Randomized trial of a left ventricular assist device as destination therapy versus guideline-directed medical therapy in patients with advanced heart failure. Rationale and design of the SWEdish evaluation of left Ventricular Assist Device (SweVAD) trial

Kristjan Karason1*, Lars H. Lund2, Magnus Dalén2, Erik Björklund3, Karl Grinnemo3, Oscar Braun4, Johan Nilsson4, Henriette van der Wal5, Jonas Holm5, Laila Hübbert6, Krister Lindmark7, Barna Szabo8, Erik Holmberg9 and Göran Dellgren10, on behalf of the SweVAD Investigators

1Departments of Cardiology and Transplantation, Sahlgrenska University Hospital, Gothenburg, Sweden; 2Departments of Cardiology and Cardiothoracic Surgery, Karolinska University Hospital, Stockholm, Sweden; 3Departments of Cardiology and Cardiothoracic Surgery, Uppsala University Hospital, Uppsala, Sweden; 4Departments of Cardiology and Cardiothoracic Surgery, Skåne University Hospital, Lund, Sweden; 5Departments of Cardiology and Cardiothoracic Surgery, Linköping University Hospital, Linköping, Sweden; 6Health, Medicine and Caring Sciences, Linköping University, Norrköping, Sweden; 7Department of Cardiology, Umeå University Hospital, Umeå, Sweden; 8Department of Cardiology, Örebro University Hospital, Örebro, Sweden; 9Regional Cancer Centre West, Sahlgrenska University Hospital, Gothenburg, Sweden; and 10Departments of Cardiothorax Surgery and Transplantation, Sahlgrenska University Hospital, Gothenburg, Sweden

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Aims
Patients with advanced heart failure (AdHF) who are ineligible for heart transplantation (HTx) can become candidates for treatment with a left ventricular assist device (LVAD) in some countries, but not others. This reflects the lack of a systematic analysis of the usefulness of LVAD systems in this context, and of their benefits, limitations and cost-effectiveness. The SWEdish evaluation of left Ventricular Assist Device (SweVAD) study is a Phase IV, prospective, 1:1 randomized, non-blinded, multicentre trial that will examine the impact of assignment to mechanical circulatory support with guideline-directed LVAD destination therapy (GD-LVAD-DT) using the HeartMate 3 (HM3) continuous flow pump vs. guideline-directed medical therapy (GDMT) on survival in a population of AdHF patients ineligible for HTx.

Methods
A total of 80 patients will be recruited to SweVAD at the seven university hospitals in Sweden. The study population will comprise patients with AdHF (New York Heart Association class IIIB–IV, INTERMACS profile 2–6) who display signs of poor prognosis despite GDMT and who are not considered eligible for HTx. Participants will be followed for 2 years or until death occurs. Other endpoints will be determined by blinded adjudication. Patients who remain on study-assigned interventions beyond 2 years will be asked to continue follow-up for outcomes and adverse events for up to 5 years.
Introduction

Mechanical circulatory support (MCS) with a left ventricular assist device (LVAD) has become an important treatment option for advanced heart failure (AdHF).1,2 The initial indication for LVAD implantation was as a temporary measure – the so-called bridge to transplantation – but a shortage of donor organs meant that patients eligible for heart transplantation (HTx) became dependent on MCS for extended periods of time. Beyond that use, the practice has developed of AdHF patients who are not eligible for a transplant receiving an LVAD as a permanent life-sustaining intervention, a strategy referred to as destination therapy (DT).3,4 The DT approach, which may offer extended survival for patients not suitable for HTx, has been rapidly increasing in certain countries, such as the USA and Germany.2,5 Also, guidelines on how to conduct the surgical, technical and medical aspects of LVAD-DT treatment have emerged.6–9 However, in other countries, healthcare givers have adopted a more restrictive, or even negative, attitude toward the use of this treatment option.10,11

Progressive technical enhancements between the first and second and third generations of LVADs have been accompanied by improvements in short- and long-term survival rates for DT.6,12 There has been a parallel decline in the incidence of major LVAD-associated complications with the use of continuous-flow devices compared with earlier pulsatile-flow LVADs.5,13 Studies have reported improved survival, functional capacity and quality of life (QoL) with long-term LVAD treatment, and both European14 and US15 heart failure (HF) guidelines identify DT as a viable management pathway for selected patients who have AdHF but are not eligible for HTx. However, the class of recommendation (IIa) and the level of evidence (B) for this therapy remain modest.

Although the case for LVADs as DT is underpinned by the results of the randomized, controlled REMATCH trial,3 and subsequent comparative device studies,16,17 LVAD implantation as DT is not accepted in many countries, including Sweden and the UK, and is undertaken only rarely. Factors contributing to this position are likely to include the limited availability of high-quality data to guide patient selection and concerns about longer-term outcomes, cost-effectiveness and complications associated with LVADs, which healthcare authorities in both Sweden and the UK consider to be unfavourable in many scenarios.18–20 Drug therapies improving outcomes for patients with AdHF that have been introduced after the publication of REMATCH include ivabradine,21 sacubitril/valsartan22 and, most recently, dapagliflozin.23 Also, cardiac implantable electronic device therapies continue to evolve, extending survival benefits in selected patients with HF.24

Developments in MCS technology, adjuvant medication, improved patient outcomes and professional and public perceptions of the potential of LVADs in AdHF are likely to result in greater use of these devices as DT in the coming years. In contrast, guideline-directed medical therapy (GDMT) has also evolved substantially in recent years, offering improved survival for patients with AdHF. Thus, many countries still consider LVAD-DT to be in a state of equipoise, not least in older HF patients displaying varying degrees of frailty and comorbidities. In these cases, healthcare providers are skeptical about the benefits of LVAD-DT, and are uncertain whether their use outweighs the burden of care and risk of complications. Thus, there is still doubt about whether LVAD-DT meets conventional cost-effectiveness criteria, which is why clinicians, health authorities and research funders in Sweden consider it justified to perform a randomized trial of guideline-directed LVAD-DT (GD-LVAD-DT) vs. GDMT in AdHF patients who are not suitable for HTx.

Study design

General

The SWEdish evaluation of left Ventricular Assist Device (SweVAD) trial (ClinicalTrials.gov ID NCT02592499) is a collaboration between all seven university hospitals in Sweden (see Appendix A for details of participating centres and investigators). It is a Phase IV, prospective, randomized, non-blinded, multicentre trial that will directly compare the impact of assignment to long-term MCS guideline-directed treatment with a continuous-flow LVAD or to GDMT delivered and adjusted according to current HF treatment guidelines on survival in a population of AdHF patients who are not eligible for HTx due to high age, frailty, and/or comorbidities. Health-economic analyses comparing both treatments will also be performed.

SweVAD will enrol 80 patients, who will be followed for 2 years or until death occurs. Crossover between study groups is highly unlikely due to participants’ eligibility for HTx and the non-occurrence of DT in Sweden outside SweVAD. Although, every effort will be made to avoid crossover, the steering group agreed upon that this may be permitted under extreme circumstances based on consensual and ethical decision making. Patients who remain on GD-LVAD-DT or GDMT beyond 2 years will be asked to participate in an extended follow-up for primary and secondary outcomes for up to 5 years. Endpoints will be determined by blinded adjudication.

The SweVAD Steering Committee (Appendix B) designed the trial and wrote the study protocol. The study was approved by
the Swedish Ethical Review Authority, and will be conducted in accordance with Good Clinical Practice and the 2002 Declaration of Helsinki. All participants will provide written informed consent prior to any study-related investigations.

Patient selection

The study population will comprise patients with AdHF [New York Heart Association (NYHA) class IIIb–IV, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile 2–6] who display signs of poor prognosis despite GDMT and who are not considered eligible for HTx. Patients compatible with INTERMACS profile 1 will be excluded from the study as they exhibit the greatest disease severity, are frequently treated with short-term MCS and display the highest risk of postoperative mortality compared with patients presenting with less severe HF (INTERMACS profile ≥2). All patients provide written informed consent before HF work-up, multidisciplinary evaluation and randomization. A full statement of inclusion and exclusion criteria is shown in Table 1 and a study flowchart is presented in Figure 1.

Randomization

After enrolment and baseline assessments, patients will be randomized in a 1:1 fashion to GD-LVAD-DT or GDMT, stratified by study centre and blocked to maintain the 1:1 ratio over time. Each study centre will be allowed to enrol a maximum of 30 randomized patients. The randomization process will be Internet-based and delivered in collaboration with a data management company (dSharp, Gothenburg, Sweden).

Patients will be admitted to hospital so that those randomized to the GD-LVAD-DT group can undergo implant surgery within 10 working days of randomization and those in the GDMT group can continue therapy. LVAD implantations will be performed at five of the participating centres (the University Hospitals of Sahlgrenska, Linköping, Skåne, Karolinska and Uppsala), all of which have relevant surgical experience. The University Hospitals of Umeå and Örebro will perform screening, inclusion and randomization of patients, and transfer those assigned to the GD-LVAD-DT group to Sahlgrenska Hospital for implantation of the pump. After hospital discharge, the study centres in Umeå and Örebro will conduct patient follow-up according to the study protocol.

For patients enrolled to the GD-LVAD-DT group surgical, technical and medical treatment will be provided according to available guidelines. This is important, in particular with respect to anticoagulation and antiplatelet therapy, infection risk, gastrointestinal bleeding, blood pressure control and other essential medical features. GDMT patients will remain under close follow-up by a HF specialist, and if an indication arises for alteration in their medical and/or electronic device regimen according prevailing HF guidelines this will be performed.

All patients will be assessed and data collected at baseline and months 2, 4, 6, 12, 18 and 24 post-enrolment (Appendix C). At each follow-up visit, information will be acquired on endpoints and adverse events. Vital parameters will be obtained and blood test acquired for biomarkers and safety measures. NYHA functional class and INTERMACS profile (for patients in NYHA class IV) will be determined. A 12-lead electrocardiogram will be performed, along with an echocardiogram, 6-min walk test and a cardiopulmonary exercise test including measurement of peak maximal oxygen uptake (VO₂). Estimated and measured glomerular filtration rates will be determined and QoL assessed using multiple questionnaires. LVAD parameters and changes in medication will be recorded. Blood tests, including whole blood and its fractions, will be collected and stored for future genetic and omics analysis. Also, myocardial tissue becoming available in connection with pump implantation will be stored for later studies of myocardial regenerative capacity (Appendix D, sub-study 3).

Study interventions

Left ventricular assist device destination therapy

The HeartMate 3 (HM3) LVAD (Abbott, Santa Clara, CA, USA) will be used in the study. The HM3 is a third-generation, continuous-flow LVAD with a magnetically levitated rotor and wide blood-flow passages designed to reduce shear stress on blood in transit. The HM3 was evaluated in a non-randomized, 50-patient trial to meet Conformité Européenne requirements. Furthermore, the device has been shown in the MOMENTUM 3 trial to be associated with a highly statistically significantly lower risk of stroke compared with its predecessor device, the HeartMate II (HMII). Patients treated with the HM3 will receive an antithrombotic regimen comprising a vitamin K antagonist, targeted to achieve an international normalized ratio of 2–3, together with aspirin (75 mg once daily). Otherwise, HM3 patients will be treated in accordance with international guidelines and recommendations.

Guideline-directed medical therapy

Patients randomized to GDMT will be treated according to the 2016 European Society of Cardiology (ESC) clinical practice guidelines on acute and chronic HF. All patients should receive a beta-blocker, an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB), together with a mineralocorticoid receptor antagonist, if tolerated and at optimally titrated doses. When appropriate, an ACEI or ARB will be switched to an angiotensin receptor–neprilysin inhibitor. Loop diuretics are to be used as needed to control fluid retention.

Other drugs that may relieve symptoms and improve prognosis can be used at the discretion of the investigator. These include, but are not limited to, ivabradine (sinus node inhibitor), hydralazine and isosorbide dinitrate (vasodilators), digoxin (inotrope), sodium–glucose cotransporter-2 inhibitors and anticoagulant agents (thromboembolic prophylaxis). In addition, intermittent infusions with the inotrope dobutamine and/or the inodilator levosimendan are allowed in decompensated patients who do not respond to intravenous administration of loop diuretics. Chronic outpatient infusion with inotropic drugs such as dobutamine or milrinone is not customary in Sweden.
Table 1 Inclusion and exclusion criteria for the SweVAD study

**Inclusion criteria**
1. Signed informed consent.
2. Adult (≥18 years).
3. Chronic heart failure for ≥45 days, or acute heart failure requiring inotropic support ≥7 days after a myocardial infarction.
4. Left ventricular ejection fraction ≤30%.
5. NYHA class IIIB–IV, INTERMACS profile 2–6.
6. At least two out of four of the following adverse prognostic criteria:
   A. Seattle Heart Failure Model Risk Calculator predicting ≤75% 1-year survival.
   B. NT-proBNP ≥2000 ng/L.
   C. Peak VO₂ ≤14 mL/kg/min or <50% of predicted peak value with the attainment of the anaerobic threshold, or unable to perform.
   D. Need for continuous or intermittent inotropic support, or ≥2 heart failure hospitalizations during last 6 months.
7. Receiving medical management with optimal doses of beta-blockers, ACE inhibitors or angiotensin receptor blockers or ARNI, and MRAs for at least 30 days if tolerated.
8. Receiving cardiac resynchronisation therapy, if indicated, for at least 45 days.
9. Receiving an implantable cardioverter defibrillator if indicated and appropriate.
10. Ineligible for HTx due to advanced age and/or comorbidities.
11. Considered suitable for the study by a multidisciplinary board

**Exclusion criteria**
1. Likely to become eligible for HTx after treatment with durable MCS (‘bridge to candidacy’).
2. Indication for revascularization, valvular surgery or other cardiac intervention expected to improve cardiac function and prognosis (e.g. CABG, PCI, TAVI or MitraClip).
3. INTERMACS profile 1 (‘crash and burn’).
4. Ongoing short-term MCS.
5. Heart failure due to restrictive cardiomyopathy, pericardial disease, active myocarditis, or uncorrected thyroid disease.
6. Untreated aortic aneurysm >5 cm.
7. Mechanical aortic valve that will not be converted to a bioprosthesis or patch.
8. Moderate-to-severe aortic insufficiency without plans for correction.
9. Technical obstacles, which pose an inordinately high surgical risk.
10. Active, uncontrolled infection.
11. Stroke within 90 days or carotid artery stenosis >80%.
12. Significant peripheral vascular disease.
13. Severe chronic obstructive pulmonary disease or severe restrictive lung disease.
14. Intrinsic hepatic disease as defined by liver enzyme values (AST or ALT or total bilirubin) >5 times the upper limit of normal or INR >2.0 not due to anticoagulant therapy.
15. Intolerance to anticoagulant or antiplatelet therapies or any other operative therapy that the patient will require based upon their health status.
16. Platelet count <50,000 per μL.
17. Measured glomerular filtration rate <20 mL/min/1.73 m² unresponsive to inotrope treatment or chronic dialysis.
18. High risk for right ventricular failure according to echocardiography and/or invasive haemodynamic measurements as judged by the investigator (>2 parameters constitute an exclusion criteria) using a combination of the following:
   A. Severe tricuspid regurgitation (3/3).
   B. Tricuspid annular plane systolic excursion <0.72 cm.
   C. Ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter >0.72.
   D. Central venous pressure >16 mmHg.
   E. Mean pulmonary artery pressure – right atrial pressure <10 mmHg.
   F. Ratio of central venous pressure to pulmonary artery wedge pressure >0.63.
   G. Right ventricular stroke work index <300 mmHg mL/m².
   H. Bilirubin >34 μmol/L.
19. Body mass index >40 kg/m².
20. Psychiatric disease, cognitive dysfunction, alcohol or drug abuse, or psychosocial issues likely to impair study compliance.
21. Female of childbearing age with a positive pregnancy test or a female who is not willing to use adequate contraceptive precautions during the study.
22. A condition other than heart failure that could limit survival to <2 years.
23. Participation in any other clinical investigation that is likely to confound study results or affect study outcome.

ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor—neprilysin inhibitor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAGB, coronary artery bypass graft; HTx, heart transplantation; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; VO₂, oxygen uptake.

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All patients who have an indication for an implantable cardioverter defibrillator and/or cardiac resynchronization therapy according to the 2016 ESC guidelines should receive such therapy before enrolment as determined by their wishes and the physician’s discretion. Further, if an indication for additional medical and/or device treatment according to prevailing HF guidelines arises after allocation to the GDMT group, the patient should be provided with such therapy.

In addition, if patients in the GDMT group develop an indication for a surgical intervention that may improve their HF situation, then this is allowed. This may include revascularization in patients with ischaemic heart disease, valvular intervention in patients with valvular disease and left ventricular reconstruction in patients with extensive scarring and remodelling of the left ventricle after myocardial infarction.

Physical therapy

Patients in both study groups will be encouraged to participate in physical therapy. Each patient will receive a tailored schedule of protocol-defined exercises designed to optimize their everyday physical functioning. Training sessions will be performed under the surveillance of a physiotherapist. The effect of training will be assessed at follow-up according to performance in the 6-min walk test. In addition, all patients will be supplied with an Apple watch to register physical activity under normal conditions. Data will be collected regularly by the study personnel and analysed in a sub-study.

Study objectives and endpoints

The primary and secondary objectives of the SweVAD study are listed in Table 2. The primary endpoint is to compare 2-year overall survival rates between GD-LVAD-DT and GDMT in a population of Swedish patients with AdHF who are ineligible for HTx. Secondary efficacy endpoints include: survival free from disabling stroke (defined for this purpose as a Modified Rankin Scale score >3); assessment of functional capacity (NYHA status, performance in the 6-min walk test and peak VO₂ at 1 and 2 years); health-related QoL as reflected by scores on the EuroQol-5D and Short Form-36 instruments and the Kansas City Cardiomyopathy Questionnaire; HF-related events; cost-effectiveness; renal function. Secondary safety endpoints comprise: hospital admissions; and adverse events (AEs) and serious adverse events (SAEs) during 2 years. Protocol-defined SAEs comprise: (i) neurological dysfunction [stroke (haemorrhagic or ischaemic), transient ischaemic attack or other non-stroke neurologic events]; (ii) cardiac arrhythmias (sustained ventricular tachycardia or ventricular fibrillation leading to anti-tachycardia pacing or defibrillation, alternatively sustained ventricular tachycardia or ventricular fibrillation leading to hospitalization); (iii) myocardial infarction; (iv) renal dysfunction; (v) major infection; (vi) major bleeding; (vii) device thrombosis; (viii) device replacement; (ix) worsening HF; and (x) right-sided HF.

Multiple sub-studies are being conducted in the SweVAD trial, including exploration of biomarkers and omics, as well as qualitative end-of-life studies of both LVAD patients themselves and their relatives. A health-economics sub-study will examine the long-term incremental cost-effectiveness ratio of LVAD-DT in this patient population. A list of contributors to these sub-studies appears in Appendix D.

Statistical methods and considerations

Based on a review of recent literature relevant to the HM3, including the MOMENTUM 3 trial, and using the Seattle Heart Failure Model.
Table 2 Primary, secondary and safety endpoints for the SweVAD study

**Primary endpoint**
1. Overall survival for 2 years.

**Secondary efficacy endpoints**
1. Overall survival for 2 years free from disabling stroke (Modified Rankin Scale >3).
2. Functional capacity
   A. New York Heart Association class
   B. 6-min walk test
   C. Cardiopulmonary exercise test with measurement of peak VO₂ and VE/VCO₂.
3. Renal function with measured glomerular filtration rate
4. Biomarkers (NT-proBNP and TnT)
5. Health-related quality of life
   A. EuroQoL (EQ-5D-5L)
   B. 36-Item Short Form Survey
   C. Kansas City Cardiomyopathy Questionnaire

**Secondary safety endpoints**
7. Hospital admissions
8. Number of adverse events and serious adverse events defined as:
   A. Neurological dysfunction (stroke/TIA/other)
   B. Cardiac arrhythmias (sustained VT or VF leading to anti-tachycardia pacing or defibrillation, alternatively sustained VT or VT leading to hospitalization)
   C. Myocardial infarction (a rise and fall in TnT levels and at least one of the following: (i) symptoms; (ii) new ECG changes; (iii) new Q-waves; (iv) new regional wall motion abnormality; (v) identification of a coronary thrombus.
   D. Renal dysfunction [an increase in creatinine of ≥25 μmol (0.3 mg/dL)].
   E. Major infection (infections requiring treatment with antibiotics or hospitalization).
   F. Major bleeding (Hgb drop ≥5 g/L or need for transfusion due to bleeding).
   G. Device thrombosis.
   H. Device replacement.
   J. Worsening HF (hospitalization for HF or need for intravenous diuretics).
   K. Right HF (development of two parameters from exclusion criterion 18).
   L. Other adverse or serious adverse event

ECG, electrocardiogram; Hgb, haemoglobin; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TIA, transient ischaemic attack; TnT, troponin T; VE/VCO₂, ventilation to carbon dioxide output ratio; VF, ventricular fibrillation; VO₂, oxygen uptake; VT, ventricular tachycardia.

it is anticipated that implantation of an LVAD as DT will deliver a 2-year survival rate of 75% and that GDMT patients will achieve a 2-year survival rate of 40%. Proceeding from those assumptions, it will require 34 patients per group (n = 68) and a total of 29 endpoint events to achieve 80% power to prove that GD-LVAD-DT is superior to GDMT using a log-rank test with a two-sided alpha value of 0.05 (Freidman approach). To provide a generous margin of error for inclusion and randomization, and taking into account of a treatment learning curve, a total of 40 patients will be recruited to each group.

All randomized patients will comprise the intention-to-treat population, which will be the primary analysis population for the primary endpoint. Patients will be analysed for the primary endpoint according to their treatment assignment, regardless of their compliance with that assignment. Thus, patients randomized to LVAD implantation who die before the intervention or who are not implanted for other reasons will still be regarded as belonging to that group. A secondary as-treated analysis will also be performed.

If a patient decides to terminate his or her participation in the study, we will be prevented from gathering secondary endpoints, which will be censored at the time of discontinuation. On the other hand, we will always be able to collect information on the time and cause of death (primary endpoint) and analyse according to intention-to-treat since this is official material in Sweden. Patient crossover is not expected to be a problem nor lead to any censoring, since all enrolled patients will display an absolute contraindication for HTx, and LVAD-DT is not available for patients with AdHF otherwise than within the setting of the SweVAD study.

Statistical testing of the primary outcome will be done using a log-rank test. For secondary endpoints, all-cause specific hazard ratios will be estimated according to the model of Fine and Gray. At study endpoint, a P-value of <0.05 will be considered statistically significant. A comparison of results across sites will be performed to identify any effects of site bias on the primary endpoint (i.e. to test whether outcomes at one or more sites with superior outcomes influence the overall primary endpoint result). Sites contributing fewer than five patients will be pooled for such analyses.

The Data and Safety Monitoring Board (DSMB) will have access to unblinded data and may, without the knowledge of the investigators, undertake analysis to evaluate the efficacy or futility of the study using the statistical method they find most suitable. If overwhelming superiority is revealed or clear futility established, enrolment will be stopped and a study report will be prepared.

Secondary endpoints will be tested at the two-sided P < 0.05 level of significance, with no adjustment for multiple comparisons and no imputation of missing data. The primary analysis population for these endpoints will be the as-treated (per-protocol) population. The secondary endpoints will be illustrated in a cumulative incidence plot analysed according to the model of competing risks developed by Fine.
and Gray. Thus, it will be evident if a higher cumulative incidence in one of the treatment arms is due to competing events and, thereby, will reveal an inappropriate low cumulative incidence in the other.

All statistical calculations and inspections will be performed according to the statistical analysis plan using the most recent version of STATA software (StataCorp LP, College Station, TX, USA).

Ethics and data security

The Swedish Ethical Review Authority has approved the protocol and amendments 1–5 inclusive. Ethical Review Authority-approved informed written consent will be secured from all patients as a prerequisite for participation in the trial (separate patient consent will be sought for follow-up beyond 2 years). Individual sites and investigators will be responsible for complying with all aspects of the reporting requirements of the Ethical Review Authority.

An electronic case report form (eCRF) for data entries will be completed for each patient enrolled in the study (dSharp Consulting, Gothenburg, Sweden). Editing, entry and cleaning of data will be performed continuously during the study period. Before database approval, a study monitor will check the eCRFs with respect to data completeness and accuracy. The investigators will be responsible for ensuring that all observations and findings are recorded correctly, completely and in a timely manner.

Patient confidentiality will be preserved in conformity with European Union General Data Protection Regulation 2016/679. Results of study investigations will be registered in hospital records and recorded in the eCRF under a specific code number, without revealing the identity of the patient. It will be the responsibility of the local investigator to ensure that the code key that links data to personal identity is stored safely at each participating hospital. Only investigators and study nurses dedicated to the SweVAD trial will be able to enter data in the eCRF and only the principal investigators will have access to all data recorded.

Study administration and oversight

A study Steering Committee comprising representatives from each centre will provide study oversight and guidance to the investigators as needed. An independent DSMB will be responsible for the overall safety of the study. The DSMB will consist of three persons with documented experience in this field and will include a statistician, a physician with experience in cardiology and epidemiology, and a qualified cardiothoracic surgeon. SAEs will be reviewed monthly during the study. Clinical and laboratory AEs will be reviewed every 4 months. All reported events will be adjudicated by an End-point Adjudication Committee. Current members of the Steering Committee, DSMB and End-point Adjudication Committee are identified in Appendix B.

A study monitor will supervise the trial by means of regular site visits. During these visits, the monitor will verify that data are authentic, accurate and complete, that the safety and rights of patients are being protected and that the study is being conducted in accordance with the currently approved protocol. Good Clinical Practice and all applicable regulatory requirements.

Current study status

Recruitment to SweVAD was originally scheduled to start in June 2016, with an anticipated recruitment time of 24 months. In response to delayed commencement at some study centres, the last date for recruitment has been extended to June 2021. To date, 40 patients have been enrolled in SweVAD. It is expected that the last patient will complete the specified 2-year observation period in June 2023.

Discussion

Long-term LVAD treatment is an accepted treatment option in some countries for HF patients ineligible for HTx. Development trends in LVAD technology and improved outcomes have made the therapy more attractive. However, due to complications, doubts about the cost–benefit ratio of the treatment and the issue of equipoise, the use of LVADs for DT has not yet been widely adopted in many countries, including Sweden. Even in nations in which this use is accepted and reimbursed, awareness of it and its implications is limited. The trend toward this form of therapy for AdHF is clear, nevertheless, and it is foreseeable that use of this costly intervention will increase. Hence there is a need for a randomized controlled trial which could help to contextualize the uses of GD-LVAD-DT and guide the future adoption of this strategy in Sweden and elsewhere.

The utility and value of MCS in the management of patients with AdHF are acknowledged in recent position papers from the Heart Failure Association of the ESC and the European Association for Cardio-Thoracic Surgery. However, due to a lack of scientific evidence, the authors state that only expert opinion concerning the permanent use of MCS can be offered. In that context, SweVAD represents a timely addition to, and enlargement of, the trial database of clinical understanding of one of the newer LVAD devices, the HM3. Detailed technical descriptions of the engineering features and operation of the HM3 have been provided in various recent reports. In brief, this device incorporates a magnetically levitated centrifugal continuous-flow circulatory pump and has the added functionality of generating an artificial pulse that may potentially attenuate intra-pump thrombosis.

The clinical significance of these features is a decreased risk of haemocompatibility-related SAEs compared with its predecessor, the HMII (which consisted of an axial continuous-flow pump with mechanical bearings), and, theoretically, a lower risk of thromboembolism than with other devices operating on similar principles. Compared with the HMII, the HM3 was associated with fewer haemocompatibility-related events during short-term (6 months) follow-up and a marked reduction in the incidence of stroke in the long-term follow-up phase (up to 2 years) of the MOMENTUM 3 trial (odds ratio 0.23, 95% confidence interval 0.08–0.63; P = 0.01). Implantation of an HM3 pump was the only independent predictor of a lower incidence of stroke in MOMENTUM 3, a finding of significance when it is considered that the occurrence of stroke of any type or of any functional severity was predictive of poor 2-year clinical outcome.
These data, combined with the demonstration of overall 2-year survival rates close to those achieved with HTx, make a persuasive case for LVAD (and specifically HM3) implantation in eligible patients with AdHF, but also highlight the potential for significant major complications associated with LVAD use. The primary findings from the ROADMAPE study indicated that use of the predecessor device, the HMII, in non-inotrope-dependent patients with milder AdHF was associated with significant improvements in physical functional status and health-related QoL at 12 months when compared with optimal medical therapy, albeit at the cost of more AEs overall and more bleeding events. Given the demonstrated superiority of the HM3 over the HMII in terms of risk of haemocompatibility-related AEs, there is a strong implied case for considering the HM3 LVAD as DT in patients who are not candidates for HTx.

There are at present no similar data from controlled trials comparing the impact of HM3 implantation (as a DT) with GDMT in patients with AdHF. SweVAD will address that deficit and may be expected to provide some early signals to guide the evolution and implementation of GD-LVAD-DT in Sweden and elsewhere, including assessment of the interplay between INTERMACS status, age, comorbidities and the success of GD-LVAD-DT. The INTERMACS category range in SweVAD of 2–6 accommodates both inotrope-dependent and -independent patients and encompasses >80% of the AdHF population. Inter alia, the study may provide insights into the practice structures, procedures and behaviours associated with the most successful delivery of GDMT.

The cost-effectiveness of LVADs has improved substantially as newer devices incorporating engineering responses to the challenges of thrombotic and rheological complications have become available. For example, the cumulative post-discharge cost of the HM3 used as DT in the MOMENTUM 3 trial was half that of the predecessor device (US$37,685 ± 4251 vs. US$76,599 ± 11,889; \( P < 0.001 \)) and the trend in most health-economic analyses is toward lower costs of use. It remains the case, however, that the cost-effectiveness of LVADs, expressed as cost per quality-adjusted life-year gained or as an incremental cost-effectiveness ratio, remains high, and often exceeds the limits commonly regarded as affordable within healthcare systems. A comparison of the medium-term benefits, costs and potential hazards of GD-LVAD-DT vs. GDMT will provide a useful reference point from which to develop DT strategies for patients with AdHF who are not eligible for HTx, and may contribute to an evolution in treatment paradigms such that assessment of patient suitability for LVAD implantation as DT may take precedence over assessment for transplant eligibility as the first stage of patient triage.

We acknowledge that the sample size of our study to evaluate the primary endpoint is not large, which is related to many factors. Sweden is a rather small country with a total population of 10 million people. We estimated that the maxim inclusion rate would be 80 patients during 2 years. Further, the costs for this study are extremely high for an investigator initiated and driven study, which also limits the sample size. Still we are optimistic that the findings will aid to the scientific knowledge with respect to the treatment with GD-LVAD-DT in patients ineligible for HTx.

Patient crossover from GDMT to LVAD-DT or from LVAD-DT to HTx would reduce the power of the study and weaken the strength of the primary intention-to-treat analysis. Still, we do not believe that crossover between groups will be a problem nor lead to significant censoring. Firstly, we only enrol patients that display an absolute contraindication to HTx, and do not include patients in which LVAD may become a bridge to candidacy. Secondly, patients allocated to the GDMT group cannot receive LVAD-DT since this therapy is not approved in Sweden outside the SweVAD study. On the other hand, the unblinded nature of the study and high mortality rates may create a bias with respect to secondary endpoints.

If the primary outcome is not significantly different between groups after 2 years, we will still be able to evaluate the 5-year results. It is evident that it will not be possible to perform a similar study any time in the future. Despite a small sample size, we will of course interpret the result in the most honest way possible. However, it will be up to the scientific community to estimate the importance of the results and decide whether the findings can be accepted to be of scientific value.

Acknowledgements

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Conflict of interest: K.K., L.H.L. and G.D. have received speakers’ honoraria from Abbott. Otherwise, none of the authors declare any conflict of interest with respect to this study.

References


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Randomized trial of a left ventricular assist device as destination therapy


Appendix A

Centers and investigators

**Sahlgrenska University Hospital, Gothenburg**
Dr. Kristjan Karason, Departments of Cardiology and Transplantation, Dr. Emanuela Bobbio, Departments of Transplantation, Dr. Göran Dellgren, Department of Cardiothoracic Surgery and Transplantation, Dr. Jakob Gäbel, Department of Cardiothoracic Surgery, Dr. Bengt Redfors, Department of Anesthesiology and Intensive Care

**Karolinska University Hospital, Stockholm**
Dr. Lars Lund, Department of Cardiology, Dr. Emil Najjar, Department of Cardiology, Dr. Michael Melin, Department of Cardiology, Dr. Magnus Dalén, Department of Cardiothoracic Surgery

**Linköping University Hospital**
Dr. Henriette van der Wal, Department of Cardiology, Dr. Peter Wodlin, Department of Cardiology, Dr. Jonas Holm, Department of Cardiothoracic Surgery

**Skåne University Hospital, Lund**
Dr. Oscar Braun, Department of Cardiology, Dr. Johan Nilsson, Department of Cardiothoracic Surgery

**Uppsala University Hospital, Uppsala**
Dr. Erik Björklund, Department of Cardiology, Dr. Karl-Henrik Grinnemo, Department of Cardiothoracic Surgery

**Umeå University Hospital, Umeå**
Dr. Krister Lindmark, Department of Cardiology, Dr. Erik Tossavainen, Department of Cardiology

**Örebro University Hospital, Örebro**
Dr. Barna Szabo, Department of Cardiology, Dr. Stella Cizinsky, Department of Cardiology

Coordinating Center
**Sahlgrenska University Hospital, Gothenburg**
Project management and study monitoring: Tina Wolmeryd.

Appendix B

Steering Committee, Data and Safety Monitoring Board and Endpoint Adjudication Committee

**Steering Committee**

**Principal investigators**
*Sahlgrenska University Hospital, Gothenburg*
Dr. Kristjan Karason, Departments of Cardiology and Transplantation, Dr. Göran Dellgren, Department of Cardiothoracic Surgery and Transplantation

**Co-investigators**
*Karolinska University Hospital, Stockholm*
Dr. Lars Lund, Department of Cardiology, Dr. Magnus Dalén, Department of Cardiothoracic Surgery

*Linköping University Hospital*
Dr. Henriette van der Wal, Department of Cardiology, Dr. Jonas Holm, Department of Cardiothoracic Surgery

*Skåne University Hospital, Lund*
Dr. Oscar Braun, Department of Cardiology, Dr. Johan Nilsson, Department of Cardiothoracic Surgery

*Uppsala University Hospital, Uppsala*
Dr. Erik Björklund, Department of Cardiology, Dr. Karl-Henrik Grinnemo, Department of Cardiothoracic Surgery

*Umeå University Hospital, Umeå*
Dr. Krister Lindmark, Department of Cardiology

*Örebro University Hospital, Örebro*
Dr. Barna Szabo, Department of Cardiology

**Data and Safety Monitoring Board**
Dr. Karl Swedberg (Professor emeritus in Cardiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden).
Dr. Bansi Koul (Consultant cardiac surgeon, Department of Cardiothoracic Surgery, Skåne University Hospital, Lund University, Lund, Sweden).
Hans Wedel (Professor emeritus of Statistics, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden)

**Endpoint Adjudication Committee**
Dr. Claes Held (Adjunct professor at UCR-Uppsala Clinical Research center, Uppsala University, Uppsala, Sweden).

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## Appendix C

### Visit schedule and assessments

An 'X' indicates at what visit an assessment is to be performed

<table>
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<th>Period</th>
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<th>Follow-up</th>
<th>Extended follow-up</th>
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\(^a\)Haematology: haemoglobin, leucocytes, thrombocytes. Biochemistry: sodium, potassium, creatinine, urea, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, glucose, albumin, international normalized ratio, activated partial thromboplastin time, N-terminal pro-B-type natriuretic peptide, troponin T, lactate dehydrogenase, C-reactive protein.

\(^b\)WBC differential count, lipid profile: total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides. Endocrine profile: TSH, T4.

\(^c\)Haemoglobin, leucocytes, thrombocytes. Biochemistry: sodium, potassium, creatinine, urea, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, glucose, albumin, international normalized ratio, activated partial thromboplastin time, N-terminal pro-B-type natriuretic peptide, troponin T, lactate dehydrogenase, C-reactive protein.

\(^d\)Only in women of childbearing potential by β-human chorionic gonadotropin, or other locally used methods.

\(^e\)A chest X-ray of maximum 3 months before screening can be accepted.

\(^f\)Only in women of childbearing potential by β-human chorionic gonadotropin, or other locally used methods.

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Appendix D

Sub-study collaborators

1. Health-economic analysis
   Lars-Åke Levin, Linköping University
2. Biomarkers
   Jonas Holm and Laila Hübbert, Linköping University
3. Myocardial tissue
   Karl-Henrik Grinnemo, Uppsala University
4. Echocardiography, right ventricular function
   Carl Meurling and Annika Bengtsson, University of Lund (reference center)
5. Echocardiography, pressure reflection
   Odd Bech-Hansen, University of Gothenburg (reference center)
6. Echocardiography ramp studies
   Emil Najjar, Karolinska Institutet, A medical university
7. Surrogate endpoint analyses
   Lars H. Lund, Karolinska Institutet, A medical university
8. LVAD acoustics and device thrombosis
   Laila Hubbert, Linköping University
9. Qualitative studies of patients with LVAD toward end of life
   Maria Laconius and Karl Hederstedt, University of Gothenburg
10. Qualitative studies of relatives of patients with LVAD toward end of life
    Susan Johansson and Eva Ryrlén, University of Gothenburg
11. Physical activity in severe heart failure with or without LVAD
    Johan Nilsson, University of Lund
12. Invasive bacterial and fungal infections after LVAD implantation
    Vanda Friman, University of Gothenburg
13. Predictors of pump thrombosis in the LVAD group
    Bengt Redfors and Hans Liden, University of Gothenburg
14. Haemostatic assessment in LVAD patients
    Anders Jeppsson and Jakob Gäbel, University of Gothenburg