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European Journal of Cardio-thoracic Surgery 32 (2007) 735–744

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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VentrAssist™ left ventricular assist device: clinical trial results and Clinical Development Plan update☆,☆☆

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Received 13 March 2007; received in revised form 16 July 2007; accepted 17 July 2007; Available online 6 September 2007

Abstract

Objectives: To summarise the primary efficacy and safety results from the first international clinical trial with the VentrAssist™ left ventricular assist device and to provide an update on the VentrAssist™ Clinical Development Plan. **Methods:** The first prospective, single-arm, multicentre international clinical trial with the VentrAssist™ in bridge-to-transplant patients (CE Mark trial) was conducted in Australia, UK and Norway between 2004 and 2006. The primary outcome measure was survival until transplant or being transplant-eligible at postoperative day 154. The number and status of other clinical trials in the VentrAssist™ Clinical Development Plan are also described. **Results:** At the completion of the CE Mark trial, 25 of the 30 patients (83%) were transplanted or transplant-eligible. There were no unexpected safety issues and no reported uncontrolled stops of the VentrAssist™ pump. The Clinical Development Plan for the VentrAssist™ currently comprises seven clinical trials: two are completed, three are ongoing and two are ready for initiation. As of January 30th, 2007, a total of 87 patients have been implanted with the VentrAssist™ at 14 centres worldwide, yielding a total exposure time of more than 43 patient-years and a maximum implant duration of 2.7 years. **Conclusions:** The efficacy and safety data from a clinical trial of the VentrAssist™ were favourable and resulted in gaining European regulatory approval for this indication. Notably, the survival success rate for the VentrAssist™ was higher than that reported for other left ventricular assist devices. The overall number of implants with the VentrAssist™ has now surpassed that of any other third-generation centrifugal device.
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Keywords: Assisted circulation; Heart-assist devices; Heart transplantation; Heart failure, congestive; VentrAssist™

1. Introduction

Chronic heart failure is a significant public health problem with poor prognosis, low survival and severely diminished quality of life [1,2]. Patients with mild-to-moderate heart failure and some with severe chronic heart failure have had limited benefit from either resynchronisation therapy or pharmacological interventions [1,3]. Although medical management ameliorates symptoms and can markedly slow disease progression [1], the definitive therapy for the end stage of heart failure remains cardiac transplantation. However, this option is only available for the small population of patients who are transplant-eligible. The increasing prevalence of heart failure particularly in the elderly, and the lack of suitable donor organs dictate that cardiac transplantation will have minimal epidemiologic impact [2].

☆ Presented at the joint 20th Annual Meeting of the European Association for Cardio-thoracic Surgery and the 14th Annual Meeting of the European Society of Thoracic Surgeons, Stockholm, Sweden, September 10–13, 2006.

☆☆ Dr John Woodard is the Chief Scientific Officer of Ventracor Limited. In addition to being clinical investigators, Drs Don Esmore and Steven Tsui are members of Ventracor's Scientific Advisory Board. In compliance with the uniform requirements for manuscripts, established by the International Committee of Medical Journal Editors, Ventracor did not impose any impediment, directly or indirectly, on the publication of the study's results. The authors acknowledge the independent medical writing assistance provided by ProScribe Medical Communications (www.proscribe.com.au) for the revised manuscript. ProScribe's services were funded by Ventracor and complied with international guidelines for good publication practice.

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doi:10.1016/j.ejcts.2007.07.028

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Fig. 1. The VentrAssist™ blood pump is encased in a welded titanium shell and features a silicone percutaneous lead.

Recognition of this issue and the declining availability of donor organs have driven the development of circulatory support devices that are potentially capable of 'permanent' mechanical support.

The ultimate aim of left ventricular assist device (LVAD) development has been to provide an alternative to heart transplantation by creating systems capable of circulatory support for an indefinite period [4]. However, this has been an elusive goal. Historically, the limited mechanical durability and unfavourable adverse event rates of early LVADs [2,4] have largely restricted their use to brief applications, such as 'bridging' transplant-eligible candidates until a suitable donor organ becomes available. The limitations associated with earlier LVADs and the requirement for further options for the aging heart failure population have catalysed the ongoing development of 'next-generation' LVADs.

The VentrAssist™ LVAD is one of the more recently developed LVADs; it has a third-generation, implantable, centrifugal blood pump with hydrodynamic suspension (Fig. 1) [5]. This LVAD has been designed for patients who potentially require long-term circulatory support. Conceived in 1998, with the first human use in June 2003 [5], the VentrAssist™ is now approved for use in Europe ('CE Marked').

In this paper, we summarise the primary efficacy and safety data from the pivotal CE Mark trial that were used in the European regulatory submission. We also provide an update on the number, type and status of the other clinical trials in the VentrAssist™ Clinical Development Plan.

2. Methods

2.1. The VentrAssist™ LVAD

2.1.1. Design

The VentrAssist™ is a third-generation centrifugal LVAD. The VentrAssist™ consists of a blood pump that is implanted in a small pocket created on the left side of the body, below the diaphragm and behind the posterior rectus sheath (Fig. 2). A cannula attached from the failing left ventricle delivers blood from the heart to the VentrAssist™ and a second cannula delivers the blood from the VentrAssist™ to the ascending aorta. A thin percutaneous lead from the pump exits the body in the upper right quadrant and connects to a system controller. The controller is powered by rechargeable, nickel metal hydride batteries worn on an external belt or backpack. The controller manages the batteries, has audible and visible user alarms, and logs and displays system parameters, such as pump speed, power and estimated flow. The VentrAssist™ weighs 298 g, measures 60 mm in diameter and runs at 1800–3000 revolutions per minute (rpm) in the normal setting. Blood pump components are hermetically sealed in titanium housing.

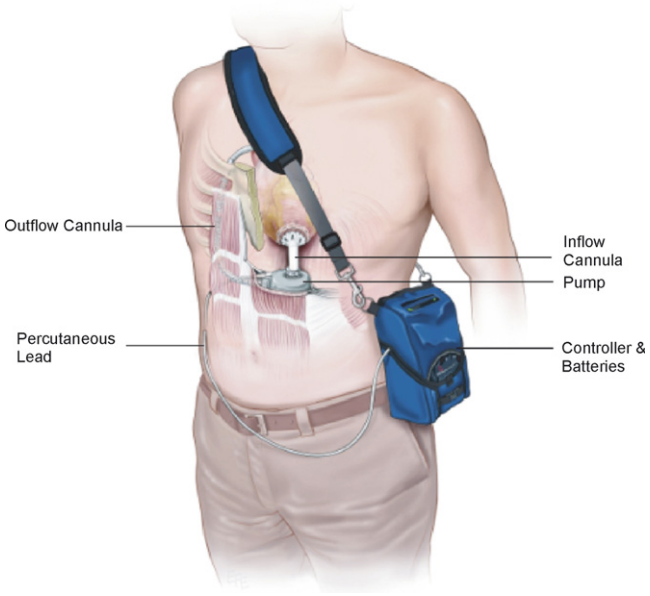


Fig. 2. The VentrAssist™ system consists of the implanted blood pump, cannulae, percutaneous lead and external patient wearables. The system is powered by rechargeable, nickel metal hydride batteries contained in a pack, which can be worn as a backpack or over the shoulder.

The VentrAssist™ has only one moving part, an impeller. The impeller comprises four small blades that are embedded with permanent magnets (Fig. 3). The impeller blades spin when an electrical current is sequentially switched between three pairs of coils contained within the pump's titanium housing. The impeller is suspended by a thin cushion of blood, within the gap of eight hydrodynamic bearings, one on each

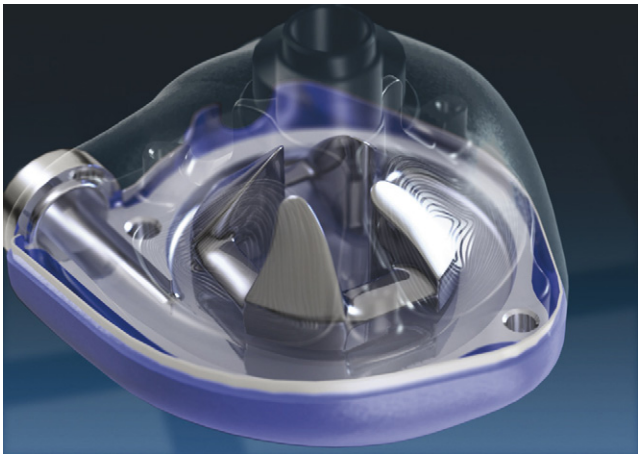


Fig. 3. Schematic view of the blood pump showing the upper bearing surface of two of the four rotor blades. The rotor integrates pumping motor and hydrodynamic bearing functions, and is coated in a black diamond-like carbon to enhance blood compatibility.

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face of the four blades. Dynamic interplay between the eight hydrodynamic bearing forces, fluid forces and gravitational forces prevents the spinning impeller from touching any part of the pump's housing.

2.1.2. Features

The VentrAssist™ was primarily designed as a permanent alternative to heart transplant for patients with heart failure. The deployment of all LVADs for DT, however, has been slower than expected due to early device reliability and durability issues. For example, in the REMATCH trial, the probability of failure with the HeartMate™ VE was 35% at 24 months and 10 of 68 implanted patients required device replacement, but eventually died [6]. To improve device reliability and durability, a number of design features were purposefully incorporated into the VentrAssist™. These features, discussed below, include: (1) hydrodynamic bearings, (2) centrifugal pump design, (3) diamond-like carbon coating and (4) biocompatible materials.

(1) Hydrodynamic bearings: Most LVADs have relied on bearings to hold the impeller blades in place, making them susceptible to wear and failure. The use of hydrodynamic bearings in the VentrAssist™ eliminated the frictional wear between the only moving part of the blood pump and the pump housing, and also resulted in unobstructed blood flow through the system. This feature should reduce the risk of device wear and the risk of stasis thrombosis. Stasis thrombosis can be caused by the flow disturbances and recirculating zones associated with the supports required by other types of bearings.
(2) Centrifugal pump design: The VentrAssist™'s centrifugal pump design contributes to an obstruction-free blood flow and a decreased risk for thrombosis by eliminating the need for extraneous structures (i.e. flow straighteners and inducers), which are characteristic of axial flow pumps. Further, because of the 'flat' flow versus pressure characteristics of the centrifugal design, flow can be reliably estimated from pump power and rotor speed [7]. This is an advantage over axial devices as they cannot be designed with an ideal flow—pressure relationship over a wide range of flows [8].
(3) Diamond-like carbon coating: Platelet activation may occur either by surface contact or excessive shear stresses in blood pumps. These activated platelets can then form adherent thrombus or platelet emboli [9]. Platelet adherence within the VentrAssist™ has been minimised by coating the blood contacting surfaces with a proprietary diamond-like carbon material. Such coatings may have a lower affinity for platelet deposition in a variety of shear environments [10].
(4) Biocompatible materials: All implanted parts of the VentrAssist™ are composed of materials that are fully biocompatible, including titanium alloys. These materials are light, strong, non-toxic and highly resistant to degradation within the body.

2.2. Surgical technique

The VentrAssist™ pump is typically implanted via a median sternotomy using conventional cardiopulmonary bypass. The pump is placed in a 'pocket' on the left side below the diaphragm, either in a pocket formed in the posterior rectus sheath or in a preperitoneal position behind the rectus. The diaphragm is reflected off the anterior chest wall to allow passage of the inflow and outflow cannulae.

Coring of the ventricular apex is generally performed using a supplied 16.5-mm diameter circular knife; some surgeons, however, prefer to make a freehand incision using scalpel and scissors. The 10 mm internal diameter silicone inflow cannula has a polyester felt flange that facilitates suturing to the apical myocardium. The ventricular anastomosis is completed using horizontal mattress sutures buttressed with Teflon pledgets. The outflow cannula is composed of a 10 mm gelatine-impregnated woven Dacron conduit with the first 18 cm covered by a fenestrated polypropylene tube that prevents kinking as the outflow traverses the epigastrium and pericardial space. The aortic anastomosis is completed in a standard end-to-side fashion.

The percutaneous lead is tunnelled through the subcutaneous fat to exit the body in the upper right quadrant. The lead is secured to the skin using adhesive patches and protected from infection with sterile dressings.

2.3. Clinical trial methods

For ethical and safety reasons, a pilot trial was conducted before the pivotal CE Mark trial commenced. The methods for these two completed clinical trials (Table 1) are described below.

2.3.1. Pilot trial

Following extensive animal trials [11], a pilot trial was conducted in Australia in 2003. The primary objective was to determine the efficacy and safety of the VentrAssist™ in a sequential, non-randomised, patient cohort. The pilot trial also offered the opportunity to establish whether any minor design modifications were required.

The trial was approved by the Human Research Ethics Committee of The Alfred Hospital, and performed in accordance with the ethical principles of the Declaration of Helsinki.

Unconventionally, we decided to perform initial implants as DT in elderly non-transplant candidates. After four DT implants, and as confidence with the VentrAssist™ grew, a protocol amendment was approved permitting high-risk, transplant-eligible patients to be implanted as a BTT. The 'high-risk' patients were defined as those unlikely to receive an approved device for BTT due to age, with a smaller body (body surface area less than 1.7 m^2) who may require a prolonged BTT (longer than 3 months) and who were suspected of having a 'covert' infection or requiring a BTT device when no suitable approved device was available. A minimal anticoagulation protocol was employed: warfarin to an international normalised ratio (INR) of 2.0—2.5 and acetylsalicylic acid at 100 mg/day. Intensive follow-up was performed for 12 months and then quarterly, or until heart transplantation.

2.3.2. CE Mark trial

This trial was a single-arm, multicentre, Phase II trial designed to support a CE Mark application. The primary

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Table 1
Overview of clinical trials in the VentrAssist™ Clinical Development Plan (as of January 30th, 2007)

Characteristic	Trial						
	Pilot trial	CE Mark trial	DT trial	BRACE trial	US BTT feasibility trial	US BTT pivotal trial	US DT pivotal trial
Status	Complete	Complete	Ongoing	Ongoing	Ongoing	Ready to initiate	Ready to initiate
Design	Prospective, single-arm, multicentre	Prospective, single-arm, multicentre	Prospective, single-arm, multicentre	Prospective, single-arm, multicentre	Prospective, single-arm, multicentre	Prospective, single-arm, multicentre	Randomised, controlled multicentre
Centres							
Number	1	7	4	15	5	Up to 20	Up to 40
Countries	Australia	Australia, NZ, UK, Norway	Australia, EU	Australia, EU	US	US	US
Timelines	June 2003—August 2006	Sept 2004—July 2006	Sept 2004[a]	June 2006[a]	July 2005[a]	2007[a]	2007[a]
Number of implants							
Target	Up to 10 patients	30 patients	Up to 15 patients	100 patients	Up to 30 patients	Up to 140 patients	Up to 250 patients
Actual[b]	9 patients (4 DT, 5 BTT)	33 BTT patients[c]	12 DT patients	9 patients[d]	12 BTT patients	NA	NA

BTT, bridge to transplant; DT, destination therapy; BRACE, better results and cost effectiveness; NA, not applicable.
[a] Completion date dependent on patient recruitment rate.
[b] The 87 patients referred to in this article comprise 75 patients implanted in clinical trials (as noted in Table 1) and 12 patients implanted under the special access scheme (as noted in the Section 2).
[c] Data from only 30 of the 33 patients (additional patients were recruited to account for potential patient dropout) were required to be analysed for regulatory approval; the results for these 30 patients are presented. Longer-term data for the 33-patient cohort will be reported separately.
[d] Data collection methods do not allow patients to be categorised as BTT or DT patients.

objective was to establish the efficacy and safety of the VentrAssist™ system.

The trial was approved by the ethics committees of the seven participating institutions in Australia, New Zealand, Norway and the United Kingdom, and performed in accordance with the ethical principles of the Declaration of Helsinki.

Patients were eligible if they were deemed appropriate for heart transplant or were likely to become transplant-eligible following LVAD implant as per institutional rules. Patients were excluded if they suffered cardiogenic shock, acute myocardial infarction or cardiac arrest in the 48 h prior to enrolment; had primary right-sided heart failure confirmed by echocardiogram, with central venous pressure greater than 15 mmHg and pulmonary artery systolic pressure greater than 60 mmHg determined by Swan-Ganz catheter; had hypertrophic obstructive cardiomyopathy or restrictive cardiomyopathy determined by transthoracic echocardiogram; possessed a prosthetic valve (biografts excepted); had a greater-than-mild aortic regurgitation; had recurrent ventricular tachycardia or ventricular fibrillation; had pulmonary hypertension, chronic renal failure, chronic liver failure or severe chronic obstructive pulmonary disease; had either a stroke within 90 days prior to enrolment or a history of cerebral vascular disease with significant extra cranial stenosis; had active sepsis or a body surface area less than 1.4 m^2.

Similar to the pilot trial, a minimal anticoagulation protocol was employed: warfarin to an INR of 2.0—2.5 and acetylsalicylic acid at 100 mg/day.

Patients were followed for 154 days following implant or until they received a heart transplant if less than 154 days. This endpoint duration was based upon the mean time to transplant at three of the trial centres. The primary outcome measure was survival until transplant or transplant-eligibility (as determined by local clinical guidelines) at post-implant day 154. Trial success was defined as (a) being transplant-eligible with the device implanted or (b) actually being transplanted at or before post-implant day 154.

Safety was assessed by the incidence and severity of adverse events, all-cause mortality and concomitant medication use. In addition, because of the known complications associated with LVADs, information regarding a number of protocol-defined, special interest, serious adverse events (SAEs) was noted. The special interest AEs were: device-related failure/malfunction, device-related infection, haemorrhage, thromboembolism, neurological dysfunction, right ventricular failure, organ dysfunction (including renal, hepatic and respiratory), haemolysis, arrhythmia, cardiac tamponade and psychiatric disorder. Neurological events were classified as 'stroke' if they were confirmed by computed tomography or the symptoms lasted more than 24 h. Event description, action taken, causality, device relationship and outcome of each SAE were recorded and adjudicated. Members of the adjudication committee, namely the participating investigators, were 'blinded' to the hospital where the events occurred and excluded from adjudicating events that occurred at their institution.

The trial design allowed statistical significance to be determined based on the results from 30 patients. The primary hypothesis tested was that the VentrAssist™ would achieve a success rate of greater than 65%. Due to the sample size, the charts of Mehta and Cain [12] were used to determine the actual number of patient successes required for a 65% success rate. At least 25 patient successes were required to achieve 65% or greater success rate. Survival data were evaluated using competing outcomes methods [13]. Kaplan—Meier survival analyses were not performed due to

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the inappropriateness of this technique for evaluating competing outcomes, particularly in small samples [14]. Safety data are presented both descriptively and as a rate per patient-month. As most adverse events with LVADs occur in the first 30 days after implantation, data are presented as rate per patient-month within the first 30 days after implantation and rate per patient-month greater than 30 days after implantation.

2.4. Clinical Development Plan

As of January 30th, 2007, the VentrAssist™ Clinical Development Plan comprises seven clinical trials: two are complete, three are ongoing and two are approaching initiation (Table 1). Conducted at sites worldwide, these trials will generate the data required for both European/Australian post-market surveillance requirements and to apply for regulatory approval of the VentrAssist™ in USA. The two completed trials have been described above and summaries of the remaining five trials are presented below.

2.4.1. DT trial

Contemporaneously with the CE Mark trial, a DT trial was initiated at six of the CE Mark trial sites. The primary objective is to generate additional data on the efficacy and safety of the VentrAssist™ for use in patients with end-stage heart failure requiring indefinite circulatory support. The primary endpoint is survival of 50% of implanted patients to 1 year and 25% to 2 years. Secondary endpoints are quality of life and functional class.

This trial is a single-arm, 15-patient, sequential, multicentre trial with all eligible patients offered the VentrAssist™. Patients participate in the trial for 2 years; thereafter, they are followed for SAEs and date of death. Inclusion and exclusion criteria are similar to the REMATCH trial [6].

2.4.2. BRACE trial

The 'Better Results and Cost Effectiveness' trial is an open, non-randomised, case-controlled observational trial being conducted at centres in Europe. The BRACE trial is not an 'intention-to-treat' trial and the inclusion criterion is 'need for mechanical left ventricular support'. For the first time, the BRACE study will allow the performance of LVAD therapy to be tested on a homogenous population for whom long-term LVAD therapy, LVAD removal following recovery or heart transplantation are equally valuable outcomes for the patient. The primary endpoint for the BRACE trial is actuarial survival at 2 years.

2.4.3. US BTT feasibility trial

The United States Food and Drug Administration (FDA) approved a 10-patient feasibility trial of the VentrAssist™ for the BTT indication. In late 2006, the FDA approved an extension to the feasibility trial to allow implantation in up to 30 patients (in total) at up to 10 centres.

2.4.4. US BTT pivotal trial

Following successful completion of the US BTT feasibility trial, the US BTT pivotal trial will commence. Data from the US feasibility and pivotal BTT trials will be consolidated to expedite the BTT submission to the FDA.

2.4.5. US DT pivotal trial

This prospective, randomised, controlled trial will use an innovative modular design. Data from this trial will be used in the DTT submission to the FDA.

2.4.6. Additional clinical experience — Australian special access scheme

Individual use of unapproved medical devices is permitted in Australia under the special access scheme (SAS). Under this scheme, 12 patients who did not qualify for the clinical trials or who required the VentrAssist™ following trial completion have been implanted with a VentrAssist™. Detailed clinical data are not collected under the SAS, although SAE reporting is performed as required by Australian post-market surveillance requirements [Active Implantable Medical Devices (AIMD). 90/385/EEC Directive, Annex 2 Section 3.1, Annex 4 Section 3 and Annex 5 Section 3.1. http://europa.eu.int/eur-lex/en/cons-leg/main/1990/en_1990L0385_index.html].

3. Results

3.1. Completed clinical trials: summary of results

3.1.1. Pilot trial

A total of nine patients were implanted with the VentrAssist™. The initial four patients (mean age 73 years) received the device as DT and the latter five patients (mean age 60 years) were high-risk BTT candidates. The patients in this trial were particularly sick, as evidenced by the high percentage who were receiving inotropic agents (100%), hospitalised (89%), in coronary care (67%), in intensive care (33%), ventilated (33%), supported by an intra-aortic balloon pump (22%) or on dialysis (22%).

All patients survived the implantation surgery; three DT and two BTT patients were discharged from the hospital at a median of 65 days (minimum 35 days, maximum 97 days). In two patients, anticoagulation was suspended to facilitate other surgical procedures.

The mean overall survival for the four DT patients was 16 months (minimum 2.4 months, maximum 32.1 months). There were three long-term DT survivors (32.1, 19 and 10.9 months of support). The fourth DT patient died 73 days after implantation, due to respiratory and cardiac arrest with secondary occult abdominal infection.

The BTT patients were implanted for an average of 4.7 months (minimum 0.9 months, maximum 16.7 months). Of the five BTT patients, one received a heart transplant at 3.9 months, one died at 0.9 months from cardiac arrest and two died at 0.9 and 16.7 months from multi-organ failure.

In the final BTT patient, the device was replaced 1.1 months post-implant when increased pump power was unexpectedly encountered. This event was due to a thin film of fibrin deposited on one blade of the pump rotor, associated with a septic, hypercoagulable state. The patient died of intracranial haemorrhage 2.6 months after the VentrAssist™ had been successfully replaced with an alternative LVAD.

The SAE profile revealed no embolic neurological events, minimal sepsis and acceptable device performance in

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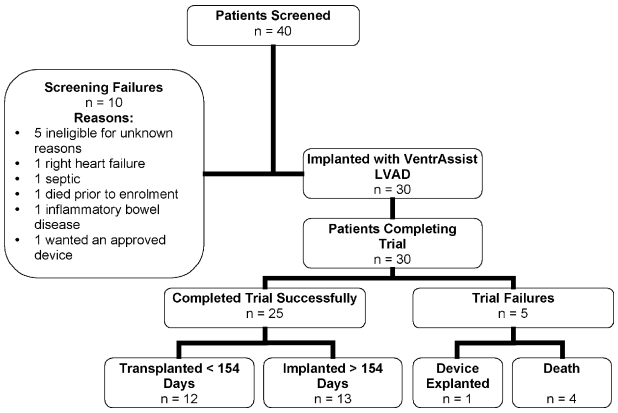


Fig. 4. Disposition of patients in the CE Mark trial.

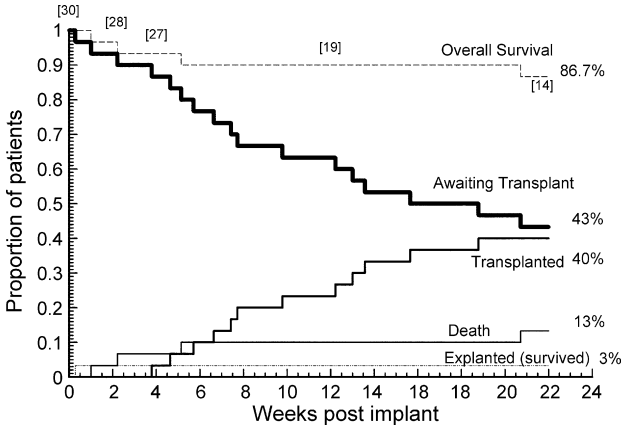


Fig. 5. Outcomes for 30 patients in the CE Mark trial, displayed as a competing outcomes plot.

difficult cases. Overall 30-day mortality was 22%. The trial accumulated a total of 7.3 patient-years of experience.

3.1.2. CE Mark trial: results summary

The results for patients who completed the trial by the database lock date (July 31st, 2006) were analysed for the CE Mark submission and a summary is presented below. Long-term follow-up data from patients in this trial are being collected and will be published separately.

Table 2
Baseline demographics and clinical characteristics of patients in the CE Mark trial (n = 30)

Characteristic	Mean ± standard deviation (minimum—maximum)
Age (years)	51 ± 16 (10—66)
Male sex (%)	80
Ethnicity	
Caucasian	28
Maori/Pacific Islander	2
Primary diagnosis	
Idiopathic cardiomyopathy (%)	63
Ischaemic cardiomyopathy (%)	37
Height (cm)	174 ± 12 (144—195)
Weight (kg)	78 ± 19 (36—117)
Body surface area (m^2)	1.93 ± 0.29 (1.20—2.42)
Female	1.56 ± 0.24 (1.20—1.79)
Male	2.03 ± 0.22 (1.51—2.42)
Body mass index (kg/m^2)	25.8 ± 5.0 (16—36)
Heart rate (bpm)	88 ± 21 (53—135)
Blood pressure	
Systolic (mmHg)	99 ± 14 (75—140)
Diastolic (mmHg)	60 ± 12 (30—86)
Mean arterial pressure (mmHg)	73 ± 10 (52—99)
Pulmonary arterial pressure	
Systolic (mmHg)	48 ± 14 (21—74)
Diastolic (mmHg)	24 ± 8 (11—42)
Pulmonary capillary wedge pressure (mmHg)	24 ± 6 (12—34)
Central venous pressure (mmHg)	13 ± 6 (4—24)
Cardiac index ($l/min/m^2$)	2.1 (0.63—3.7)
Pulmonary vascular resistance (dyne s/m^2)	262 ± 244 (72—899)[a]
Transpulmonary gradient (mmHg)	10 ± 4.57 (3—19)
Left ventricular ejection fraction (%)	17 ± 7 (6—37)
Serum creatinine (mmol/l)	0.121 ± 0.049 (0.06—0.28)

[a] Data available for 10 patients.

3.1.3. Participants

Of 40 patients screened, a total of 30 patients had completed the trial by July 31st, 2006 (Fig. 4). Patients were predominantly male and the mean age was 51 years, which is typical for the BTT population (Table 2). All 30 patients survived the implantation procedure. Of these 30 patients, 21 were discharged from hospital after a mean duration of 43 days. Of these 21 patients, 6 were never readmitted during the study. The remaining 15 patients were readmitted a total of 32 times during the study, for a mean duration of 9 days (minimum 1 day, maximum 32 days) per readmission.

3.1.4. Efficacy

Trial success occurred in 83% of patients (Fig. 5). Of the 25 patients with trial success, 12 patients received a heart transplant between postoperative days 32 and 142. The remaining 13 patients were eligible for a heart transplant at study endpoint (day 154). Of the five patients who did not achieve success, four died during the trial (postoperative days 10, 21, 39 and 148). The fifth patient was explanted on postoperative day 4 and implanted with biventricular assist devices. This patient was later successfully transplanted. Due to inclusion of this patient, the overall survival rate (86.7%) at the trial endpoint was slightly higher than the trial success rate (83%).

The mean device support time as of database lock was 167 days (standard deviation 135 days; minimum 4 days, maximum 486 days). Of note, 6 of the 13 patients remaining on VentrAssist™ support beyond 154 days went on to receive a heart transplant (postoperative days 210, 232, 244, 282, 325 and 486), 6 remained on the transplant waiting list and 1 patient died (postoperative day 372) after an intracranial bleed.

High levels of haemodynamic support were recorded after implantation. The mean cardiac output on the day following implantation was 4.8 l/min, corresponding to a cardiac/pump index of 2.5 $l/min/m^2$ (median 2.3 $l/min/m^2$). These outputs were achieved at low pump speeds (approximately 2000 rpm).

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Table 3
Protocol-defined, device-related serious adverse events (SAEs) in the CE Mark trial

SAE	≤30 days after implant		>30 days after implant	
	# SAEs	# SAEs per patient-month	# SAEs	# SAEs per patient-month
Device-related infection	3	0.11	13	0.17
Local				
Percutaneous lead exit site	1	0.04	5	0.07
Pump pocket	0	0.00	3	0.04
Systemic (sepsis)	2	0.07	5	0.07
Haemorrhage	4	0.14	1	0.01
Thromboembolism (non-neurological)	3	0.11	1	0.01
Neurological event				
Transient ischaemia attack	0	0.00	0	0.00
Stroke	5	0.18	1	0.01
Right ventricular failure	0	0.00	0	0.00
Organ dysfunction				
Renal	1	0.04	0	0.00
Hepatic	0	0.00	0	0.00
Respiratory	0	0.00	0	0.00
Haemolysis	1	0.04	0	0.00
Arrhythmia	0	0.00	0	0.00
Cardiac tamponade	14	0.50	0	0.00
Psychiatric disease	0	0.00	0	0.00
System malfunction				
Outflow cannula leak	2	0.07	0	0.00
Initial pump non-restart following elective stop	1	0.04	0	0.00
Inappropriate alarms	0	0.00	2	0.03
Accidental percutaneous lead transection	1	0.04	0	0.00
Total	35	NA	18	NA

NA, not applicable.

3.1.5. Safety: serious adverse events and deaths

Of the 76 SAEs, 53 were classified as protocol-defined, device-related SAEs and 23 were classified as 'other' as they did not meet the predefined special interest SAE criteria.

The most common protocol-defined, device-related SAE was infection, with 16 events occurring in 11 patients (Table 3). Although cardiac tamponade occurred in nine patients, none of the reported tamponade events was deemed to be caused directly by the device. These events were judged as either technical bleeds (due to lack of haemostasis at surgery) or due to a coagulopathy. All of these tamponade events occurred in the first half of the trial. There were no protocol-defined, device-related SAEs related to hepatic dysfunction, respiratory dysfunction, arrhythmia and psychiatric disease.

No patients died or suffered significant clinical sequelae as a result of pump failure or malfunction. There were two isolated early incidents involving intraoperative outflow cannula leaks that were remedied at the time by the surgeon and, ultimately, by a design change to a seal on the outflow assembly. On day 4 post-implant, one patient developed severe clinical instability with right heart failure and hypotension, despite the device showing high flow estimates. The patient was taken to theatre for a controller exchange and during an elective lead exchange the pump failed to restart. The patient received cardiopulmonary resuscitation and was then implanted successfully with biventricular assist devices. Subsequent examination of the pump revealed a fibrin clot present on the underside of the rotor blade. This situation was likely due to a combination of poor filling of the LVAD due to right heart failure; presumed sepsis may have also played a role. A system design change was implemented to mitigate this issue. Software changes were made to correct two instances of alarms that occurred despite no alarm condition being present. One misadventure was reported with the system in which the percutaneous power lead was accidentally transacted by a mobile X-ray machine on the day of implant. In this case, the pump was successfully replaced as an emergency procedure.

The causes of the 23 'other' device-related SAEs were: ventricular/atrial thrombus that was not identified by computed tomography ($n = 5$), pericardial effusion that did not cause tamponade ($n = 3$), right heart failure where the central venous pressure was <20 mmHg ($n = 1$), haemolysis where the plasma-free haemoglobin was <0.2 g/l for at least two consecutive days ($n = 3$), infections that were related to a previously counted infection ($n = 6$), lethargy ($n = 2$), occlusion of the inflow cannula by cardiac trabeculae ($n = 1$), multi-organ failure ($n = 1$) and chest remaining open for an extended period ($n = 1$).

The four deaths in the trial were due to multi-organ failure ($n = 1$), cerebral haemorrhage ($n = 1$), haemodynamic instability with respiratory dysfunction and positive blood cultures ($n = 1$) and hypotension with an ischaemic bowel ($n = 1$). Investigators determined that only one death was device-related. This death actually resulted from accidental destruction of the percutaneous lead on the day of implantation; urgent device replacement was required and

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performed successfully. The patient died 148 days later following an embolic stroke, with recurrent methicillin-resistant staph aureus pneumonia complicating the attendant bulbar palsy.

3.1.6. Neurological events

Most (80%) patients did not experience a neurological SAE. Of the six patients who experienced 'strokes', two experienced haemorrhagic strokes and four experienced embolic strokes. Of the two patients with haemorrhagic strokes, one died from the event and the other died 29 days after the stroke due to haemodynamic instability/respiratory dysfunction, with positive blood cultures. Of the four embolic stroke patients, three have been transplanted (post-implant days 32, 52 and 325) and one patient is ongoing. The outcomes for these patients were: a complete recovery with no sensory or motor deficit ($n = 2$); some focal neurological deficit but no sensory deficit ($n = 1$); sensory deficit (touch) and no motor deficit ($n = 1$). Most (83%) strokes occurred within the first 30 days following implantation. Strokes occurred at only four of the seven centres.

3.1.7. Renal and hepatic function

Measures of renal function (serum creatinine) and hepatic function (serum bilirubin) improved after implantation. At baseline, 53% of the trial success patients had a recorded history of renal impairment/failure, with a mean serum creatinine of 0.121 mmol/l (upper limit of the normal range). At the last visit, mean serum creatinine was reduced to 0.106 mmol/l, which was within normal limits. Similarly, at baseline, hepatic disorders were noted in 20% of the trial success patients, as indicated by a serum bilirubin concentration of 30 μmol/l (upper limit of the normal range = 20 μmol/l). At the trial endpoint, mean serum bilirubin for these patients decreased to 9 μmol/l, suggesting an improvement in organ function.

3.1.8. Concomitant medication

As expected, medication administration altered considerably following implantation. Use of all cardiac-related medications, except calcium channel antagonists, fell from baseline to last visit. As expected, the use of inotropes, digoxin, diuretics and vasopressors, which were being used before implantation to treat congestive heart failure, was reduced after implantation, commensurate with mechanical support of the circulation and unloading of the left ventricle. Antiarrhythmic and beta-blocker use declined slightly. Only four patients were being treated with inotropes at their last visit and these patients did not achieve trial success (three patients died and one patient was explanted).

3.2. Clinical Development Plan: summary of experience

Considerable progress has been made on the development and execution of the VentrAssist™ Clinical Development Plan (Table 1).

Indeed, the overall clinical experience with the VentrAssist™ now represents the largest experience of any third-generation centrifugal device worldwide. As of January 30th, 2007, 87 patients, who have been entered into clinical trial and clinical experience programmes at 14 centres worldwide, have been implanted successfully with a VentrAssist™ (Table 1). Collectively, these implants have yielded a cumulative support time of more than 43 patient-years and a maximum implant duration of 2.7 years. Of these 87 patients, 27 are ongoing (alive on device), 33 have been transplanted, 1 patient has recovered (device explant with native heart recovery) and 26 have died on the device. The mean support duration for ongoing device patients is 103 days (range 1—832), mean support duration for transplanted patients is 98 days (range 4—486), support duration for the patients with recovery is 377 days and mean support duration for patients who died on device is 49 days (range 2—977).

4. Discussion

This is the first report that summarises the efficacy and safety profile of the VentrAssist™ LVAD, based on data from an international, multicentre clinical trial. This report also presents an update on the ongoing clinical deployment of the VentrAssist™ LVAD across Europe, Australasia and USA, with summaries provided of the completed, ongoing and planned clinical trials.

In the CE Mark trial, the primary efficacy outcome measure (survival until transplant or transplant-eligibility) was achieved by 83% of patients implanted with a VentrAssist™. This result compares favourably with published reports of 65—70% of patients achieving survival to transplant success with other LVADs [13]. The success rate achieved with the VentrAssist™ in the multicentre CE Mark trial is particularly notable given that each centre had to progress through an inevitable 'learning curve'. As an example of the ability for each centre to develop proficiency with the VentrAssist™, tamponade events were confined to the first half of the study.

Morbidity and mortality association with anticoagulation management of patients with mechanical support continues to challenge clinicians. The anticoagulation prophylaxis regimen used in the completed trials was relatively simple; the INR was monitored and acetylsalicylic acid used empirically. The INR level was relatively modest, compared to that recommended for other devices [15,16]. Despite the low levels of anticoagulants used, perioperative bleeding was an issue in early patients, and two of the five deaths in the CE Mark trial were associated with bleeding. Paradoxically, some patients required surgery for non-LVAD related conditions following implant and anticoagulation was suspended, without incident, for periods of up to 1 week. This may indicate that the anticoagulation regimen could perhaps be tailored for individual patients and changing medical conditions, rather than the empirical level of anticoagulation thought to be 'required' for the LVAD.

The ultimate demand for LVADs is thought to be as a permanent form of mechanical assistance. The demand for permanent assistance reflects the mismatch between transplant organ availability and the increasing incidence of heart failure in the aging population, in both developed and developing countries, the increasing prevalence of risk factors for heart failure and the supply—demand imbalance in clinical heart transplantation [17]. In this respect, the results reported thus far after a relatively short follow-up

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period can only begin to indicate whether the VentrAssist™ is suitable for long-term use. However, the low linearised rate of SAEs after implant and the absence of mechanical failure auger well for longer implant durations. Confidence in the VentrAssist™ system has also been strengthened by the fact that none of the early patients in the pilot trial died as a result of device failure or malfunction and also by the successful outcomes in the home discharge cohort. The VentrAssist™ LVAD represents one of the new generation of smaller, potentially more reliable, 'next-generation' LVADs. These LVADs may make long-term circulatory assist available to a wider range of the heart failure population; particularly those who are non-transplant eligible or those with smaller body habitus. The ongoing and forthcoming clinical trials will provide more definitive data regarding the long-term therapeutic potential of the VentrAssist™ LVAD.

5. Conclusion

The number of implants with the VentrAssist™ has now surpassed that of any other third-generation centrifugal device. A pilot trial with the VentrAssist™ showed the potential of the device in a broad spectrum of challenging heart failure patients. A prospective, multicentre, international clinical trial has confirmed the favourable efficacy and safety profile of the VentrAssist™ patients. The Clinical Development Plan for the VentrAssist™ currently comprises seven clinical trials; data from these trials have and will be used in international regulatory submissions and ongoing post-market surveillance studies.

Acknowledgements

The authors would like to acknowledge the patients, their families and medical staff for their involvement in this study.

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Appendix A. Conference discussion

Dr M. Pasic (*Berlin, Germany*): Thank you, Professor Esmore, for a nice presentation and really excellent results. When we see that 6-month survival is 83% after left ventricular assist device implantation, it's really excellent results.

What is the reason for these excellent results?

Dr Esmore: I think I showed from the inclusion data that all the patients were at that 2 l/m^2 or below in regard to their cardiac index.

In the pilot trial, 33% of the patients were on balloon pumps, 2 were ventilated, 2 were on dialysis, of the 9 patients. In the bridge trial, 33% were on balloon pumps and 7% were actually on ECMO at the time of device implant. And all of them have had other procedures, either cardiological or open-heart surgery. So these were not a highly selected group of patients. They're actually quite a complex, what we might call more 'real world' cohort of patients. They were not highly selected in the setting of taking a young bridge group, implanting for 50 or so days and transplanting them. That is not the current challenge to mechanical support devices. So that's why in the pilot trial we went straight to destination therapy and more complex bridge patients to challenge the device. In the CE mark bridge trial we moved towards the more conventional patient and then achieving recovery and the 83% successful bridge rate.

And a point I would also make is this is actually a multicentre trial. Some of the units have only done 3 cases ever of mechanical support and are still getting good results with the VentrAssist LVAD. That means the device is user friendly. I think the units themselves have shown experience in transplantation, et cetera, but not necessarily huge experience in VAD capabilities. But they have been able to actually add mechanical support to their clinical arm successfully with this device.

Dr Pasic: What should be done when you implant left ventricular assist device and you see the patient has right ventricular failure and needs mechanical support for the right ventricle, what should be done?

Dr Esmore: Well, I think we're always mindful of that. The quoted figures are that around about 10% of patients will need an RVAD in volume displacement pumps. And it has been said by informed people the incidence might be twice as high with continuous flow pumps.

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We basically adopt a protocol of using nitric oxide prophylactically. As soon as the patient is ready to come off, we will have nitric oxide(20—40 ppm)inhalation and wean that over a period of days.

I think bleeding is an important surrogate for potential right heart failure, and we have done much to minimize that with antifibrinolytics and hopefully good haemostasis.

So I think that the low RVAD deployment rate is a reflection of the device's capabilities, but also the fact that, as I said, despite this being a multicentre trial, each of the groups have been able to actually optimize right heart function and demonstrate right heart function (RHF) improvement to get the results reported. The overall 30-day mortality was 6%: a couple of patients who died were gravely ill at the time of implant, basically had significant inotropic support for the right side, but were not considered bad enough to be mechanically supported on the right side; they just didn't get over that hill. Perhaps in retrospect they may have benefited from interim RVAD support. One of them developed, I think, mesenteric ischaemia. Another progressed to multi-organ failure and passed away at 30—40 days. But overall, the experience has been favourable. As I said, some of the units have Thoratec, Novacor and Heartmate-1 devices, pumps that are actually said to be easier to use in the setting of avoiding right heart support but with the VentrAssist they still achieved an acceptable incidence of RHF.

Dr J. Lahpor (*Utrecht, The Netherlands*): Very interesting device. You were mentioning that you had moderate thromboembolic rates. Can you elaborate more on that and tell us how many TIAs and strokes there were.

Dr Esmore: In the pivotal trial, I don't think you have this curve here, but in 30 patients there were 4 events. Two of those were during the perioperative period. One patient woke up, he was fine for 24 h and had an event: he was dysarthric for some days, however that settled and he was successfully transplanted. Another patient had a complex early course and developed bleeding, went back to the theatre twice, developed low flows, intracavity thrombus in the L ventricle, and had that opened and evacuated. He had an embolic event, but no associated hemiplegia or hemiparesis, I think it was to the occipital lobe. He was successfully transplanted with no long-term deficit.

Another patient had an intracerebral bleed at day 21. The day before he said, 'I haven't felt this good for 2 years.' And one of the other speakers have mentioned, it developed in the presence of what appears to been therapeutic anticoagulation.

And the only other documented event which I truly believe was embolic was a patient out at 148 days. He had an event producing bulbar palsy; he developed an issue with swallowing and clearing of sputum. The resultant aspiration and refractory MRSA pulmonary sepsis saw support withdrawn.

And even back in the pilot trial, which I'm not specifically reporting, these were 70-year-olds and there were only a couple of neurological events, 1 intracerebral bleed and 1 TIA over 7.5 years cumulative VentrAssist support. These patients on continuous flow support, would sit down at a year and a half out and crack jokes with you. And this was not a 48-year-old bridge on 50 days support, but elderly males on permanent support. In those patients the incidence of neurological events was minimal.

And, of course, any thromboembolic events don't necessarily have to be caused by the LVAD. They can come from the native heart, from the aorta or attendant carotid or intracerebral disease. So cumulative events are very, very small in this high-risk elderly population.

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