement for left ventricular assist device use? Recommendations based on a systematic review. Can J Cardiol. 2013;29(12):1712-20.

Dembitsky WP. REMATCH and beyond: the cost of treating heart failure using an implantable left ventricular assist device. Semin Cardiothorac Vasc Anesth. 2006;10(3):253-5.

Miller LW, Guglin M, Rogers J. Cost of ventricular assist devices: can we afford the progress? Circulation. 2013;127(6):743-8.

Moreno SG. Letter by moreno regarding article, "cost-effectiveness analysis of continuous flow left ventricular assist devices as destination therapy". Circ Heart Fail. 2012;5(2):e50.

Morgan JA, Oz MC. Cost-effectiveness of left ventricular assist devices. Expert Rev Pharmacoecon Outcomes Res. 2003;3(4):427-32.

Neyt M, Van den Bruel A, Smit Y, De Jonge N, Vlayen J. The cost-utility of left ventricular assist devices for end-stage heart failure patients ineligible for cardiac transplantation: a systematic review and critical appraisal of economic evaluations. Ann Cardiothorac Surg. 2014;3(5):439-49.

No detailed economic data (n=4):

Hernandez, A. F. , A. M. Shea, C. A. Milano, J. G. Rogers, B. G. Hammill, C. M. O'Connor, K. A. Schulman, E. D. Peterson and L. H. Curtis. "Long-Term Outcomes and Costs of Ventricular Assist Devices among Medicare Beneficiaries." JAMA 300, no. 20 (2008): 2398-406.

Miller LW, Nelson KE, Bostic RR, Tong K, Slaughter MS, Long JW. Hospital costs for left ventricular assist devices for destination therapy: lower costs for implantation in the post-REMATCH era. J Heart Lung Transplant. 2006;25(7):778-84.

Mulloy DP, Bhamidipati CM, Stone ML, Ailawadi G, Kron IL, Kern JA. Orthotopic heart transplant versus left ventricular assist device: a national comparison of cost and survival. J Thorac Cardiovasc Surg. 2013;145(2):566-73; discussion 73-4.

N.G. S, K.J. H, B. L, M.M. M, R.C. S, L. T, et al. Unplanned hospital readmissions after heartmate II implantation. Frequency, risk factors, and impact on resource use and survival. JACC Heart Fail. 2013;1(1):31-9.

No preliminary results (n=1)

Mishra V, Geiran O, Fiane AE, Sorensen G, Andresen S, Olsen EK, et al. Costs and reimbursement gaps after implementation of third-generation left ventricular assist devices. J Heart Lung Transplant. 2010;29(1):72-8.

No referring to more complete report (n=1)

Clarke A, Pulikottil-Jacob R, Connock M, Suri G, Kandala NB, Maheswaran H, et al. Cost-effectiveness of left ventricular assist devices (LVADs) for patients with advanced heart failure: analysis of the British NHS bridge to transplant (BTT) program. Int J Cardiol. 2014;171(3):338-45.

Appendix 7.Manufacturer Questionnaire

Agenas is carrying out afull HTA report on "LVAD (Left Ventricular Assist Device) in addition to maximal medical therapy (MMT) in end stage heart failure". You are receiving this request to integrate information and data relative to the LVAD (in patients with end stage heart failure who are not eligible or immediately eligible for cardiac transplant: bridge to transplantation or destination therapy) to be used in our report for the Italian Ministry of Health (MoH). This will be a public document, so we ask you not to release any confidential information. Please also be aware that the aim of the HTA activities is to conduct a factual assessment of the performance of this class of devices. We are interested in the factual accuracy of the document but the interpretation of those facts is our role. Thank you for your help. Your help will be acknowledged according to your wishes in the final report that will be published, after a public consultation phase, on the MoH and Agenas websites.

Manufacturer/Distributor: _____

Name of technology: _____

Contact Person: _____

Questions for the manufacturer/distributor

Health problem and current use of technology

1. Which group(s) of patients represents the target population for your LVAD?
2. Which other devices or therapies can be considered as the main comparators[5] of LVAD?
3. Are there specific ICD9-CM (ICD10-CM) codes that identify the use of the LVAD (and comparators) in the hospital discharge database?
4. Up to now, how many of your LVADs have been used in Italy? How many around the world?
5. Up to 2015, june 1th, how many Italian hospitals use your technology? (Please specify if private or public providers).

Description and technical characteristics of technology

6. What is the current phase of development of the model on the market?
7. How many versions/evolutions of the device have been launched to the last version?

[5] Comparator is the standard intervention against which the intervention under assessment is compared. The comparator may include no intervention or best supportive care.

8. [In case of two or more versions] Could you describe the differences between the generations of your device?
9. Could you describe the principle of action and the main characteristics of the different component of the LVAD?
10. What is/are the indication(s) of use of the technology?
11. What are the warnings, precautions, contraindications for the use of the technology?
12. What disposables and supplies are needed to use the LVAD?
13. Does the technology require specific equipment/tools? If yes, please provide descriptions and CND codes for all of them.
14. Are there similar devices/therapies/procedures that can be considered as "competitors" of your technology? (please specify device names and manufacturers)

Regulatory aspects

15. What is the risk classification the technology?
16. Has your device obtained the CE mark? If yes, When? (please report month and year)
17. Has your device been approved by the FDA?
    17.a If yes, when? (Please report month and year)
    17.b If not, please report details on the FDA approval status (if any).
18. When was your device launched in Italy? And which is the medical devices' repertory number of the Italian Ministry of Health?
19. What is the reimbursement status of the technology in Italy?
20. Are you aware of any difference in the reimbursement of the technology across the Italian Regions? If yes, please provide specific regional reimbursement status.
21. Are you aware of any difference in the reimbursement of the technology across Europe? If yes, please provide specific national reimbursement status.
22. Does the technology require further specific regulations (eg. environmental safety) ?

Clinical Effectiveness and Safety

23. Are there comparative clinical studies (on humans) published/ongoing aimed to compare your device versus other treatments? (if yes, please report full references)
24. Can you specify the ID number(s) of the ongoing trial(s) (e.g. CTRN)?
25. Are there non-comparative clinical studies (on humans) published/ongoing aimed to report on effectiveness and safety of your device? (if yes, please report full references)
26. Is there any register for data collection and patient's follow-up? If yes, who runs it? (please specify web-link and/or key-person name and e-mail address)

Costs and economic evaluation

27. What is the list price of your technology? (please, indicate the price, VAT excluded, for all the equipment needed for the implantation procedure)
28. Please fill the table below with all the relevant items for a single procedure:

Item	Number of units	Price per unit (VAT excluded)

29. What is the real cost of your technology (VAT excluded) in the Italian market?
30. Are there economic evaluation studies published/ongoing reporting on your technology? (if yes, please provide full references).

Organisational aspects

31. Which professionals (nurses, doctors, and other professionals) use and manage the LVAD? Describe the staff involved for the implantation procedure in terms of skills and number of units as well as in the patient management after the implant?
32. Is there the need of training for the staff members?
    33.a If yes, who provides it?
    33.b How much does this training cost and who funds it?
33. Do you have any report about the learning curve of the procedure? (please provide full references).
34. How does the procedure using your device differ from the standard of care in terms of need of additional/special equipment/tool, complexity, dedicated human resources?