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Clinical benefits of partial circulatory support in New York Heart Association Class IIIB and Early Class IV patients☆,☆☆

Bart P. Meyns[a,*], Andre Simon[b], Stefan Klotz[c], Thorsten Wittwer[d], Christian Schlensak[e], Filip Rega[a], Daniel Burkhoff[f,g]

[a] Department of Cardiac Surgery, University of Leuven, Leuven, Belgium
[b] Division of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany
[c] Department of Thoracic and Cardiovascular Surgery, University of Muenster, Münster, Germany
[d] Department of Cardiothoracic Surgery, University of Cologne, Cologne, Germany
[e] Department of Cardiothoracic Surgery, University of Freiburg, Freiburg, Germany
[f] CircuLite, Inc., Saddle Brook, NJ, USA
[g] Department of Cardiology, Columbia University, New York, NY, USA

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Abstract

Objective: Full mechanical support with a left-ventricular assist device (LVAD) is generally limited to end-stage heart-failure patients. We have been studying the safety and efficacy of the partial support Synergy® Pocket Micro-pump as bridge-to-transplant in a less-sick group of patients as a prelude to a study of its use for destination therapy. **Methods:** The CircuLite® Synergy device is implanted via a small right-sided thoracotomy with an inflow cannula in the left atrium and an outflow graft connected to the right subclavian artery without the use of extracorporeal circulation. The micro-pump is the size of an AA battery, sits in the 'pacemaker' pocket subcutaneously in the right clavicular groove and pumps up to 3.0 l min^{-1} from the left atrium to the right subclavian artery. **Results:** The device has been implanted in 27 patients awaiting cardiac transplant (22 males), age 54.8 ± 10.0 years with ejection fraction (EF) 21 ± 6%, mean arterial pressure 73.5 ± 8.8 mm Hg, pulmonary capillary wedge pressure (PCWP) 27.5 ± 7.8 mm Hg and cardiac index (CI) 2.0 ± 0.4 l min^{-1} m^{-2}. Duration of support has ranged from 6 to 281 days. Right-heart catheterization showed significant hemodynamic improvement in the short- and intermediate term after implant, with increases in CI from 2.0 ± 0.4 to 2.8 ± 0.6 l min^{-1} m^{-2} ($p < 0.001$) and reductions in PCWP from 28 ± 6 to 18 ± 7 mm Hg ($p = 0.002$) at an average of 9.5 ± 5.5 weeks. **Conclusions:** The Synergy device provides partial hemodynamic support and its use is associated with significantly improved hemodynamics, thus appearing to interrupt and partially reverse the progressive hemodynamic deterioration typical of end-stage heart failure. Ongoing efforts are aimed at demonstrating additional clinical benefits and continuing to further improve the risk/benefit ratio.

Keywords: Mechanical support; Partial support; Chronic heart failure

1. Introduction

Use of left-ventricular assist devices (LVADs) for treating end-stage heart failure is becoming increasingly accepted among the surgical and cardiology community worldwide. There have been major advances, particularly recently, in improving device durability. However, because LVAD implantation requires a relatively major surgery (sternotomy, cardiopulmonary bypass) that is associated with significant risks of severe adverse events, LVAD use is still generally restricted to the most critically ill patients with a short life expectancy. In such patients, the benefits, in terms of improved survival to transplant and, when used as 'destination therapy' (DT), improved overall survival have been demonstrated [1].

We previously introduced the CircuLite® Synergy® Pocket Micro-pump (CircuLite, Inc., Saddle Brook, NJ, USA), which is a small (AA battery-sized) blood pump that is implanted with an off-pump, right-sided minithoracotomy procedure [2,3]. The device pumps blood from the left atrium to the right subclavian artery at a rate of approximately 3 l min^{-1}. As such, the device provides partial hemodynamic support; part of the blood flow is therefore provided by native heart function. The fundamental concept is that implantation of a smaller device requiring a less-invasive surgery would justify its use in patients, who are less sick than those currently receiving LVADs.

We recently reported on the acute and chronic hemodynamic effects of the device [3], and showed continued

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☆☆ B. Meyns is member of the scientific advisory board for CircuLite. D. Burkhoff is an employee of CircuLite Inc.

* Corresponding author. Address: Department of Cardiac Surgery, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16 344260; fax: +32 16 344616.
E-mail address: Bart.Meyns@uz.kuleuven.be (B.P. Meyns).

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hemodynamic improvements over an average of ~3 months of support, suggesting that the hemodynamic off-loading of the heart by the pump promotes some degree of recovery of native heart function. The purpose of the present report is to summarize the current status of the European multicenter CircuLite Synergy Pocket Micro-pump system.

2. Patients and methods

The CircuLite Synergy device is undergoing a multicenter study in Europe involving the University of Leuven, Belgium; the Hannover Medical School, Hannover, Germany; the University of Muenster, Germany; the University of Cologne, Germany; and the University of Freiburg, Germany.

Patients were included in this study according to the following criteria: age between 18 and 70 years; on the cardiac transplant waiting list with a predicted waiting time >6 months; in the New York Heart Association Class (NYHA) IIIB or IVA despite appropriate treatment with diuretics, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockade and β-blocker as tolerated; ambulatory; not inotropic dependent; and with limitations in the activities of daily living. Exclusion criteria included acute decompensated heart failure, acute post-cardiotomy heart failure, existing thrombus in the left atrium, mechanical mitral or aortic valve, significant aortic regurgitation, severe depressed renal function (serum creatinine > 2.5 mg dl^{-1}), elevated liver enzymes >2 times the upper limit of normal, and contraindication to anticoagulation. The preoperative evaluation also included a right-heart catheterization, a transthoracic echocardiography, and spiroergometry. These data were presented to an independent clinical review committee (CRC) composed of two heart-failure surgeons and one heart-failure cardiologist. The purpose of the CRC was to ensure, to the extent possible from a review of clinical data, that the patient was not 'too sick' to potentially derive clinical benefit from ~3.0 l min^{-1}, and that there were no unforeseen contraindications for implantation.

The Synergy device has been described previously [3] (Fig. 1). In brief, the pump is the size of an AA battery, weighing ~25 g and having an outer body diameter of 14 mm and a length of 49 mm. The pump has a magnetically stabilized, hydrodynamically levitated rotor that spins at 20 000–28 000 rpm. The inflow cannula is made of silicone reinforced with nitinol with a length of 20.5 cm and an inner diameter of 6 mm and has a Dacron cuff on the tip made of titanium to enhance healing. The outflow graft is a 1-mm-thick polytetrafluoroethylene (PTFE) prosthesis with an inner diameter of 8 mm and is trimmed to fit during the implant. A percutaneous lead connects the micro-pump to a rechargeable dual battery pack system and controller.

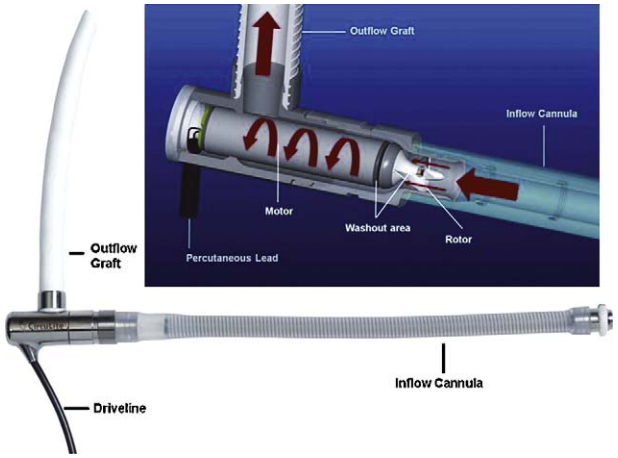

Fig. 1. The CircuLite Synergy Pocket Micro-pump with inflow and outflow graft and a cross-section of the pump (see text for details).

The surgical implant procedure has also been described previously [3]. In brief, after induction of anesthesia, an ~4 cm subclavicular incision is made and the right subclavian artery is isolated. A subcutaneous pocket is formed anterior to the right pectoralis muscle similar to a pacemaker pocket. Thereafter, a 10-cm anterolateral thoracotomy in the 4th right intercostal space is performed. The pericardium is opened with respect to the phrenic nerve, and, after full heparinization, two 4/0 polypropylene purse-string sutures are placed in the left atrium between the insertions of the right upper and lower pulmonary veins. After insertion of a guidewire and confirmation of the position in the left atrium with transesophageal echocardiography, the nitinol-reinforced silicone-inflow cannula is inserted on a trocar over the guidewire using the Seldinger technique and secured with the two purse-string sutures. The proximal end of the inflow cannula is tunneled through the 2nd intercostal space to exit the thorax in the area of the subcutaneous pocket. The micro-pump is then tested and the PTFE outflow graft is sized to the proper length and anastomosed to the subclavian artery. The micro-pump percutaneous lead is then tunneled to exit the body over the right upper quadrant of the abdomen. The micro-pump is deaired retrograde via the subclavian artery and the inflow cannula is connected to the pump. After insertion of a chest tube and drain in the pump pocket, the wounds are closed in layers.

After surgery, the patients are taken to the intensive care unit (ICU) and generally extubated within 4 h. Normally, the patient is kept in the ICU for approximately 1 day following the procedure. Thereafter, the patient is brought to the regular medical ward, ambulated, and physical therapy is initiated.

After appropriate training of patients and family members on how to change the batteries and how to deal with potential controller alarms, patients are discharged home. Hospital discharge has occurred in as little as 10 days, but has generally been between 14 and 20 days (median of 17 days).

Patients were anticoagulated with aspirin (100 mg day^{-1}) and warfarin with a goal to achieve an international normalized ratio (INR) value of 2.5–3.0.

2.1. Statistics

Descriptive statistics are used to summarize data with the results expressed as means with standard deviations, unless otherwise noted. Comparison of data between time points was made with paired *t*-tests. All calculations were performed with Microsoft Excel.

This study was conducted following the Declaration of Helsinki and approval was given by all local institutional human research and ethics committees. All patients provided informed consent to participate in this study.

3. Results

3.1. Patient characteristics

Patient characteristics of the 27 patients currently included in the study are summarized in Table 1. For comparison, similar data reported for the HeartMate II bridge-to-transplant population [4] are also provided. Patients were mainly male with ischemic cardiomyopathy. One-third of the patients had prior cardiac operations with sternotomy (eight coronary artery bypass grafting (CABG), including one CABG plus aortic valve replacement, one CABG plus mitral valve replacement, and one Dor procedure). A total of 44% of the patients were in permanent atrial fibrillation and more than two-thirds had an implantable cardioverter defibrillator. Hemodynamic and echocardiographic baseline parameters confirm an end-stage heart-failure population with reasonably well-preserved end-organ function (Table 2), and were remarkably similar to those reported for the HeartMate II bridge-to-transplant population [4]. Medication use was appropriate for end-stage heart failure (Table 3). The main differences with respect to the HeartMate II population [4] are that the current population was more frequently treated with β-blockers, ACE inhibitors or angiotensin receptor blockers, and less frequently treated with inotropic agents.

To date, the total experience includes 8.6 patient-years of support with an average duration of support of 118 days (median 122, range: 6–281 days).

3.2. Acute and chronic hemodynamic effects for partial mechanical support

At 24 h after surgery, estimated pump flow was 2.97 ± 0.39 l min^{-1} with a range of 2.3–3.5 l min^{-1}. With this additional pump output, hemodynamic improvements assessed at 24 h following surgery included an increase of the total cardiac index (CI) (from 2.0 ± 0.4 to 3.3 ± 0.9 l min^{-1} m^{-2}, $p < 0.001$), and decreases of the pulmonary systolic pressure (from 55 ± 15 to 53 ± 14 mm Hg, $p = 0.34$) and pulmonary diastolic pressure (from 27 ± 9 to 21 ± 5 mm Hg, $p = 0.002$). At an average follow-up of 9.5 ± 5.5 weeks, data available from 12 patients showed

Table 1. Patient demographic data ($n = 27$) compared to those for HeartMate II ($n = 133$) [4].

	CircuLite		HeartMate II	
	Mean	SD	Mean	SD
Age (years)	54.8	10.0	50.1	13.1
BSA (M2)	1.9	0.2	2.0	0.3
BMI (kg/M2)	25.6	3.4	26.8	5.9
	N	%	*N*	%
Gender				
Male	22	82%	105	79%
Female	5	19%	27	21%
CHF etiology				
ICM	22	82%	49	37%
DCM	5	19%	84	63%
INTERMACS class				
2	1	4%		
3	1	4%		
4	25	93%		
Cardiovascular history				
Diabetes mellitus	6	22%		
Atrial fibrillation	12	44%		

BMI, body-mass-index; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy.

Table 2. Baseline functional data ($n = 27$) compared to those for HeartMate II ($n = 133$) [4].

	CircuLite		HeartMate II	
	Mean	SD	Mean	SD
Hemodynamics				
HR (bpm)	79	15	92	18
SBP (mm Hg)	98	13	96	15
DBP (mm Hg)	63	8	62	11
MAP (mm Hg)	73	9	73[a]	12
CVP (mm Hg)	13	5	13	8
PAP (S, mm Hg)	54	15	53	14
PAP (D, mm Hg)	27	9	28	9
PAP (M, mm Hg)	37	9	36	10
PCWP (mm Hg)	27	8	26	8
CO (l min^{-1})	3.8	0.8	4.0[a]	1.2
CI (l min^{-1}/M2)	2.0	0.4	2.0	0.6
SVR (Wood units)	15.1	4.4	14.9[a]	3.8
PVR (Wood units)	2.6	1.2	3.0	1.5
Echocardiography				
EF (%)	21	6	16	6
LVEDD (cm)	11.3	14.9	n/r	
MR (grade)	1.7	0.7	n/r	
AR (grade)	0.3	0.5	n/r	
Peak VO_2 (ml kg^{-1} min^{-1})	9.8	2.4	n/r	
Laboratory findings				
BNP (pg ml^{-1})	6273	5422	n/r	
Sodium	136	5	133	5
Creatinine (mg dl^{-1})	1.4	0.5	1.4	0.5
Estimated CrCl	67.5	23.1	75.1	36.8
Total bilirubin (mg dl^{-1})	0.9	0.6	1.2	0.8
LDH (mg dl^{-1})	344	166	376	371
AST (U l^{-1})	28	12	104	287
ALT (U l^{-1})	37	22	67	168

n/r, not reported; MAP, mean arterial pressure; CVP, central venous pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance, PVR, pulmonary vascular resistance; EF, ejection fraction; LVEDD, left-ventricular end-diastolic diameter; M%R, mitral regurgitation; BNP, brain natriuretic peptide; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a] Values estimated from reported cardiac output and pulmonary pressures.

Table 3. Baseline medical treatments ($n = 27$) compared to those for HeartMate II ($n = 133$) [4].

	CircuLite		HeartMate II	
	N	%	*N*	%
Treatments				
ICD	19	70%	98	74%
CRT	5	19%	64	48%
Diuretic	27	100%	109	82%
β-Blocker	21	78%	51	38%
ACE inhibitor	19	70%	40	30%
ARB	5	19%	7	5%
Aldactone	20	74%	n/r	
Aspirin	13	48%	40	30%
Warfarin	4	15%	2	2%
Statin drug	14	52%	n/r	
Inotrope(s)	2	7%	118	89%

n/r, not reported; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 4. Comparison of hemodynamic parameters at baseline and after an average (±SD) of 9.5 ± 5.5 weeks of follow-up.

Parameter	Baseline Mean ± SD	Follow-up Mean ± SD	*p*
Mean arterial pressure (mm Hg)	74 ± 10	81 ± 9	0.11
Pulmonary wedge pressure (mm Hg)	28 ± 6	18 ± 7	0.002
Cardiac index (l min^{-1} m^{-2})	2 ± 0.4	2.8 ± 0.6	<0.001
Pulmonary systolic pressure (mm Hg)	59 ± 12	45 ± 9	0.01
Pulmonary vascular resistance (Wood units)	3.1 ± 1.4	1.9 ± 0.9	0.01
Systemic vascular resistance (Wood units)	20 ± 6	16 ± 4	0.006

Table 5. Rates of key serious adverse events reported in the Synergy study compared to those reported for HeartMate II [4]. Numbers are events per patient-year and are reported separately for the first 30 days (the perioperative events) and for >30 days.

Adverse event category	Event rate per patient-year			
	CircuLite (*N* = 28)		HeartMate II (*N* = 133)	
	0–30 days	>30 days	0–30 days	>30 days
Bleeding – all reported events	6.95	0.52	12.74	0.91
Driveline or pump pocket infection	0.46	0.13	0.00	0.45
Local infection, not device related	0.46	0.52	3.63	0.64
Sepsis	0.46	0.13	1.77	0.39
Renal failure	0.46	0.00	1.47	0.08
Hemolysis	0.00	0.39	0.29	0.02
Hepatic dysfunction	0.46	0.00	0.20	0.02
Stroke	0.46	0.13	0.69	0.08
TIA	0.46	0.26	0.20	0.08
Worsening left heart failure	0.00	0.52	n/r	0.00
Hepatic dysfunction	0.46	0.00	0.20	0.02
Right-heart failure	0.00	0.13	1.57	0.12
Pleural effusion	0.46	0.13	n/r	0.00
Total	14.82	5.87	30.21	3.77

n/r, not reported.

sustained improvements in all parameters, including clinically and statistically significant reductions in pulmonary and arterial resistances (Table 4).

3.3. Adverse events

Given the baseline characteristics for patients entering this trial, severe adverse events (SAEs) were expected and have been similar in nature to those reported for LVADs. However, at this initial point, it is encouraging that the frequency of SAEs experienced by the Synergy patients, particularly in the first 30 days following surgery, appears to occur at a significantly reduced rate to those reported for other LVADs (Table 5). Reported SAEs have included bleeding requiring transfusion or return to the operating room; infections (including sepsis from any cause, driveline or pocket infections, and infections not necessarily related to the device); and strokes. Overall, including all reports for Synergy patients, SAEs during the first 30 days occurred at approximately half the rate as that reported for HeartMate II (14.8 events patient-$year^{-1}$ vs 30.2 events patient-$year^{-1}$, respectively) [4]. SAEs occurring after the first 30 days for Synergy occurred at a slightly higher rate compared with HeartMate II (5.9 events patient-$year^{-1}$ vs 3.8 events patient-$year^{-1}$, respectively) [4]; these numbers include pump thrombosis or exchange for any reason as an adverse event, which accounted for about a third of the events reported after the first 30 days of support.

4. Discussion

The Synergy device was designed with the purpose of providing a smaller, less invasively implantable assist device that would benefit patients with severe symptomatic heart failure with no other treatment option, who were not yet sick enough to justify implantation of a full-support ventricular support device. In this regard, the comparison of the current patients to those implanted in the HeartMate II bridge-to-transplant study [4] is very interesting. The patients had similar baseline demographic characteristics and, most surprisingly, almost identical hemodynamic profiles and end-organ function. The major difference was that these baseline hemodynamic characteristics were observed in the Synergy patients with greater use of standard heart-failure therapy (i.e., more ACE inhibitor, angiotensin receptor blockade (ARB), and β-blocker use) and less inotropic support than in the HeartMate II population. This is consistent with the notion that development of intolerance to standard heart-failure medical therapy (which usually manifests as a gradual reduction of drug dosing by the treating clinician), along with worsening symptoms, may identify patients who are approaching a stage where early intervention with a device such as the Synergy device should be considered.

Original theoretical work indicated [5], and early clinical experiences [2,3,6] supported the hypothesis that, when applied prior to significant end-organ dysfunction and becoming inotrope dependent, partial support with the Synergy device can indeed provide adequate support and

interrupt the progressive hemodynamic deterioration characteristic of severe heart failure. The currently reported average 3-month follow-up data on 12 patients supports this hypothesis by showing sustained improvements in all hemodynamic parameters, including clinically and statistically significant reductions in pulmonary and arterial resistances (Table 4).

The other important hypothesized feature of the Synergy device was that its lesser invasive nature (small size, no sternotomy, and no cardiopulmonary bypass) would be associated with less adverse events in the short- and long term. Upon comparing the reported events to those of the HeartMate II, this hypothesis continues to be confirmed for the first 30 days following surgery. In the longer term, there are a slightly more number of events currently observed with the Synergy device. These events are mainly due to pump thromboses requiring devices exchanges. The sponsor has made modifications to the Synergy device that reduced, but did not eliminate, the rate of thrombosis. Ongoing efforts are underway to further reduce such events. It is important to note that, in the event a pump needs to be exchanged, it can be accomplished in a relatively simple 90-min closed-chest procedure that is similar to a pacemaker exchange.

Development of right-heart failure is of significant concern with the use of full-support LVADs. As shown in Table 5, this has not emerged as a significant factor with the current partial-support device. Interestingly, preoperative pulmonary artery systolic pressures have ranged between 26 and 90 mm Hg, indicating a wide range of right-ventricular function at baseline. It could be argued that, in contrast to a full-support VAD, which can abruptly increase cardiac output to 6–7 l min^{-1} and acutely overload the right ventricle, the acute increase in cardiac output resulting from the Synergy system is of the order of only 1.0–1.5 l min^{-1}. Although there is currently limited experience and many factors contribute, final conclusions about this should await sufficient experience. Nevertheless, it could be that concerns about development of right- heart failure will be less with a partial-support device.

The long-term goal for using the Synergy pump is for DT. Although only relatively short-term clinical data are so far available, durability testing of the device under conditions that mimic *in vivo* use (e.g., temperature, fluid viscosity, and pulsatile pressure head at physiological levels) is quite advanced. Nine pumps have been running in a mock circulatory loop for 30 months. These pumps are disassembled and evaluated at monthly intervals with no evidence of significant wear on the pivot bearing. These finding indicate that, from a mechanical perspective, the current pump design is robust and should pose no obstacle for pump use for long-term DT.

5. Conclusion

For the majority of patients studied thus far, partial mechanical support with the CircuLite Synergy Pocket Micropump interrupts the progressive hemodynamic deterioration typical of end-stage heart failure. Overall, the rate of SAEs is lower than reported for a full-support VAD, especially during the 30-day perioperative period. Thus, the available data support the concept that earlier intervention with a smaller, partial-support device implanted with a lesser invasive procedure can provide substantial clinical benefits to patients with severe heart failure not yet sick enough to justify implantation of a full-support left-ventricular support device.

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Appendix A. Conference discussion

Dr G. Gerosa (*Padova, Italy*): I was not lucky enough to receive the manuscript in advance to discuss this paper. I would like to elaborate a little bit, because I believe you stated at the end of your abstract that we should anticipate timing of insertion with this device, but I would like to say that we probably should anticipate timing of insertion with all LVADs currently available.

Nevertheless, you have shown roughly a 14% death rate. Can you elaborate a little bit on the deaths of those patients? And then you had a nearly 50% pump exchange. Can you elaborate on that as well? And the final question, do you think we could use this device as an RVAD in those 10–20% of patients in which right-ventricular failure after LVAD insertion occurs?

Dr Meyns: The first question was to elaborate on the deaths. Four patients died, two of sepsis infection; every case is individually sad, of course. One, for instance, was at home, came back to have his catheterization according to the protocol and had an infection from the catheterization itself and died afterwards. Two patients died of stroke. One of those was a patient that left the study, stopped taking his Coumadin, and then came back three months later with a completely thrombosed system and stroked. So these were the deaths.

Concerning the pump thrombus, that, of course, limits the durability of the pump, and I think that the durability of the pump in a bridge-to-transplant trial might be acceptable. If we move this forward towards destination therapy, which is the goal, the durability of the pump needs to be prolonged. An easy way to do that is, for instance, to use an alternating speed algorithm to make sure that the pump is washed out, which is not what we are doing today, and which in the meantime in the animal trials has shown that the pump durability is prolonged by doing that. So this is definitely what is needed in order to bring this therapy from bridge to transplantation to destination therapy.

And I didn't get your third question.

Dr Gerosa: Could you use this device as an RVAD?

Dr Meyns: Only as an LVAD. It runs from the left atrium to the subclavian artery. So it only supports the left heart, and so far we have no experience with supporting the right heart.

Dr T. Wahlers (*Cologne, Germany*): Since we have learned quite a lot with the application of the device, what is your current recommendation for anticoagulation, since 50% failed and stroke was a major issue in your patients?

Dr Meyns: That is a very good question. The protocol said that we would use Coumadin and low dose of aspirin, and it is logical to assume with the given rate to increase the anti-aggregation protocol, that is logical to do, and I think that is the recommendation, yes.