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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Left Ventricular Assist Device as Permanent Support in Patients with End-Stage Heart Failure

[LVAD som permanent behandling vid terminal hjärtsvikt]

Running title: LVAD in heart failure

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Are there any conflicts of interest for the proposer or any of the participants in the HTA group?

No

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The last literature search was updated in February 2013

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.

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Summary of the Health Technology Assessment

Method and patient group

Subjects with severe heart failure are most commonly treated with pharmacological therapy. In selected cases an implantable automatic defibrillator and/or resynchronisation therapy may be of additional benefit. However, in some patients with end-stage heart failure these therapies are insufficient. Mechanical circulatory support (MCS) can be an alternative in these subjects. The goal of MCS is to support the circulation until transplantation (bridge to transplantation), or until the heart recovers (bridge to recovery), or as a permanent treatment option. The third alternative, which is called destination therapy (DT), is a possible option for selected patients who are not eligible for heart transplantation due to advanced age or comorbidities.

Question at issue:

Does mechanical circulatory support with left ventricular assist devices (LVAD) reduce morbidity, improve quality of life, and prolong survival in patients with end-stage heart failure not eligible for heart transplantation in comparison to optimal medical treatment?

Patients, Intervention, Comparison, Outcome (PICO1 and PICO2)

P = Patients with end-stage left ventricular heart failure despite optimal medical treatment
I_1 = Left ventricular assist device with pulsatile flow (PF-LVAD)
C_1= Optimal medical treatment (OMT)

I_2 = Left ventricular assist device with continuous flow (CF-LVAD)
C_2= Left ventricular assist device with pulsatile flow (PF-LVAD)

O = Survival, quality of life (QoL), functional capacity (NYHA classification, 6 minute walk test, exercise test) and biomarkers of heart failure. Complications such as infections, haemorrhages, thromboembolic events, neuropsychological functions

Studied risks and benefits for patients of the new health technology

The systematic literature search identified one randomised controlled trial (RCT) and one non-randomised controlled study that have evaluated the effects of PF-LVAD in comparison to OMT, and one RCT and two non-randomised controlled studies that have evaluated the effects of PF-LVAD in comparison to CF-LVAD in patients with terminal heart failure.

Pulsatile flow LVAD in comparison to optimal medical management (PICO1)

Conclusions: Pulsatile LVAD as destination therapy probably increases survival (GRADE ⊕⊕⊕O), and may improve the functional capacity (GRADE ⊕⊕OO) in patients with terminal left ventricular heart failure in comparison with OMT. It is uncertain whether the treatment has any effect on quality of life (GRADE ⊕OOO)

Continuous flow LVAD in comparison to pulsatile flow LVAD (PICO2)

Conclusions: Continuous flow LVAD as destination therapy probably increases survival in patients with terminal left ventricular heart failure in comparison with PF-LVAD (GRADE ⊕⊕⊕O). While both PF and CF flow devices have been shown to improve quality of life and functional outcome compared to baseline, there is only low quality evidence that CF may improve quality of life more than PF (GRADE ⊕⊕OO), and it is uncertain whether the effect on functional capacity differs between CF and PF. (GRADE ⊕OOO).

Complications
Long-term MCS is hampered by several complications such as device malfunction, infections (20 – 60 %), bleeding (15 – 30 %), thromboembolic events (5 – 25 %) and right ventricular failure (10 – 40 %). The rate of adverse events has steadily declined over time with improved techniques.

Ethical aspects
Introduction of a DT program raises several ethical issues. The self-esteem and self-image of the individual patient probably vary between subjects, but may be affected in both positive and negative ways. The patient will still be dependent on assistance from family members and/or health care providers, and the physical integrity is affected. Without additional economic resources there is a substantial risk that DT will reallocate current resources from the needs of other patient categories.

Economical aspects
The present cost for the currently most used continuous flow device, the HeartMate II, is 750 000 SEK (about 82 000 €) with an additional 125 000 SEK (≈14 000 €) for necessary accessories. At Sahlgrenska University hospital eight patients had a HeartMate II implanted as MCS for 12 months or longer during 2010-2012. The average cost per patient for the first year was about 1.5 million SEK (about 160 000 €).

Concluding remark:
Treatment with LVAD as DT increases survival in patients with terminal heart failure. It is costly and hampered by several serious complications. During the last decade costs have come down and the rate of complications have started to decline.

Mekaniskt vänsterkammarstöd som permanent behandling vid terminal hjärtsvikt

Metod och målgrupp:
Avancerad hjärtsvikt behandlas huvudsakligen farmakologiskt. I utvalda fall kan en automatisk defibrillator eller så kallad resynkroneringsterapi sättas in i hjärtat. Hos en del patienter med uttalad hjärtsvikt är dessa behandlingar emellertid inte tillräckligt effektiva. Ett alternativ är då mekaniskt cirkulationsstöd (MCS). Målet med MCS är att ge cirkulatoriskt stöd i väntan på hjärttransplantation ("bridge to transplantation"), eller tills hjärtfunktionen återhämtar sig ("bridge to recovery"), eller som permanent stödjande behandling. Det sistnämnda benämns "destination therapy" (DT), och är en möjlig behandling hos utvalda patienter som på grund av ålder eller annan svår samtidig sjuklighet inte är kandidater för hjärt transplantation. Denna HTA-utredning omfattar denna sistnämnda patientgrupp.

Frågeställning:
Minskar vänsterkammarstöd med mekanisk cirkulatorisk terapi, "left ventricular assist devices (LVAD)" dödlighet och sjuklighet hos patienter med terminal hjärtsvikt, och förbättras deras livskvalitet jämfört med optimal medicinsk behandling?

PICO

P = Patienter med svår kronisk vänsterkammarsvikt, trots optimal medicinsk behandling

I_1 = Mekaniskt vänsterkammarstöd för permanent bruk med pump som ger pulsativt flöde (PF-LVAD)
C_1 = Optimal medicinsk handläggning

I_2 = Mekaniskt vänsterkammarstöd för permanent bruk med pump som ger kontinuerligt flöde (CF-LVAD)
C_2 =Mekaniskt vänsterkammarstöd för permanent bruk med pump som ger pulsativt flöde (PF-LVAD)

O = Överlevnad, livskvalitet, funktionsförmåga (NYHA, 6 MWT, arbetsprov) och andra markörer för hjärtsvikt, samt infektioner, blödningar, tromboembolism och neuropsykologiska funktioner

Kunskapsläge och evidensgradering:
Den systematiska litteratursökningen identifierade en randomiserad kontrollerad studie (RCT) och en icke-randomiserad kontrollerad studie som analyserat effekten av PF-LVAD jämfört med optimal medicinsk behandling, och en RCT och två icke-randomiserade kontrollerade studier som analyserat effekten av PF-LVAD jämfört med CF-LVAD hos patienter med terminal hjärtsvikt.

LVAD med pulsativt flöde jämfört med optimal medicinsk behandling (PICO1)
Slutsatser: I jämförelse med optimal medicinsk behandling förlänger LVAD med pulsativt flöde, som "destination therapy", överlevnaden hos patienter med terminal hjärtsvikt (GRADE ⊕⊕⊕O). Behandlingen kan förbättra patienternas funktionsförmåga (GRADE ⊕⊕OO), men det är osäkert om den har någon effekt på livskvalitet (GRADE ⊕OOO).

LVAD med kontinuerligt flöde jämfört med LVAD med pulsativt flöde (PICO2)
Slutsatser: I jämförelse med LVAD med pulsativt flöde förlänger LVAD med kontinuerligt flöde överlevnaden hos patienter med terminal hjärtsvikt (GRADE ⊕⊕⊕O). Såväl livskvalitet som funktionsförmåga förbättras troligen av båda behandlingarna men det vetenskapliga underlaget som stöd för att CF-LVAD och PF-LVAD skiljer sig åt i effekt är begränsat (GRADE ⊕⊕OO). Det är även osäkert om de har olika effekt på funktionsförmågan (GRADE ⊕OOO).

Komplikationer
Långtidsbehandling med MCS försvåras av flera olika komplikationer som pumpdysfunktion, infektioner (20 – 60 %), blödningar (15 – 30 %), tromboemboliska händelser (5 – 25 %) högerkammarsvikt (10 – 40 %). Parallellt med förbättrad teknik har frekvensen av olika bieffekter stadigt sjunkit under senare år.

Etiska aspekter:
Ett behandlingsprogram med MCS har ett antal etiska konsekvenser. Effekten på individens självkänsla och självbild varierar sannolikt mellan olika patienter och de kan påverkas såväl positivt som negativt. Patienten kommer inte vara helt obereoende av andra utan förblir till viss del beroende av hjälp från familjemedlemmar och hälso- och sjukvårdspersonal. Den fysiska integriteten påverkas. Om inte nya ekonomiska resurser tillförs hälso- och sjukvården är risken stor att ett program med permanent MCS till patienter med terminal hjärtsvikt kommer att ta resurser för andra patientkategorier.

Ekonomiska aspekter:
Kostnaden för den idag mest använda CF-LVAD, HeartMate II, är 750 000 SEK. Ytterligare 125 000 SEK tillkommer för nödvändiga tillbehör. På Sahlgrenska Universitetssjukhuset har åtta patienter fått en HeartMate II inplanterad som MCS för längre än 12 månader under åren 2010-2012. Den genomsnittliga behandlingskostnaden per patient för det första året var cirka 1,5 miljoner SEK.

Slutsatser:
Mekaniskt vänsterkammarstöd som permanent behandling kan förlänga överlevnaden hos patienter med terminal hjärtsvikt och minska 1-årsdödligheten med cirka 30 % . Behandlingen är förenad med hög kostnad och försvåras av flera allvarliga komplikationer. Under senare år har kostnaderna minskat och även komplikationsfrekvensen har sjunkit.

Abbreviations

ACE	Angiotensin converting enzyme
BIVAD	Biventricular assist device
BTT	Bridge to transplantation
CF	Continuous flow
CPET	Cardiopulmonary exercise test
CRT	Resynchronization therapy
DT	Destination therapy
ICD	Implantable cardioverter defibrillator
LVAD	Left ventricular assisted device
MCS	Mechanical circulatory support
NYHA	New York Heart Association
OMT	Optimal medical treatment
PF	Pulsatile flow
QALY	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
RVAD	Right ventricular assist device
RVF	Right ventricular failure
VAD	Ventricular assist device

The Patient Category and the Present Treatment

Heart failure and degree of severity

Heart failure is a clinical syndrome attributable to disturbances in cardiac function. The dysfunctions may have various underlying causes. The heart failure syndrome is multifaceted and not readily defined. Below are three definitions that describe heart failure from different viewpoints.

1. Acute and hemodynamic viewpoint
   - a pathological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues, or to do so only from an elevated filling pressure. (Braunwald E. 1997)
2. Chronic and neurohumoral viewpoint
   - a clinical syndrome characterized by abnormalities of left ventricular function and neurohormonal regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity. (Packer M. 1992)
3. Clinical and diagnostic viewpoint
   - a clinical syndrome in which patients have the following features: symptoms typical of heart failure *and* signs typical of heart failure *and* objective signs of a structural or functional abnormality of the heart at rest. (European Society of Cardiology 1995)

The syndrome is characterized by inability of the heart to maintain adequate blood flow and/or normal filling pressures during physical activity or in later stages also at rest. A number of neurohumoral compensatory mechanisms are activated in order to maintain the circulation. Over time they have a deleterious effect on the heart with further deterioration of cardiac function. A vicious cycle arises. If untreated this leads to a continuous decline of cardiac function and progressive worsening of the symptoms. Clinical symptoms consist mainly of fatigue, breathlessness and fluid retention. This frequently leads to hospitalisation. Quality of life is impaired and mortality is high.

During work up of a heart failure patient, it is important to evaluate the underlying cause of cardiac failure, the degree of cardiac dysfunction and the functional capacity of the patient. Pharmacologic treatment is aimed at reducing the deleterious effects of neurohumoral activation and to alleviate fluid retention. In selected patients a pacemaker system may improve left ventricular dyssynchrony and an implantable defibrillator can prevent sudden cardiac death. In terminal heart failure, mechanical circulatory assist devices or heart transplantation can be an alternative to palliative care.

Heart failure is a serious condition with an increased

- risk of premature death
- risk of permanent illness or damage, or reduced quality of life
- risk of disability and impaired health-related quality of life

The prevalence and incidence of heart failure

In a recently published report the prevalence of chronic heart failure in Sweden was estimated to 2 % (Zarinkoub R et al. 2013). The mean age of heart failure patients was 77 years, and more than 90 % of the patients were 60 years or older. The estimated incidence rate of chronic heart failure was 3.8/1000. The 5-year survival rate from first diagnosis was 48 %, which is considerably lower than in the general Swedish population matched for age and sex (95%).

In other community-based cohorts the annual survival rate in patients diagnosed with mild heart failure (NYHA I-II) has been shown to be around 95 %, whereas the 1-year survival rate for those diagnosed with severe heart failure (NYHA IV) has been reported to below 50 %.

Present treatment of heart failure

The goal of treatment is to relieve symptoms, optimize cardiac function and increase longevity. This can be achieved in most cases with the currently available treatment alternatives. They include different pharmacological, electric, mechanical and surgical options. On the other hand, it is also important to identify patients in the terminal phase of the disease, who are not suitable for advanced treatment with devices, mechanical pumps or heart transplantation. These patients should receive supportive and palliative care to provide relief from symptoms and other distress associated with end-stage heart failure.

Pharmacological intervention is the cornerstone of heart failure treatment. It is well documented that neurohumoral blockade of the sympathetic nervous system and the renin-angotensin-aldosteron-system reduce symptoms, improve cardiac function and increase survival. Four different pharmaceutical groups are currently recommended for treatment of heart failure; beta blockers, ACE-inhibitors, angiotensin II receptor blockers, and mineralcorticoid receptor antagonists. Diuretics are frequently used to control fluid retention. Other drugs that sometimes are used are ivabradin (sinus node inhibitor), digoxin (inotropic agent), hydralazine and isosorbiddinitrate (vasodilators), and anticoagulant agents (thromboembolic prophylaxis).

About one third of all patients with heart failure die suddenly, mainly due to a ventricular tachyarrhythmia. The implantation of a cardioverter defibrillator (ICD) reduces mortality in patients with moderate to severe systolic heart failure. One third of patients with heart failure has an intraventricular conduction disturbance that can cause left ventricular dyssynchrony with less efficient ventricular emptying and, often, mitral regurgitation. Cardiac resynchronization therapy (CRT) can improve cardiac function in these patients, relieve symptoms, improve functional capacity, and improve survival. Currently, patients who fulfil the criteria for CRT treatment most often also receive an ICD.

Also surgical interventions may be indicated for specific underlying or contributing causes of heart failure. These include revascularization in patients with ischemic heart disease, valvular surgery in patients with valvular disease, and left ventricular reconstruction in patients with extensive scarring and remodelling of the left ventricle after myocardial infarction. For a small minority of heart failure patients heart transplantation may be indicated. The indication for heart transplantation is terminal heart failure with severe symptoms, poor prognosis, and no remaining treatment alternatives. However, due to organ shortage this treatment is only available to a limited number of patients (approximately 50 annually in Sweden).

Contraindications to a cardiac transplant are high pulmonary vascular resistance, active infection, widespread atherosclerotic disease, drug abuse, malignant disease, recent thromboembolism, significant renal or liver disease, or other serious non-reversible co-morbidies. At Sahlgrenska University Hospital 20-30 heart transplantations are performed each year including approximately 5-7 recepients from the Region Västra Götaland.

Selected patients with progressive heart failure in whom pharmacological and/or resynchronisation therapy are insufficient can be treated with mechanical circulatory support (MCS). The goal of MCS is to support the circulation until transplantation (bridge to transplantation) or until the heart recovers (bridge to recovery), or to offer a permanent treatment option, which has been called destination therapy (DT). Presently, DT is not available as a treatment alternative in routine clinical practice in Region Västra Götaland, Sweden. In countries such as USA and Germany the number of patients who receive MCS as DT has now exceeded that of patients treated with heart transplantation.

Numbers of patients per year who are candidates for LVAD as destination therapy
Potential candidates for DT are patients with end-stage heart failure who are not considered suitable for heart transplantation due to advanced age and/or severe co-morbidities.

Examples of customary criteria for identification of end-stage heart failure are the following:

- Left ventricular ejection fraction ≤ 35%
- Max VO_2 ≤ 14 ml/kg/min on cardiopulmonary exercise test (CPET)
- 6 minute walking distance ≤ 300 m
- More than one hospitalisation during 6 months
- Intolerance of ACE-inhibitors and/or beta-blockers
- Low systolic blood pressure (< 90 mmHg)
- Inotrope dependence in-hospital and difficult to wean
- Worsening renal and/or liver function
- Worsening right ventricular function.

Apart from advanced age, there are several co-morbidities that render heart failure patients ineligible for heart transplantation, but not for treatment with destination therapy: Examples of such co-morbidities are: BMI ≥ 30 kg/m^2, increased pulmonary vascular resistance, cancer treatment within 5 years, and reduced pulmonary, renal and/or liver function. However, only a small fraction of all patients with end-stage heart failure should be considered candidates for DT. For example, it is vital that potential DT candidates are emotionally stable and able to comply with MCS treatment. Absolute contraindications for MCS include active infection, widespread atherosclerotic disease, terminal disease other than heart failure, dialysis, severe liver cirrhosis, alcohol or drug abuse, and untreated psychiatric disease.

Thus, identification of potential candidates for DT is a highly selective process. It is estimated that around 5-10 patients would fulfil the criteria for DT each year in Region Västra Götaland.

The normal pathway of patients with terminal heart failure through the health care system
Patients who are considered candidates for heart transplantation undergo a thorough in-hospital work-up before they are discussed at a multidisciplinary board. The board consists of cardiologists, thoracic surgeons, thoracic anaesthesiologists, heart failure nurses and patient coordinators. The work-up includes extensive laboratory investigations and a thorough investigation of cardiac function with echocardiography and cardiac catheterisation. Further functional capacity is evaluated with CPET and/or 6-minute walking test. Renal function is assessed by glomerular filtration rate and pulmonary function is estimated by spirometry. An odontologist evaluates the dental status.

The patients who are accepted for transplantation ofte receive MCS as bridge to transplantation. Patients that are declined heart transplantation due to advanced age or comorbidities continue to receive conventional heart failure treatment, often combined with supportive and/or palliative care.

The work-up and decision process for DT is very similar to that used for heart transplantation.

The New Health Technology – Left Ventricular Assisted Device

Description of left ventricular assisted device

A ventricular assist device (VAD) is a mechanical circulatory device that is used to partially, or completely, replace the function of a failing heart. It takes blood from a ventricle of the heart and pumps it to the circulation, and thereby secures perfusion of vital organs. A VAD can support the left ventricle (LVAD), the right ventricle (RVAD), or both ventricles (BIVAD).

A VAD consists of a small pump, a tube that carries blood from a heart ventricle into the pump, and another tube that carries the blood from the pump to either the pulmonary artery (RVAD) or the aorta (LVAD). It also has a driveline that connects the pump to a power source through a control unit. The figures illustrate a LVAD (Courtesy of Thoratec corporation).

VADs can be divided into two main categories. Firstly, pulsatile flow (PF) pumps that mimic the natural pulsing action of the heart (first generation VADs), and secondly, continuous flow (CF) devices that generate continuous blood flow with either a centrifugal or an axial pump (second generation VADs). Patients treated with a VAD require life-long anticoagulation therapy in order to prevent thrombus formation and thromboembolic complications.

The group's understanding of left ventricular assist devices as destination therapy in patients with terminal heart failure

The use of LVADs for DT has steadily increased, especially in countries such as Germany, France, Belgium, Switzerland, Austria, Canada and USA. In 2010 there were 79 destination-therapy centres in USA certified to perform implantation of LVADs. According to the INTERMACS registry (only including US patients) approximately 1000 patients received LVAD as DT-therapy in 2012, and another 800 patients received LVAD as bridge-to-transplantation (BTT).

Some patients that initially have been regarded as excellent BTT candidates will eventually not become eligible for heart transplantation due to progression of co-morbidities or new complications. On the other hand, some patients being identified, as DT-candidates will after LVAD implantations improve in such a way that they become suitable for a cardiac transplantation.

In 2012 approximately 700 patients had an LVAD implanted in Germany, and only 300 heart transplantations were performed. This means that most patients with terminal heart failure receive a LVAD initially, and later it is decided whether they should be listed for transplantation or remain on DT.

There is no Swedish VAD registry, but there is some information available on DT in Sweden from a company registry (Vingmed AB, the sales representative for Thoratec and the Heart Mate II). In total, 25 patients have received a LVAD (Heart Mate II) for DT in Sweden between 2005 and 2013 (survival range 2 - 2216 days, mean age 63 years, 22 males, 18 patients had ischemic cardiomyopathy). Among these patients, six (24 %) died within 90 days. The remaining 19 patients have survived for a mean of 815 days (with 9 patients still alive). Six of the patients (24 %) patients eventually underwent heart transplantation, again underlining that DT patients on LVAD may improve to such an extent that they become suitable candidates for transplantation. It seems necessary to have a DT program in order to give all patients a chance to become transplanted, even if the majority will remain on LVAD for the rest of their lives. Thus, DT-therapy as an entity and definition is slowly becoming obsolete. If permanent LVAD treatment is not available, patients with transplant precluding comorbidities that might resolve during mechanical support will not get an opportunity for transplantation.

During the last decade, the LVAD technology has progressed to become standard therapy in some medical centres. It is important that all centres that provide DT use best-practice guidelines to maintain outcomes that are comparable to those of existing centres of excellence.

The ethical concerns raised by DT will require extensive information to patients and their families, and also a detailed DT program that will meet the needs of patients and other family members. Examples of prerequisite conditions before introducing a program with destination therapy include:

1. Participation of a multidisciplinary care team, including palliative care specialists
2. Adopting a concise plan of care for anticipated device-related complications
3. Planning for anticipated end-of-life care and timing of device deactivation

The Central Question at Issue

Does mechanical circulatory support with left ventricular assist devices (LVAD) reduce morbidity, improve quality of life, and prolong survival in patients with end-stage heart failure not eligible for heart transplantation, in comparison to optimal medical treatment?

PICO

P= Patients, I= Intervention, C= Comparison, O=Outcome

PICO 1

P = Patients with end-stage left ventricular heart failure despite optimal medical treatment
I = Left ventricular assist device with pulsatile flow (PF-LVAD)
C = Optimal medical treatment (OMT)
O = Survival, quality of life (QoL), functional capacity (NYHA classification, 6 minute walk test, exercise test) and biomarkers of heart failure. Complications such as infections, haemorrhages, thromboembolic events and neuropsychological functions

PICO 2

P = Patients with terminal left ventricular heart failure despite optimal medical treatment
I = Left ventricular assist device with continuous flow (CF-LVAD)
C = Left ventricular assist device with pulsatile flow (PF-LVAD)
O = Survival, quality of life, functional capacity (NYHA classification, 6 minute walk test, exercise test) and biomarkers of heart failure.
Complications such as infections, haemorrhages, thromboembolic events and neuropsychological functions

Review of the Quality of Evidence

Search strategy, study selection and references – appendix 1
During February 2013 two librarians (TS, AL) performed systematic searches in Medline, PubMed, Embase, the Cochrane Library and a number of HTA-databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in appendix 1. The librarians conducted the literature searches, selected studies, and independently assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. After reading the articles in full text they made a second selection of articles. Any disagreements were resolved in consensus. The articles that remained were sent to the other participants in the HTA group, who read the articles independently of one another, and then decided in a consensus meeting which articles that should be included.

The literature search identified a total of 1231 articles (after removal of duplicates). The librarians then excluded 1095 articles after reading their abstracts. Another 136 articles were excluded by the librarians after reading the articles in full text. The remaining 56 articles were sent to the group, and 26 of them were finally included in the report. There were two randomised controlled trials (RCT, four publications) and three non-randomised controlled studies (three publications). Twelve were case series, five were systematic reviews, and two were health economy analyses. The controlled studies have been critically appraised using modified checklists from the Swedish Council on Health Technology Assessment regarding randomized controlled trials and cohort studies.

The present knowledge of left ventricular assist devices as destination therapy in patients with terminal heart failure

<u>PICO 1 – comparison of PF-LVAD with OMT</u>

Two HTA reports have concluded that LVAD with pulsatile flow improves survival and quality of life. One was published in 2005 by the NIHR Coordinating Centre for Health Technology Assessment (NCCHTA) in Southampton, UK (Clegg AJ et al. 2005), and the other in 2007 by the German Agency for HTA of German Institute of Medical Documentation and Information (Angermayr L et al. 2007).

The systematic literature search identified one randomised controlled trial (RCT) and one non-randomised controlled study that have studied the effects of PF-LVAD in comparison to OMT in patients with end-stage heart failure. In the RCT 61 patients were treated with OMT and 68 patients were treated with the pulsatile LVAD HeartMate I. The trial had no major problems concerning directness, study limitations or precision. The non-randomised study was smaller and the two study groups were not balanced with regard to socio-economic status. The patients in the control group consisted of patients who did not choose, or did not have the financial resources, to undergo LVAD implantation.

Mortality (Appendix 4a)
The RCT reported a significantly ($p< 0.01$) higher one-year survival in the PF-LVAD group (52 %) compared to the OMT group (23 %). The two-year survival rates were 23 %, and 8 % respectively (ns). In the non-randomised study, the corresponding 1-year survival rates were 27 % and 11% ($p>0.05$).
Conclusion: Pulsatile LVAD as destination therapy probably increases survival in comparison with OMT in patients with end-stage left ventricular heart failure.
Moderate quality of evidence (GRADE ⊕⊕⊕O).

Quality of life (Appendix 4b)
The RCT analysed quality of life after one year using three different questionnaires. Due to the high mortality rate QoL-scores were only available in six OMT and 23 PF-LVAD patients. The SF-36 Emotional role and Beck Depression Inventory scores were significantly better in the PF-LVAD group, but no difference between the study groups was seen in Minnesota Living with heart Failure scores.
Conclusion: It is uncertain whether PF-LVAD improves the quality of life in comparison with OMT in patients with end-stage left ventricular heart failure.
Very low quality of evidence (GRADE ⊕OOO)

Functional capacity (Appendix 4c)
Both the RCT and the non-randomised study analysed functional capacity after one-year follow-up. Due to the high mortality rate only six OMT-patients and 23 LVAD-patients were tested in the RCT. Both the ability to "walk one block without any physical limitation" and SF-36 physical function score were significantly better in the PF-LVAD group than in the OMT group. In the non-randomised study 11 of 18 patients in the OMT and 22 of 37 patients in the PF-LVAD group were evaluated by the NYHA classification. At the last assessment all patients in the OMT were still in NYHA class IV, while 85 % of the patients in the PF-LVAD group had improved to NYHA class I-II.
Conclusion: PF-LVAD may improve the functional capacity in comparison with OMT in patients with end-stage left ventricular heart failure.
Low quality of evidence (GRADE ⊕⊕OOO)

PICO 2 – comparison of CF-LVAD with PF-LVAD

Two published reviews have assessed the effects of the newer continuous flow devices (CF-LVAD) in patients with end-stage heart failure. One is a systematic review from the Department of Veteran Affairs, US, published in 2011 (Rector TS et al. 2012). It concludes that one single study provides moderate evidence that the use of the HeartMate II LVAD increases patient survival, with fewer complications and fewer hospitalizations compared to the older pulsatile flow LVAD HeartMate I. The other review is from Quebec (INESS) published in 2012 (Sas G et al. 2012). It concludes that CF-LVAD can be considered a clinically effective therapeutic option compared to optimal medical treatment for appropriate patients in both BTT and DT patients.

The systematic literature search identified one RCT and two non-randomised controlled studies that have studied the effects of PF-LVAD in comparison to CF-LVAD in patients with end-stage heart failure. In the RCT the patients were randomised in a 2:1 ratio. Thus, 134 patients received a continuous flow HeartMate II and 66 patients received a pulsatile flow HeartMate I. The study had some

problems with directness and precision (see Appendix 7, SoF table). The two non-randomised trials had major problems, as most of the pulsatile LVADs were implanted some years before the continuous flow devices came in use. Thus, the patient study groups with PF-LVADs must be regarded as historical controls.

Mortality (Appendix 5a)
The RCT reported a one-year survival of 68 % in the CF-LVAD group and 55 % in the PF-LVAD group. The survival was significantly better ($p< 0.01$) in the CF-LVAD group after two years with a survival rate of 58 % in comparison to 24 % in the PF-LVAD group. Both the non-randomised studies reported significantly higher two-year survival rates in the patients who received a CF-LVAD.
Conclusion: Continuous flow LVAD as destination therapy probably increases survival in patients with end-stage heart failure in comparison with pulsatile flow LVAD.
Moderate quality of evidence (GRADE ⊕⊕⊕O).

Quality of life (Appendix 5b)
Only the RCT analysed the quality of life. This was done after one year and two years follow-up using two different questionnaires. However, the small numbers of patients at the two-year follow-up did not allow any meaningful analyses. QoL improved in both LVAD groups in comparison to baseline. According to Minnesota Living with Heart Failure questionnaire, QoL was significantly better in the CF-LVAD group compared to the PF-LVAD group after one year, whereas the difference in the Kansas City Cardiomyopathy questionnaire did not reach statistical significance ($p = 0.06$).
Conclusion: PF-LVAD may improve the quality of life in patients with end-stage left ventricular heart failure in comparison with PF-LVAD.
Low quality of evidence (GRADE ⊕⊕OO)

Functional capacity (Appendix 5c)
Only the RCT analysed functional capacity. As for the QoL analyses, only the data at 12-month follow-up allowed a meaningful comparison. Both study groups experienced early, and sustained, improvement of functional capacity. However, there was no significant difference between the two groups.
Conclusion: It is uncertain whether CF-LVAD and PF-LVAD differ in their effects on functional capacity.
Very low quality of evidence (GRADE ⊕OOO).

Complications (Appendix 6)
Long-term MCS is hampered by several complications such as device malfunction, infections, bleeding, thromboembolic events and right ventricular failure (RVF). The rate of adverse events has steadily declined with improved techniques (second generation LVAD vs first generation).

Infections are a significant problem. They often occur at the driveline exit site. The reported incidence is up to 40 % per year (events/patient/year). Sepsis is also common with reported incidence rates varying from 20 % to 60 % in different studies. Infections that involve the pump itself are uncommon, but are serious since long-term eradication is nearly impossible.

Bleeding events are common. Perioperative bleeding occurs, in particular in patients with previous cardiac operations and/or coagulopathy related to hepatic dysfunction. Re-exploration due to a post-operative bleeding has been reported to be required in 15 – 30 %. Bleeding complications during long-term follow-up are also frequent, in particular gastrointestinal bleeding, with incidence rates up to 50 % (events/patient/year).

Patients with LVADs may also suffer thromboembolic complications. The reported incidence of ischemic stroke varies between 5 - 25 %. Pump thrombus may occur, and sometimes necessitates pump replacement if aggressive anticoagulation or thrombolytic therapies are not successful.

It is essential that the right ventricular function is adequate for an LVAD to function normally. Right ventricular failure occurs in10 - 40 % of patients who receive LVAD as bridge-to-transplantation.. The incidence of RVF in adequately selected patients for DT is not known. Treatment includes optimization of the right ventricular function, management of pulmonary vasoconstriction, and in some cases temporary support with a right ventricular assist device.

Ongoing research?

A search in the ClinicalTrials database (www.clinicaltrials.gov) July 4, 2013, using the search terms (heart-assist device OR left ventricular assist device OR left ventricular assist system OR ventricular assist device OR VAD OR LVAD OR LVAS) AND (destination OR permanent OR non-transplant OR long-term OR ineligible OR "not eligible" OR "not candidate" OR non-candidate) identified 33 studies with regard to LVADs. Five studies were relevant for the present questions at issue.

Two studies will compare the CF-LVAD HeartMate II with optimal medical therapy. Both of them are being performed in the USA. One of them is an RCT (REVIVE-IT), and it is currently recruiting patients. The estimated completion date is December 2016. The other study one is a non-randomised study that is ongoing. Its estimated completion date is December 2015.

Another two RCTs are ongoing. They compare either the LVADs Jarvik 2000 with Heart Mate II (estimated completion date December 2016), or the HeartWear LVAD with “any other FDA approved LVAD” (estimated completion date May 2017). Both are being performed in the USA. The former is still recruiting patients whereas the other is not.
A fifth study is ongoing in Belgium. It is a non-randomised study that will compare the efficacy of HeartMate II with historical controls.

Which medical societies or health authorities recommend left ventricular assist devices as destination therapy in patients with terminal heart failure?

In the European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 DT it is recommended for highly selected patients, who have end-stage heart failure despite optimal pharmacological and device therapy, and who are not suitable for heart transplantation, but are expected to survive over one year with good functional status, to improve symptoms, and reduce the risk of heart failure hospitalization and of premature death (Eur Soc Cardiol. 2012)

The 2013 ACCF/ American Heart Association Guidelines for the Management of Heart Failure also recommended DT with durable MCS to prolong survival for carefully selected patients with stage D heart failure with reduced ejection fraction (ACCF/AHA 2013).

In the Swedish National Guidelines for Cardiovascular Diseases from 2008 it is concluded that DT may improve survival, functional capacity and quality of life in patients with advanced heart failure (NYHA IIIB-IV) that receive OMT and are not eligible for heart transplantation (Socialstyrelsen 2008). However, the ratio of cost to quality-adjusted life-year (QALY) was considered to be very high. In these guidelines, which are those available in Sweden today, DT is not recommended for routine use. Instead it is advocated that further results from on-going studies should be awaited.

Ethical Aspects

See Appendix 8

Organisation

When can left ventricular assist device for destination therapy be put into practice at the hospital?
Immediately.

Is left ventricular assist device for destination therapy used in other hospitals in Region Västra Götaland, Sweden?
No. At the present, DT is not available for patients with end-stage heart failure in Region Västra Götaland. In the Stockholm Region there is currently a treatment program with DT, and up until now a total of 15-20 patients have received this treatment (Dr LH Lund, Karolinska University Hospital, Stockholm, Sweden, personal communication October 2013).

Will there be any consequences of left ventricular assist device for destination therapy for the personnel?
Currently, mechanical circulatory support systems are frequently utilized as BTT, and the hospital personnel are already familiar with the treatment. Introduction of DT would lead to an increased number of patients with long-term follow-up.

Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Region Västra Götaland?
Yes. Initial, follow-up of the patients will take place at the outpatient clinic of the Department of Cardiology Sahlgrenska Hospital. Later on follow-up visits will also be necessary at the local hospitals. However, there will only be a few patients (less than 10) requiring follow-up during the first years after the initiation of a DT program.

Economy Aspects

Present costs of a continuous flow left ventricular assist device
The current cost for the CF-LVAD HeartMate II implant kit is 750,000 SEK (≈82,000 €), and for accessories 125,000 SEK (≈14 000 €).

During 2010-2012, 8 patients had an implanted HeartMate II as mechanical circulatory support for 12 months or longer. The average cost for the first year was about 1.5 million SEK (including the cost of the implant kit and accessories) ranging between 1.4-2.7 million SEK (≈153,000 – 295,000 €). The cost was related to the number of in-hospital days, especially the number of days in the intensive care unit. The average length of hospital stay was 50.5 days (range 29-95).

As a comparison, three patients with terminal heart failure (NYHA class III-IV) who have been followed for more than one year with OMT were identified. The costs for these patients between June 2011 to May 2012, i.e. one year, were 132,000 SEK (≈14,000 €) , 759,000 SEK (≈144,000 €) and 1,909,000 SEK (≈208,000 €), respectively. Also in these cases the yearly costs was directly related to the length of hospital stay (range: 17- 134 days).

In the calculations of the costs for CF-LVAD and OMT above, the costs of home care are not included (due to different management systems).

In 2010, the average cost for heart transplantation was approximately 1.25 million SEK (≈136,000 €). This includes only the surgical procedure and the postoperative hospital stay. The costs of follow-up and later hospitalisations are not included.

Expected costs of left ventricular assist device in patients with terminal heart failure
See 9a.

Total change of cost of left ventricular assist device in patients with terminal heart failure
The cost of 10 patients treated with LVAD (see 2d) during the first year is estimated to be about 15 million SEK. Assuming that the corresponding cost for a patient treated with OMT is 750,000 SEK, the change in cost will be an increase of 7.5 million SEK.

Since patients with LVAD are expected to live longer this will add further increments in the total costs during the following years. It is difficult to estimate this additional cost.

Can the use of left ventricular assist device in patients with terminal heart failure be adopted and used within the present clinic budget?
No.

Are there any available analyses of health economy? Cost advantages or disadvantages?
There is no Swedish cost-effectiveness analysis.

In the German HTA report (Angermayer 2007), which was based predominately on studies of the first generation LVADs, i.e. PF-LVADS, the conclusion was that “the incremental costs per quality-adjusted life years (QALYs) may be between 200 000 and 600 000 € for DT”. Similar

conclusions were made in a British expert review from 2008 that could identify four published cost-effectiveness studies (Hutchinson 2008). However, they also pointed out that the methodological quality in the majority of the studies was poor, as was their generalizability.

A Canadian HTA report published in 2012 concluded that the cost-effectiveness of Heart Mate II was "unfavourable" regardless of the initial indication (Sas 2012). However, the conclusions were based predominantly on experiences of HeartMate II and mostly as BTT. Since these patients relatively soon get a transplant, the real cost benefit of the LVAD is therefore underestimated when data are extrapolated to the DT indication.

There have been no studies that directly have compared CF-LVADS with OMT. Rogers et al. used data from the REMATCH trial and the Heart Mate II trial to indirectly estimate the cost-effectiveness of using the CF-LVAD Heart Mate II (Rogers 2012). Compared with medical management the CF-LVAD had higher 5-year costs ($360 407 versus $62 856) and QALYs (1.87 vs 0.37). The incremental cost-effectiveness ratio of the CF-LVAD was estimated to be $198 184 per QALY (this corresponds to about 1.2 million SEK/QALY).

Unanswered Questions

Important gaps in scientific knowledge

There are no published RCTs that have compared the outcomes of modern CF-LVADs with OMT with regard to survival, functional capacity, or quality of life. Such a trial would presently be of great interest, since pharmacological treatment, resynchronization therapy, and the overall management of heart failure have improved during the last decade (after the publication of the RCT that initially compared PF-LVAD with OMT). It is of interest to point out that such a trial is presently considered unethical in the USA.

Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?

Yes. We are interested in starting a prospective, randomized multicentre trial in Sweden evaluating the HeartMate II® LVAD versus OMT in patients with severe heart failure (NYHA IIIb-IV) that are not eligible for heart transplantation. In such a study we would aim to include 100-120 patients and randomize them to HM II or OMT in a 1:1 ratio. The primary outcome would be a composite endpoint of survival, freedom from debilitating stroke and improved functional capacity. Patient recruitment would be expected to take 18 months and each included patient would be followed for 18 months.

The Departments of Cardiology and Thoracic Surgery at all Swedish University Hospitals have shown interest in such a study and are willing to participate. A reference group with participants from all university hospitals has been engaged to work on a study protocol. The initial response from the LVAD industry (Thoratec) has been positive and negotiations with respect to specific terms regarding such a study are ongoing. The project will, however, need additional funding and applications for study grants are being prepared.

Appendix 1, Search strategy, study selection and references –
Question(s) at issue:

Does mechanical circulatory support with left ventricular assist devices (LVAD) reduce morbidity, improve quality of life, and prolong survival in patients with terminal heart failure, in comparison to optimal medical treatment?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

PICO 1
P = Patients with terminal left ventricular heart failure despite optimal medical treatment
I = Implantation of a left ventricular assist device with pulsatile flow (PF-LVAD)
C = Optimal medical treatment (OMT)
O = Survival, quality of life (QoL), functional capacity (NYHA classification, 6 minute walk test, exercise test) and biomarkers of heart failure. Complications such as infections, haemorrhages, thromboembolic events, neuropsychological functions

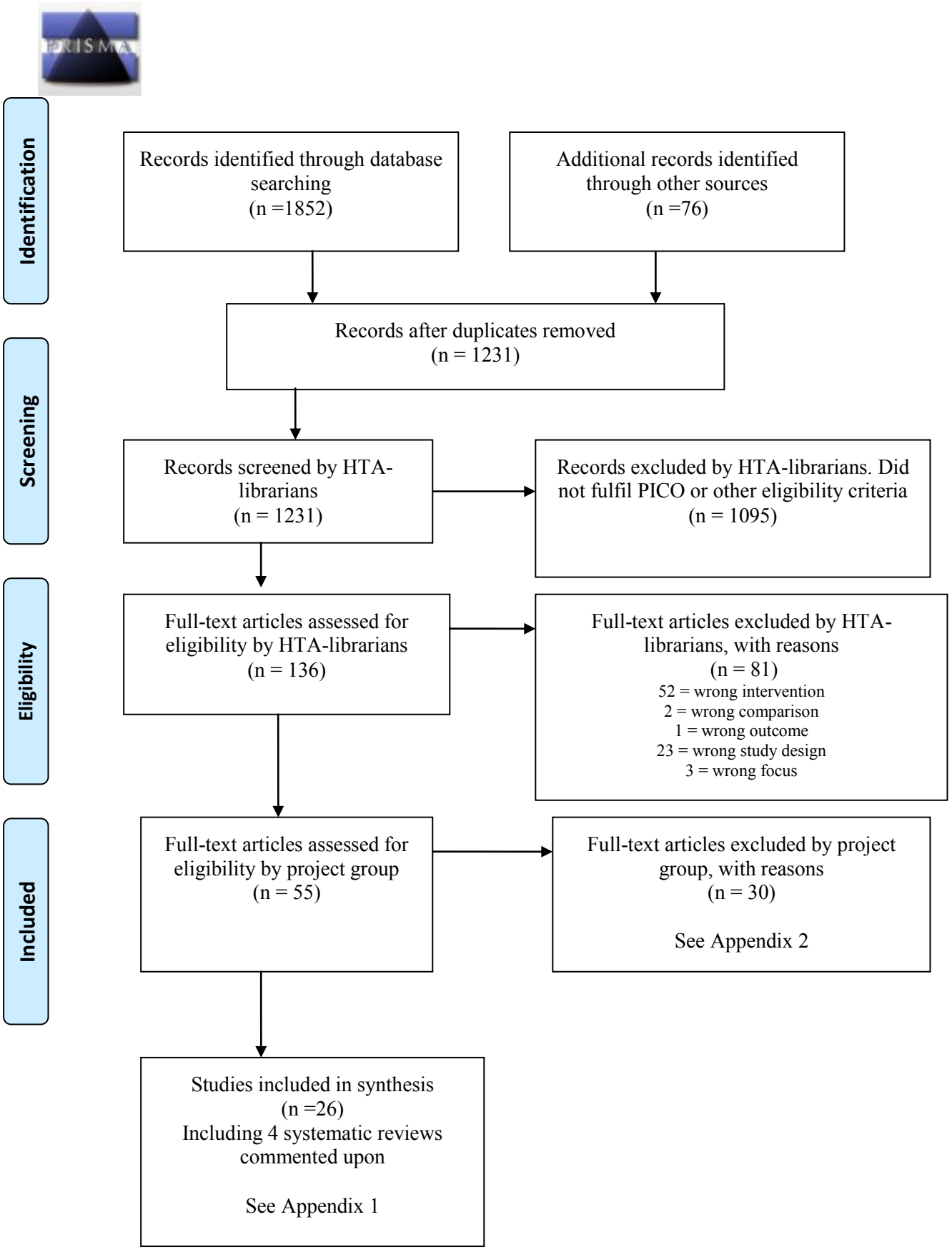
PICO 2
P = Patients with terminal left ventricular heart failure despite optimal medical treatment
I = Implantation of a left ventricular assist device with continous flow (CF-LVAD)
C = Implantation of a left ventricular assist device with pulsatile flow (PF-LVAD)
O = Survival, quality of life, functional capacity (NYHA classification, 6 minute walk test, exercise test) and biomarkers of heart failure. Complications such as infections, haemorrhages, thromboembolic events, neuropsychological functions

Eligibility criteria

Study design:
Randomized controlled trials
Non-randomized controlled trials
Case series if ≥ 30 patients
Systematic reviews

Language:
English, Swedish, Danish, Norwegian
Publication date:
2000-

Selection process – flow diagram



Search strategies

Database: Medline & Medline in process (OVID)
Date: 2013-02-26
No of results: 786

#	Searches	Results
1	exp Heart Failure/	79663
2	exp Ventricular Dysfunction, Left/	19737
3	heart failure.ab,kw,ti.	96006
4	(left adj3 ventric$4 adj3 dysfunction$1).ab,kw,ti.	13158
5	1 or 2 or 3 or 4	142421
6	exp Heart-Assist Devices/	7680
7	heart-assist device$1.ab,kw,ti.	106
8	left ventric$4 assist device$1.ab,kw,ti.	3102
9	left ventric$4 assist system$1.ab,kw,ti.	338
10	ventric$4 assist device$1.ab,kw,ti.	5143
11	(VAD or LVAD or LVAS).ab,kw,ti.	6602
12	6 or 7 or 8 or 9 or 10 or 11	12798
13	((destination adj3 therapy) or permanent or non-transplant$ or nontransplant$ or non transplant$ or longterm or long-term or long term).ab,kw,ti.	553532
14	((ineligible or "not eligible" or "not candidate$1" or non-candidate$1) adj4 transplant$).ab,kw,ti.	301
15	13 or 14	553741
16	5 and 12 and 15	1035
17	(animals not (animals and humans)).sh.	3673442
18	(comment or editorial or letter).pt.	1217538
19	16 not 17	1003
20	19 not 18	980
21	**limit 20 to (yr="2000 -Current" and (danish or english or norwegian or swedish))**	**786**

Database: PubMed
Date: 2013-02-26
No of results: 81

Search	Query	Items found
#32	**Search #30 AND #31**	**81**
#31	Search (pubmednotmedline[sb] OR in process[sb] OR publisher[sb])	1900735
#30	Search #28 NOT #29	836
#29	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3757147
#28	Search #26 NOT #27	859
#27	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1219963
#26	Search #9 AND #18 AND #22 Filters: Publication date from 2000/01/01; Danish; English; Norwegian; Swedish	882
#23	Search #9 AND #18 AND #22	1111
#22	Search #19 OR #21	562736
#21	Search (ineligible[tiab] OR "not eligible"[tiab] OR "not candidate*"[tiab] OR non-candidate*[tiab]) AND transplant*[tiab]	322

#19	Search (destination[tiab] AND therapy[tiab]) OR permanent[tiab] OR non-transplant*[tiab] OR nontransplant*[tiab] OR non transplant*[tiab] OR longterm[tiab] OR long-term[tiab] OR long term[tiab]	562481
#18	Search #11 OR #12 OR #13 OR #14 OR #16 OR #17	13338
#17	Search VAD[tiab] OR LVAD[tiab] OR LVAS[tiab]	6877
#16	Search ventricle* assist device*[tiab] OR ventricul* assist device*[tiab]	5736
#14	Search left ventric* assist system*[tiab]	415
#13	Search left ventric* assist device*[tiab]	3769
#12	Search heart-assist device*[tiab]	106
#11	Search "Heart-Assist Devices"[Mesh]	7669
#9	Search #2 OR #4 OR #5 OR #8	151926
#8	Search left[tiab] AND ventric*[tiab] AND dysfunction*[tiab]	25459
#5	Search heart failure[tiab]	97970
#4	Search "Ventricular Dysfunction, Left"[Mesh]	19681
#2	Search "Heart Failure"[Mesh]	79697

Database: EMBASE 1974 to 2013 February 25 (OVID SP)
Date: 2013-02-26
No of results: 860

#	Searches	Results
1	exp heart failure/	264726
2	exp heart left ventricle function/	30457
3	heart failure.ti,ab,kw.	143477
4	(left adj3 ventric$4 adj3 dysfunction$1).ti,ab,kw.	19064
5	1 or 2 or 3 or 4	317750
6	exp heart assist device/	8672
7	heart-assist device$1.ti,ab,kw.	488
8	left ventric$4 assist device$1.ti,ab,kw.	4638
9	left ventric$4 assist system$1.ti,ab,kw.	418
10	ventric$4 assist device$1.ti,ab,kw.	7786
11	(VAD or LVAD or LVAS).ti,ab,kw.	9971
12	6 or 7 or 8 or 9 or 10 or 11	17588
13	((destination adj3 therapy) or permanent or non-transplant$ or nontransplant$ or non transplant$ or longterm or long-term or long term).ti,ab,kw.	723616
14	((ineligible or "not eligible" or "not candidate$1" or non-candidate$1) adj4 transplant$).ti,ab,kw.	510
15	13 or 14	723984
16	5 and 12 and 15	1805
17	(animal not (animal and human)).sh.	1361790
18	16 not 17	1796
19	**limit 18 to (embase and (danish or english or norwegian or swedish) and yr="2000 -Current" and (article or conference paper or "review"))**	**860**

Database: The Cochrane Library
Date: 2013-02-26
No of results: 84
Cochrane reviews 0
Other reviews 6
Trials 53
Technology assessments 20
Economic evaluations 5

ID	Search	Hits
#1	MeSH descriptor: [Heart Failure] explode all trees	4914
#2	MeSH descriptor: [Ventricular Dysfunction, Left] explode all trees	1479
#3	heart next failure:ti,ab,kw (Word variations have been searched)	8961
#4	left near/3 ventric* near/3 dysfunction*:ti,ab,kw (Word variations have been searched)	2043
#5	#1 or #2 or #3 or #4	10047
#6	MeSH descriptor: [Heart-Assist Devices] explode all trees	146
#7	heart-assist next device*:ti,ab,kw (Word variations have been searched)	150
#8	left next ventric* next assist next device*:ti,ab,kw (Word variations have been searched)	61
#9	left next ventric* next assist next system*:ti,ab,kw (Word variations have been searched)	3
#10	ventric* next assist next device*:ti,ab,kw (Word variations have been searched)	84
#11	VAD or LVAD or LVAS:ti,ab,kw (Word variations have been searched)	213
#12	#6 or #7 or #8 or #9 or #10 or #11	344
#13	**#5 and #12**	**84**

Database: CRD
Date: 2013-02-26
No of results: 39

Line	Search	Hits
1	("heart failure")	1239
2	(left ventric* dysfunction*)	89
3	MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES	511
4	MeSH DESCRIPTOR Ventricular Dysfunction, Left EXPLODE ALL TREES	91
5	#1 OR #2 OR #3 OR #4	1282
6	MeSH DESCRIPTOR Heart-Assist Devices EXPLODE ALL TREES	48
7	(heart-assist device*) OR (left ventric* assist device*) OR (left ventric* assist system*) OR (ventric* assist device*) OR (VAD OR LVAD OR LVAS)	73
8	#6 OR #7	73
9	**#5 AND #8**	**39**

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited 2013-02-27
2 results

Reference lists
A comprehensive review of reference lists brought 76 new records

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Appendix 2 – Included studies with control groups– design and patient characteristics.
PF-LVAD = Pulsatile flow left ventricular device, CF-LVAD = Continuous flow left ventricular device, OMT =Optimal medical therapy.

Author, Year, Country	Study Design	Study Duration (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years (sd))	Men (%)	Outcome variables
Rose, 2001 USA	RCT	0 – 2.5	PF-LVAD OMT	68 61	66 (9) 68 (8)	78 82	1) Mortality 2) Functional capacity 3) Quality of life
Rogers, 2007 USA	Non-randomised controlled study	0 – 3.5	PF-LVAD OMT	37 18	60 (11) 58 (10)	92 78	1) Mortality 2) Functional capacity 3) Quality of life
Slaughter, 2010 USA	RCT	2	PF-LVAD CF-LVAD	66 134	63 (12) 62 (12)	92 81	1) Mortality 2) Functional capacity 3) Quality of life
Drews, 2010 Germany	Non-randomised controlled study	2	PF-LVAD CF-LVAD	64 110	64 (3) range 60 -73 67 (4) range 60 – 80	95 89	1) Mortality
Kirklin, 2012 USA	Non-randomised controlled study	0 – 5.5	PF-LVAD CF-LVAD	127 1 160	54.7 63.6	Not reported	1) Mortality

Appendix 3. Excluded articles - Left venticular assist device as destination therapy

Study (author, publication year)	Reason for exclusion
Adamson 2011	To few cases
Adzic 2013	No new information
Aggarwal 2013	Not included in PICO
Backes 2012	Mixed population
Barbone 2004	To few cases
Brush 2010	Not included in PICO
Cowger 2013	Wrong question
Coyle 2010	Not included in PICO, mixed population
Drakos 2010	Mixed population
Drews 2011	Mixed population
Girling 2007	Theoretic model of cost-effectiveness in LVAD patients
Hasin 2012	Unclear data
Holman 2009a	Not included in PICO, predictors
Holman 2009b	Substudy of another study
Kushnir 2012	Mixed population
Lietz 2009	Not included in PICO, analysis of risk factors
Lietz 2007	Not included in PICO, risk score
Long 2008	To few patients
Oz 2003	Presentation only of absolute costs of PF-LVADs. No health economy analysis.
Petrucci 2012	Not included in PICO
Raymond 2010	Question not included in PICO
Rogers 2010	Not included in PICO
Slaughter 2011a	Substudy of Slaughter 2009 (included)
Slaughter 2011b	Effect not included in PICO
Stevenson 2004	Not included in PICO, risk factor analysis
Struber 2008	Mixed population
Teuteberg 2012	Not included in PICO, risk score analysis
Topilsky 2011b	Not included in PICO, echocardiographic predictors
Westaby 2010	Unclear data
Vrotec 2009	Mixed population

Appendix 4. **LVAD pulsative flow in comparison with optimal medical management**
Outcome variables: a) Mortality b) Functional capacity c) Quality of life

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n= Follow-up	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
a) Mortality										
Rose, 2001	USA	RCT	I: 68 C: 61 FU: Not reported	I: 0 C: 2	<u>1-year survival</u> 52% p=0.002 <u>2-year survival</u> 23% NS	<u>1-year survival</u> 25% <u>2-year survival</u> 8%		?	+	+
Rogers, 2007	USA	Non-randomised controlled study	I: 37 C: 18 FU: 12 months	Not reported	<u>1-year survival</u> 27% p=0.02	<u>1-year survival</u> 11%	Patients in the control group chose not to undergo LVAD implantation, which resulted in socio-economical imbalance.	-	-	-

Appendix 4. **LVAD pulsative flow in comparison with optimal medical management**
Outcome variables: a) Mortality b) Functional capacity c) Quality of life

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n= Follow-up	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
b) Functional capacity										
Rose, 2001	USA	RCT	I: 68 C: 61	I: 0 C: 2	<u>Walking one block (not limited at all)</u> 16/23 p=0.04 <u>SF-36 (physical)</u> 46 (sd 19) p=0.01	<u>Walking one block (not limited at all)</u> 1/11 <u>SF-36 (physical)</u> 21 (sd 21)		?	+	+
Rogers, 2007	USA	Non-randomised controlled study	I: 37 C: 18	Not reported	<u>NYHA</u> 85% Class I-II	<u>NYHA</u> 0% Class I-II	No statistical inference test	-	-	-
c) Quality of life										
Rose, 2001	USA	RCT	I: 68 C: 61	I: 0 C: 2	<u>MLHF-score</u> 41 (sd 22) p=0.11	<u>MLHF-score</u> 58 (sd 21)	MLHF=Minnesota Living with Heart Failure questionnaire	?	+	+
Rogers, 2007	USA	Non-randomised controlled study	I: 37 C:18	Not reported	MLHF-score and SF-36 “improved”		Too few OMT patients for meaningful comparison.	-	-	-

Appendix 5. **LVAD continuous flow in comparison with pulsatile flow LVAD**
Outcome variables: a) Mortality b) Functional capacity c) Quality of life

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n= Follow-up	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
a) Mortality										
Slaughter, 2009	USA	RCT	I: 134 C: 66 FU: 2 years	I: 19 C: 32	<u>1-year survival</u> 68% <u>2-year survival</u> 58% p=0.008*	<u>1-year survival</u> 55% <u>2-year survival</u> 24%		?	+ (?)	?
Drews, 2010	Germany	Non-randomised controlled study	I: 110 C: 64 FU: 2 years	Not reported	1-year survival: 36% 2-year survival: 26% p=0.0017*	1-year survival: 15% 2-year survival: 12%		-	-	?
Kirklin, 2012	USA	Non-randomised controlled study	I: 1,160 C: 127	Not reported :	<u>1-year survival</u> 76% <u>2-year survival</u> 67% p<0.0001*	<u>1-year survival</u> 68% <u>2-year survival</u> 45%	Historical controls	-	?	+

Appendix 5. **LVAD continuous flow in comparison with pulsatile flow LVAD**
Outcome variables: a) Mortality b) Functional capacity c) Quality of life

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n= Follow-up	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
c) Functional capacity										
Slaughter, 2009	USA	RCT	I: 134 C: 66 FU: 1 year	I: 19 C: 32	<u>6 minutes walk test</u> n=61 318 meters (sd 164), NS <u>NYHA</u> 76% Class I-II NS	<u>6 minutes walk test</u> n=12 306 meters (sd 145) <u>NYHA</u> :61% Class I-II		?	+ (?)	?
d) Quality of life										
Slaughter, 2009	USA	RCT	I: 134 C: 66 FU: 1 year	I: 19 C: 32	<u>MLHF-score</u> 34(sd 22) p=0.03	<u>MLHF-score</u> 44 (sd 23)	MLHF=Minnesota Living with Heart Failure questionnaire	?	+ ?)	?

Appendix 6 Complications

Author. year	Country	Number of patients n= Length of follow-up	Type of device	Infections	Bleeding	Neurological complications	Comments
Dembitsky. 2004	USA	n=68 unclear	PF-LVAD	Sepsis 0.51 Local 0.35	0.6	0.44	Events/patient/Year Data from REMATCH
Drews. 2010	Ger-many	n=64 mean 157 days	PF-VAD	27 %	3 %	Stroke: 20%	Cause of mortality
Holman. 2004	USA	n=68 median 408 days	PF-LVAD	42 %			Sepsis Data from REMATCH
Lazar. 2004	USA	n=68 unclear	PF-LVAD			Neurological event: 44 % Stroke: 16 %	Data from REMATCH
Long. 2005	USA	n=42 mean 232 days	PF-LVAD	Sepsis: 0.19 Local: 0.45 Percutaneous: 0.04	Perioperative: 0.15 Later: 0.38	0.15	Events/Patient/Year
Park. 2005	USA	n=68 3 year	PF-LVAD	Sepsis: 30 %	Perioperative bleeding: 1.5 %	10 %	REMATCH 3-year data Cause of mortality
Richenbacher. 2003	USA	n=68 unclear	PF-LVAD	Sepsis 0.53 Local: 0.33 Percutaneous or pocket site: 0.36	Late bleeding: 0.53		Data from REMATCH Events/Patient/Year
Rogers. 2007	USA	n=37 6 months	PF-LVAD	0.25		Cerebrovascular dysfunction: 0.11 Stroke: 0.08	Events/patient-month
Rose. 2001	USA	n=68 median 408 days	PF-LVAD	Sepsis: 0.6 Local: 0.39 Driveline: 0.41	0.56	0.39	The REMATCH trial Events/patient/Year

Appendix 6 Complications

Author. year	Country	Number of patients n= Length of follow-up	Type of device	Infections	Bleeding	Neurological complications	Comments
Aggarwal. 2012	USA	n=101 unclear	CF-LVAD		23%		Gastrointestinal bleeding
Drews. 2010	Ger-many	n=110 mean 281 days	CF-LVAD	22 %	6 %	Stroke: 25%	Cause of mortality
Goldstein. 2012	USA	n=2006 8 months	CF-LVAD	9.8 %			Driveline infections. Data from INTERMACS
Kirklin. 2012	USA	n=1160 1 year	CF-LVAD	8.1	11.9	1.86	Events/100 patient-months
Kirklin. 2013	USA	n=6561	Mostly CF-LVAD	Device related infections 15 %. 1 year 30 % 2 years		11 %. 1 year 17 %. 2 years	Data from INTERMACS
Daneshmand. 2010	USA	60 unclear	CF-LVAD	35 %			Driveline infection
Morgan. 2012	USA	n=86 median 176 days	CF-LVAD		22 %		Gastrointestinal bleeding
Park. 2012	USA	n=281 median 1.7 years	CF-LVAD	Sepsis: 0.27 Local: 0.49 Device related: 0.27	Requiring surgery: 0.14	Neurological event: 0.2 Stroke 0.08	Events/Patient/Year
Sharma. 2012	USA	n=143 unclear	CF-LVAD	Driveline: 12 %			Events/Patient/Year
Slaughter. 2009	USA	n=134	CF-LVAD	Sepsis: 0.39 Device related: 0.48	Requiring surgery: 0.23	Stroke: 0.13 Other neurological event: 0.17	RCT Events/Patient/Year Total 211 patient-years
Topilsky 2011a	USA	n=83 30 days	CF-LVAD	59 %	82%	14 %	

Appendix 7 - Summary of Findings.
RRR = Relative Risk Reduction; ARR = Absolute Risk Reduction. MLHF=Minnesota Living with Heart Failure. 6MWT=6-minute walk test.

Outcome variable **Number of studies**	**Design**	**Study limitations**	**Consistency**	**Directness**	**Precision**	**Publication bias**	**Magnitude of effect**	**Relative effect (95%CI)**	**Absolute effect (95%CI)**	**Quality of evidence GRADE**
PF-LVAD versus optimal medical therapy										
Mortality 2	1 RCT 1 non-randomised study	No serious limitations	No inconsistency	Some uncertainty (?)[1]	Uncertain precision (?)[2]	Unlikely	Not relevant	1-year: RRR: 33 % 18%	1-year: ARR: 27% 16 %	⊕⊕⊕◯
Quality of life 2	1 RCT 1 non-randomised study	Very serious limitations (-2)[3]	No inconsistency	Some uncertainty (?)	Serious imprecision (-1)[4]	Unlikely	Not relevant	MLHF score (0-105): - 29 %	MLHF score (0-105): -17 points	⊕◯◯◯
Functional capacity 2	1 RCT 1 non-randomised study	Very serious limitations (-2)[3]	No inconsistency	Some uncertainty (?)	Serious imprecision (-1)[4]	Unlikely	Very large	SF-36 physical score (0-100): + 52 %	SF-36 physical score (0-100): + 24	⊕⊕◯◯

Appendix 7 - Summary of Findings.
RRR = Relative Risk Reduction; ARR = Absolute Risk Reduction. MLHF=Minnesota Living with Heart Failure. 6MWT=6-minute walk test.

Outcome variable **Number of studies**	**Design**	**Study limitations**	**Consistency**	**Directness**	**Precision**	**Publication bias**	**Magnitude of effect**	**Relative effect (95%CI)**	**Absolute effect (95%CI)**	**Quality of evidence GRADE**
CF-LVAD versus PF-LVAD										
Mortality	1 RCT 2 non-randomised studies	Some limitations (?)[5]	No inconsistency	Some uncertainty (?)	Uncertain precision (?)[2]	Unlikely	Not relevant	1-year: RRR: 27% 24 % - 52%	1-year: ARR: 13% 20% - 31 %	⊕⊕⊕◯
Quality of life	1 RCT	Some limitations (?)[5]	No inconsistency	Some uncertainty (?)	Serious imprecision (-1)[4]	Unlikely	Not relevant	MLHF score (0-105): - 23 %	MLHF score (0-105): -10 points	⊕⊕◯◯
Functional capacity	1 RCT	Some limitations (-2)[5]	No inconsistency	Some uncertainty (?)	Very serious imprecision (-1)[4,6]	Unlikely	Not relevant		6MWT: +12 meters	⊕◯◯◯

High quality of evidence = ⊕⊕⊕⊕
Moderate quality of evidence = ⊕⊕⊕◯
Low quality of evidence = ⊕⊕◯◯
Very low quality of evidence = ⊕◯◯◯

Footnotes:
1. Unclear recruitment and randomization of eligible individuals
2. Wide 95 % confidence interval
3. Selected group of survivors analysed.
4. Few patients
5. Per protocol analysis
6. 95 % confidence interval not stated

Appendix 8 Ethical analysis

1. From the patient's perspective, how does destination therapy (DT) affect the patient's quality of life and life expectancy?
The patient will have a longer life expectancy, probably with better quality of life and functional capacity. In addition, DT may resolve the contraindication to heart transplantation and thereby restore transplant eligibility, with further expected improvement in quality of life and life expectancy.

2. How severe is the patient's need that the DT must meet?
The mortality of end stage heart failure is very high, and it is associated with severely reduced functional capacity, poor quality of life and frequent hospitalisations. The 1-year survival for patients diagnosed with severe heart failure (NYHA IV) on optimal medical treatment is below 50 %.

3. Does DT influence the view on humanity or human dignity?
No, probably not from the view of other individuals. However, to have a mechanical device implanted in your own body may affect the subject's self-esteem and self-image.

4. Can DT affect the patient's ability and possibility to be independent?
DT is likely to improve the functional capacity and, thereby, the independency of the patient. However, continuous need for electric power either from a power base unit or from batteries may in other ways limit independency. The patient will also need assistance to change the bandages around the driveline. Thus, total independence will not be achieved.

5. If implemented, does DT require any special steps to not compromise the patient's autonomy?
DT is likely to introduce a specific challenge to the patient with respect to autonomy. In this respect it is important to inform the patient extensively about the treatment, including potential benefits and risks. Also, of importance for the patient's autonomy is that the DT program should include the following:

1. Participation of a multidisciplinary care team, including palliative care specialists
2. Adopting a concise plan of care for anticipated device-related complications
3. Planning for anticipated end-of-life care and timing of device deactivation

6. How does DT affect the patient's physical, moral and personal integrity?
The moral and personal integrity will most probably not be negatively affected by DT. However the physical integrity is interrupted by the highly invasive nature of the implantation procedure.

7. Is DT cost-effective?
Attempts to estimate the cost-effectiveness of DT have reported that incremental costs per quality-adjusted life years (QALYs) are very high. Thus, the cost-effectiveness of DT is questionable.

8. How does DT affect resources?
DT is a costly treatment. Except for the costs of the device and accessories, DT requires the use of operation rooms, beds in the intensive care units (sometimes for long periods of time), many days in the hospital wards, and frequent outpatient follow-up visits. DT complications will also use resources for clinical work-up and treatment. All of this will compete with the needs of other patient categories. Thus, unless additional resources can be provided there is a substantial risk that DT will reallocate current resources from other medical needs.

9. Is DT in conflict with professional values?
In our opinion, the benefits of DT in highly selected patients will outweigh its risks and, therefore, are not in conflict with professional values.

10. Does DT change the role of the professional in relation to the patient?
DT is demanding for patients and their families. The patient must be able to comply with the system, e.g. exchange batteries, and interpret and react to signals from the system monitor. The bandages around the driveline exit site must be changed regularly with an aseptic technique.

11. Does DT affect, or does it put any new demands on, a third party?
DT is likely to be challenging for the patient's family, already from the postoperative phase and during rehabilitation when the patient is getting accustomed to a new life situation. The treatment also demands frequent follow-up visits. Bandage exchanges around the driveline exit site requires assistance. This is often performed by family members or by professional health care providers.

12. Is there any legislation of relevance with regard to DT?
No.

13. Is there any risk of conflict between DT and values of the society, or values of different groups?
To prolong life with a mechanical device may be in conflict with the beliefs and norms of some groups in our society.

14. Is there a risk that an introduction of DT will cause a conflict with particular interests?
No, probably not.

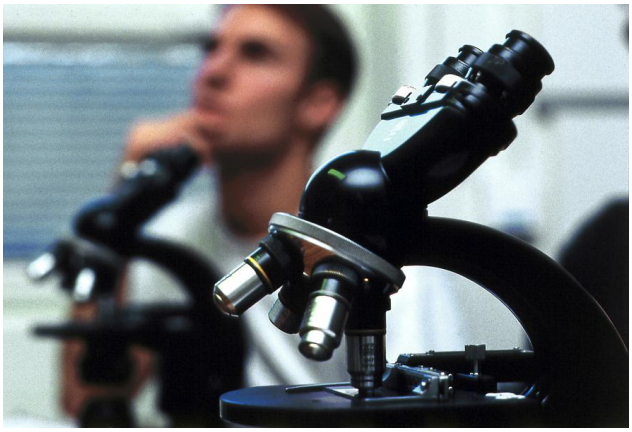
15. Can an introduction of DT influence the trust of the health care system?
DT is a high-risk treatment for severely debilitated patients and may generate several complications. Thus, in order to maintain the credibility of the health care system it is of utmost importance to inform patients and their families about both the benefits and the risks of the treatment. Also, prerequisite algorithms for clinical work-up, treatment of possible complications, and other difficult situations that may arise should be established before a DT program is adopted.

CONCLUSIONS

Introduction of a DT program raises several ethical issues. The self-esteem and self-image of the individual patient probably varies between subjects, but may be affected in both positive and negative ways. The patient will still be dependent on assistance from family members and/or health care providers, and the physical integrity is affected. Without additional economic resources there is a substantial risk that DT will reallocate current resources from the needs of other patient categories.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

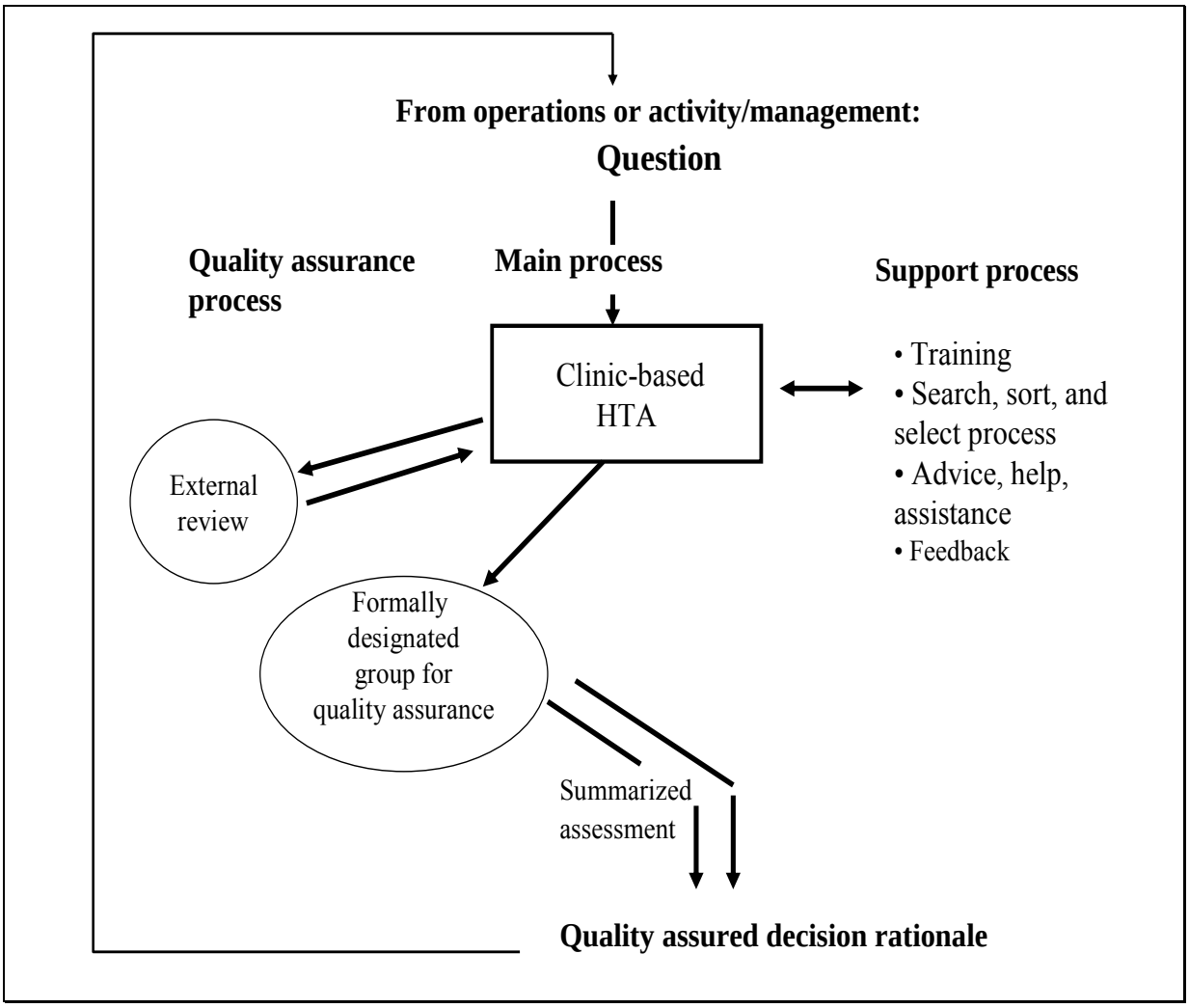
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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