

Increased pulsatility index is associated with adverse outcomes in left ventricular assist device recipients

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Abstract

Aims Recipients of left ventricular assist devices (LVAD) are exposed to increased risk of adverse clinical events. One of the potential contributing factors is non-pulsatile flow generated by LVAD. We evaluated the association of flow patterns in carotid arteries and of increased arterial stiffness with death and cerebrovascular events in LVAD recipients.

Methods and results We analysed data from 83 patients [mean age 54 ± 15 years; 12 women; HeartMate II (HMII), *n* = 34; HeartMate 3 (HM3), *n* = 49]. Pulsatile and resistive indexes, atherosclerotic changes in carotid arteries (measured by duplex ultrasound), and arterial stiffness [measured by Endo-PAT 2000 as the augmentation index standardized for heart rate (AI@75)] were evaluated 3 and 6 months after LVAD implantation. Sixteen patients died during follow-up (27.3 months; interquartile range 15.7–44.3). After adjusting for the main variables examined, the pulsatility index measured at 3 months was positively associated with increased hazard ratios (HR) for death and cerebrovascular events [HR 9.8, 95% confidence interval (CI) 1.62–59.42], with HR increasing after adding AI@75 to the model (HR 18.8, 95% CI 2.44–145.50). In HM3 recipients, HR was significantly lower than in HMII recipients (HR 0.31, 95% CI 0.11–0.91), but the significance disappeared after adding AI@75 to the model (HR 0.33, 95% CI 0.09–1.18).

Conclusions The risk of death and cerebrovascular events in LVAD recipients is associated with increased pulsatility index in carotid arteries and potentiated by increased arterial stiffness. The same risk is attenuated by HM3 LVAD implantation, but this effect is weakened by increased arterial stiffness.

Keywords Mechanical circulatory support; Pulsatility index; Clinical events

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Introduction

Use of the left ventricular assist device (LVAD) in patients with end-stage heart failure is considered a standard treatment in routine care.¹ Although it undoubtedly results in improved survival and life quality, LVAD recipients are nonetheless exposed to particular adverse clinical events.^{2–4}

Therefore, early identification of patients at high risk of serious clinical events is of great importance. The pathophysiology of vascular changes in LVAD recipients has been the

subject of intensive research^{5–8} but is still not fully understood. The data are surprisingly sparse on the role of structural changes and blood flow patterns detectable in the peripherally located arteries of LVAD recipients. One potential method for assessing risk of future vascular and other complications in LVAD recipients is simple, non-invasive duplex ultrasound examination of the carotid arteries. According to several studies, LVAD has definitive impacts on carotid arterial structure and blood flow.^{9,10} However, impacts on clinical outcomes have yet to be evaluated and, as one parallel study has revealed, factors closely associated

with flow pulsatility such as arterial stiffness may in fact contribute to increased risk.¹¹

On the basis of these assumptions, we conducted a prospective single-centre study to examine the association of morphological changes and flow patterns in carotid arteries with death and cerebrovascular events after LVAD implantation. In the present study, we analysed potential association of pulsatile and resistive indexes in carotid arteries with stroke-free survival. In addition to that, we analysed if these associations are modified by atherosclerotic changes and arterial stiffness.

Methods

This single-centre prospective observational study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practices, and the International Organization for Standardization (ISO 14155:2020, Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice). The study protocol was approved by the regulatory boards and ethics committees of the participating institutions. All patients were required to provide their written informed consent prior to inclusion in the study.

From 2014 to 2018, a total of 83 patients were enrolled in the study (mean age 54 ± 15 years; 12 women). All patients were diagnosed with end-stage heart failure and met the institutional criteria for LVAD implantation performed using the HeartMate II (HMII) axial continuous-flow LVAD (Abbott, Abbott Park, Illinois, USA & St. Jude Medical, Pleasanton, California, USA) ($n = 34$) or the HeartMate 3 (HM3) fully magnetically levitated centrifugal-flow LVAD (Abbott, Abbott Park, Illinois, USA) ($n = 49$) for an indicated bridge to heart transplantation or destination therapy. HMII was implanted via the subcostal approach in 7 patients and via sternotomy in 27 patients. HM3 was implanted via left anterolateral mini-thoracotomy and via upper J mini-sternotomy in 12 patients and via full median sternotomy in 37 patients. A short-term mechanical circulatory support was administered in seven patients (six HMII and one HM3) preceding implantation of the durable LVAD.

Heparin was continuously and intravenously applied as a bridge until reaching the international normalized ratio (INR) target anticoagulation range for warfarin. The INR anticoagulation therapy target post-implantation was 2–2.5 for HMII and 2.0–2.7 for HM3. Aspirin (100 mg per day) was administered only in HM3 recipients. In 15 HM3 recipients who had taken part in a previous study, the INR anticoagulation therapy target was adjusted to 1.5–1.9.¹²

Baseline characteristics, medical history, laboratory measurements, and medications were collected. Ultrasound and arterial stiffness measurements were performed at pre-

specified time-points 3 and 6 months after implantation (± 15 days). The median follow-up time was 27.3 months [interquartile range 15.7–44.3]. Examiners (JP and PW) were blinded to the clinical and laboratory data, including the type of LVAD used.

Carotid parameters including pulsatility and resistive indexes

Carotid arteries were examined using the Toshiba APLIO 50 XV (Tochigi, Japan) ultrasound system with a 7.5–10 MHz linear array transducer. Patients were examined in the supine position. With the neck rotated 45° in the direction opposite to the site being examined, a transducer was placed just above the right clavicle.

The presence of atherosclerosis was classified using the Belcaro score,¹³ which evaluates the degree of pre-clinical atherosclerosis based on ultrasound criteria, graded from the normal appearance of intima-media thickness (Class I) to plaque with stenosis >50% (Class IV). The mean Belcaro score for the sites of the left and right carotid arteries was used for subsequent analysis. More detailed description of the carotid examination procedure is described at supporting information.

Ultrasound examinations of the right carotid artery were completed in 83 individuals, with a Belcaro score established for both sites in all participants. To assess potential differences between the right and left carotid arteries, in 39 (at 3 months) and 21 (at 6 months) individuals, flow patterns were established on both sides.

Establishment of arterial stiffness

Arterial stiffness was measured using Endo-PAT 2000 software (Endo-PAT 2000®, Itamar Medical, Israel) as the augmentation index (AI).^{14,15} This technique involves the use of a finger probe to assess digital volume changes accompanying pulse waves. AI was calculated using a computerized automated algorithm (software version 3.1.2) from peripheral arterial tone pulses recorded during the baseline period. Lower AI values (including negative values) reflect better arterial elasticity. The AI result is used to indicate sex-matched, non-selective populations. For subsequent analysis, we used AI values normalized to a heart rate of 75 bpm (AI@75). Detailed description of the entire procedure is described at supporting information.

Diagnosis of clinical events and stroke

Causes of death and cerebrovascular events were established by clinical assessment and/or autopsies

according to standard procedures, with the exception of two cases of sudden death. Presence and type of stroke were confirmed by clinical assessment and positive computed tomography (CT) scans. In two patients, discrepancies between positive clinical signs and negative CT scans were detected, with data on these patients added to the clinically assessed analysis. In addition, one fatal haemorrhagic stroke was established post-mortem during autopsy.

Statistical methods

Data are expressed as mean \pm standard deviation, median (interquartile range), or frequency (percentage). Longitudinal changes in carotid haemodynamics and the lumen were analysed using a paired *t*-test. Differences between HMII and HM3 patients were compared using the independent-samples *t*-test, Mann–Whitney U-test, or χ^2 test as appropriate. The Kaplan–Meier plot was used to visualize stroke-free survival, with differences between groups analysed using the log-rank test. Cox regression was used to determine factors associated with stroke-free survival. The proportional hazard assumption was tested and fulfilled for all regression models. All statistical tests and confidence intervals (CI) were two-sided using a significance level of 0.05. The Kolmogorov–Smirnov test and the Shapiro–Wilk test were used to test the normality of the data.

Results

Study parameters and changes during follow-up

All 83 patients were Caucasian (mean age 54 ± 15 years; 12 female patients) and indicated for implantation of HMII ($n = 34$) or HM3 ($n = 49$). Ischaemic aetiology of heart failure was present in 38 patients (45.8%), with a bridge to transplant the predominant indication for implantation (73.5%). In the majority (78.3%) of patients, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profiles were 2–4 (Table 1). HM3 recipients were typically older, displayed increased prevalence of hypertension and atrial fibrillation, and had higher brain natriuretic peptide concentrations compared with patients implanted with HMII (Table 1). Three months after implantation when duplex ultrasound of the carotid arteries and AI measurements were performed, patients with HM3 had more advanced carotid atherosclerosis, a moderately higher diameter of the lumen of the carotid arteries, moderately higher PI and RI and significantly lower AI@75 (Table 2).

Between 3 and 6 months, no significant changes in PI, RI, or lumen diameter (mean changes) were observed. None of the other study parameters changed significantly during this period. No differences between the HMII and HM3 groups were observed for the above parameters. We observed no differences between the right and left carotid arteries (measured in 39 patients at 3 months) regarding main parameters under study (PI and RI), and no haemodynamically significant

Table 1 Characteristics of patients prior to implantation according to the type of left ventricular assist device used

Variable	All patients, $n = 83$	HeartMate II, $n = 34$	HeartMate 3, $n = 49$	HMII vs. HM3, <i>P</i>
Women, n (%)	12 (14.5)	5 (14.7)	7 (14.3)	0.99
Age (years)	54.4 ± 14.9	48.3 ± 15.6	58.6 ± 12.9	0.002
Body mass index (kg/m^2)	26.5 ± 4.8	26.3 ± 4.9	26.6 ± 4.7	0.78
Arterial hypertension, n (%)	37 (44.6)	12 (35.3)	25 (51.0)	0.08
Ischaemic aetiology of heart failure, n (%)	38 (45.8)	14 (41.2)	24 (50.0)	0.43
History of thromboembolic disease (%)	6 (7.2)	2 (5.9)	4 (8.2)	0.99
History of atrial fibrillation (%)	42 (50.6)	12 (35.3)	30 (61.2)	0.02
Diabetes mellitus, n (%)	18 (21.7)	7 (20.6)	11 (22.4)	0.84
Active smoking, n (%)	10 (12.0)	6 (17.6)	4 (8.3)	0.30
INTERMACS 1/2/3/4/5, n (%)	4/15/35/15/14 (5/18/42/18/17)	3/10/13/4/4 (9/29/38/12/12)	1/5/22/11/10 (2/10/45/22/20)	0.11
Systolic blood pressure (mmHg)	106.1 ± 13.4	106.5 ± 11.7	105.8 ± 14.5	0.81
Ejection fraction of left ventricle assessed by echocardiography (%)	18.7 ± 5.9	19.2 ± 8.1	18.4 ± 3.7	0.53
Brain natriuretic peptide factors (BNP) (ng/L)	1610 (791–2845)	2080 (1003–2964)	1436 (682–2291)	0.06
Lactate dehydrogenase (LDH) units	4.0 (3.3–5.9)	4.6 (3.7–7.8)	3.7 (3.2–5.1)	0.78
Glycaemia (mmol/L)	5.8 ± 1.7	5.8 ± 1.8	5.9 ± 1.7	0.69
LDL cholesterol (mmol/L)	2.09 ± 0.76	2.06 ± 0.86	2.11 ± 0.68	0.81

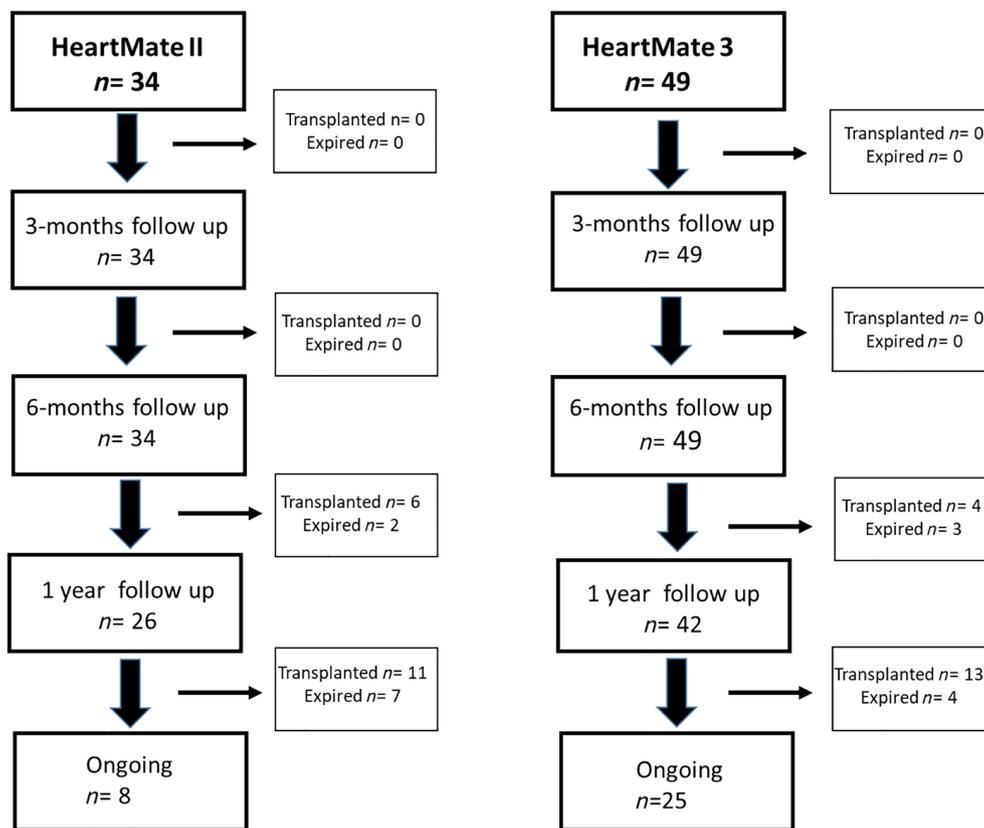
INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Data expressed as mean \pm SD.

Table 2 Characteristics of patients 3 months after implantation according to the type of left ventricular assist device used

Variable	All patients, <i>n</i> = 83	HeartMate II, <i>n</i> = 34	HeartMate 3, <i>n</i> = 49	HMII vs. HM3, <i>P</i>
Aortic valve: open/partially closed/closed (%)	60/12/11 (72.3/14.5/13.3)	26/6/2 (76.5/17.6/5.9)	34/6/9 (69.4/12.2/18.4)	0.23
Belcaro score	2.5 (1.5–3.0)	2 (1–3)	2.5 (2–3)	0.04
Lumen of carotid arteries	6.02 ± 0.78	5.81 ± 0.74	6.11 ± 0.80	0.09
Pulsatility index of carotid arteries	0.50 ± 0.24	0.44 ± 0.18	0.54 ± 0.26	0.05
Resistive index of carotid arteries	0.36 ± 0.12	0.33 ± 0.09	0.38 ± 0.13	0.04
Augmentation index (AI@75)	22.5 (2–39.0)	31 (22–43)	11 (–12–29)	0.001

Data expressed as mean ± SD

Figure 1 Flow chart of patients under study according to the type of left ventricular assist device.

carotid stenosis was detected over the whole course of the study.

Incidence and characteristics of clinical events

Out of the 83 patients enrolled in the study, 16 died (HMII *n* = 9, HM3 *n* = 7). Regarding cause of death, 4 patients died due to stroke: 1 ischaemic and 3 haemorrhagic (HMII *n* = 1/haemorrhagic, HM3 *n* = 3/1 ischaemic, 2 haemorrhagic). Five patients died due to sepsis (HMII *n* = 3, HM3 *n* = 2), 3 died due to multiorgan failure (HMII *n* = 2, HM3 *n* = 1), 2 died due to right heart failure (HMII *n* = 1, HM3 *n* = 1), and 2

due to sudden death of unknown cause (all implanted with HMII). The first fatal event occurred 233 days after implantation of LVAD (HM3). In total, 34 patients were transplanted (HMII *n* = 17, HM3 *n* = 17) (Figure 1).

Four patients (HMII *n* = 2, HM3 *n* = 2) suffered from non-fatal ischaemic strokes (Modified Rankin Scores at the time of stroke: 2, 4, 4, and 5). Fifteen patients experienced adverse events related to non-surgical bleeding: seven in the gastrointestinal tract (HMII *n* = 1, HM3 *n* = 6), three in the urinary tract (HMII *n* = 2, HM3 *n* = 1), two in the respiratory tract (all HM3), and three in other locations (all implanted with HM3). In four patients, LVAD was replaced due to thrombosis (HMII *n* = 3, HM3 *n* = 1). One patient with HMII and six

patients with HM3 were transiently treated by RVAD (mean duration of 30.6 days) shortly after implantation of LVAD, which was successfully removed in all patients. In two patients, HMII was replaced by HM3: in one patient due to a technical fault with pump stop alarms, and in the other patient due to pump thrombosis.

Association between carotid artery haemodynamic/atherosclerotic parameters and death and strokes

In patients with PI above the median at 3 months, the Kaplan–Meier curve indicated lower stroke-free survival. However, using the log-rank test, this difference was not statistically significant (log-rank $P = 0.19$, Figure 2). Additionally, in patients who developed stroke, the mean PI at 3 months was higher than in those free of stroke (0.82 ± 0.45 vs.

0.46 ± 0.18), albeit of borderline statistical significance ($P = 0.06$). In patients with HMII, stroke-free survival was lower than in patients with HM3 as indicated by the Kaplan–Meier curve, but again the difference was not statistically significant (log-rank $P = 0.14$, Figure 3).

Nevertheless, when using Cox regression and considering age, sex, atrial fibrillation, and HM type, PI was a strong predictor of stroke [hazard ratio (HR) 9.81, 95% CI 1.62–59.42] and HM3 implantation was associated with a protective effect (HR 0.31, 95% CI 0.11–0.91). When arterial stiffness (AI@75) was added to the statistical model, we detected a more robust effect of higher PI on the risk of death and cerebrovascular events (HR 18.80, 95% CI 2.44–145.50) and a weakening of the protective effect of HM3 (HR 0.33, 95% CI 0.09–1.18) (Table 3).

Discussion

Our main finding is that a higher pulsatility index measured in carotid arteries 3 months after LVAD implantation was independently and strongly associated with increased incidence of death and cerebrovascular events. This association became even stronger when arterial stiffness was taken into account. Moreover, we found no association between morphological atherosclerotic changes in the carotid arteries and incidence of clinical events or the pulsatility index, the latter parameter being mutually independent of arterial stiffness.

The effect of particular blood flow patterns in carotid arteries on clinical events including strokes in LVAD recipients were to our best knowledge not studied or published. For this reason, we discuss data from studies of vasculature including carotid arteries after LVAD implantation and from experimental studies of LVAD.

Few studies have focused on vascular changes, including the carotid arteries, after LVAD implantation. In a cross-sectional study of 16 chronic LVAD patients,

Figure 2 Impact of pulsatile index measured in the right carotid artery on stroke-free survival in patients treated by left ventricular assist device (Kaplan Meyer).

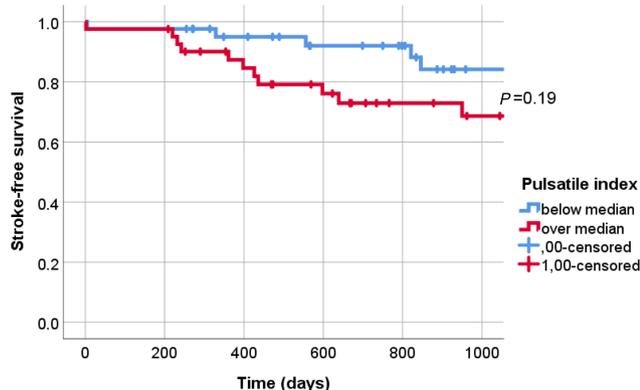


Figure 3 Impact of left ventricular assist device type (HeartMate II vs. HeartMate 3) on stroke-free survival (Kaplan Meyer).

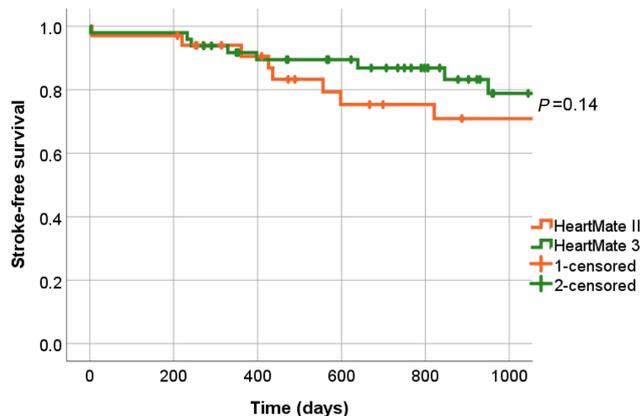


Table 3 Multivariate Cox regression of factors associated with stroke-free survival including (Model 1) and excluding (Model 2) arterial stiffness

Variable	HR	95% CI	P
Model 1			
Age	0.99	0.96–1.04	0.97
Sex (female)	0.50	0.09–2.70	0.42
Pulsatility index	9.81	1.62–59.42	0.01
HeartMate 3 vs. HeartMate II	0.31	0.11–0.91	0.03
Atrial fibrillation	2.03	0.66–6.25	0.22
Model 2			
Age	0.99	0.96–1.03	0.78
Sex (female)	0.43	0.08–2.38	0.33
Pulsatility index	18.8	2.44–145.50	0.005
HeartMate 3 vs. HeartMate II	0.33	0.09–1.18	0.09
Atrial fibrillation	1.96	0.59–6.55	0.27
Augmentation index (AI@75)	1.02	0.98–1.05	0.25

CI, confidence interval; HR, hazard ratio.

continuous-flow LVAD support was associated with lower carotid artery compliance, distensibility, and incremental elastic modulus.¹⁶ Another study focused on carotid arteries in 13 patients revealed that while peak systolic velocity was diminished after LVAD placement in both the internal and common carotid arteries, mean flow velocities in the same arteries remained stable.¹⁷ Moreover, further piece of evidence of vascular changes after LVAD implantation stems from our study describing changes in circulating endothelial progenitor cells and stem cells, which are both considered markers of vascular impairment in LVAD recipients.^{5–7} In these studies, changes in these markers indicated that improvements in haemodynamic parameters may have negated the deleterious effects of non-pulsatile flow during the first 3 months, but pathological activation of the vasculature and endothelium was detected 6 months. These findings are consistent with another study on 83 LVAD patients, where patients with optimized haemodynamics had greater freedom from haemocompatibility-related adverse events.¹⁸ Several other human studies have described the unfavourable effects of LVAD on the aortic wall^{10,17,19} and peripheral vasculature.²⁰ In addition, an experimental study of 23 calves, comprising a detailed analysis of vascular changes caused by a novel partial-support circulation pump, demonstrated arterial remodelling with subsequent altered haemodynamics in peripheral vessels.²¹

All of the above findings strongly indicate that vascular impairment after LVAD implantation makes LVAD recipients sensitive to clinical events and this risk could be strongly influenced also by pulsatility patterns, even in the presence of non-pulsatile or low-pulsatile flow.

Alternative explanation for our findings is that increased PI only reflected LVAD function and/or just pre-existing pathological changes in the vasculature. Another potential cause is that LVAD with non-pulsatile flow may have triggered further changes in a pre-existing imbalance between the microcirculation of the heart and peripheral and cerebral circulation.²² Consequently, PI values may have solely reflected these processes responsible for subsequent clinical events.

Additional interesting finding was that HM3 was independently associated with a significantly decreased risk of death and cerebrovascular events compared with HMII. In agreement with the results of the Final Report of the MOMENTUM 3 Study (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3),²³ this protective effect was moderately attenuated after accounting for arterial stiffness. One possible explanation is that the novel features of HM3, especially enhanced haemocompatibility,²⁴ serve to suppress the deleterious effect of relative increased pulsatility index despite being attenuated by higher arterial stiffness (*Table 3*). In our study, therefore, the potential advantages of HM3 implantation may have been counterbalanced by the presence of increased arterial stiffness.

Our study is limited by its observational character (reverse causation cannot be excluded) and the relatively low incidence of fatal events. The incidence of stroke, in particular, was lower than that reported in other publications, including MOMENTUM 3, the largest of these studies.²⁵ Stroke incidence was 6% during the first year after implantation and 9.6% across the whole study, a reduction perhaps attributable to the younger age profile and lower representation of women compared with previous larger studies.^{3,23} In our group, the mean age was 54.4 ± 14.9 years compared with 60.0 ± 12.0 years in the HMII group and 59.0 ± 12.0 years in the HM3 group of the MOMENTUM study.²³ In addition, the representation of women was only 14.5% compared with 19.2% in the MOMENTUM study²³ and even to 21.5% in the INTERMACS study.³ On the other hand, we observed no differences in the main clinical risk factors such as primary cardiac diagnosis, heparin-induced thrombocytopenia, nutritional status, severe diabetes mellitus, dialysis, and anaemia.

Another important possible explanation for some different findings compared with other studies is the specific anticoagulation and antiplatelet therapy strategy, especially in patients with HMII. Compared with the final report of the MOMENTUM study,²³ we found lower incidence of stroke in the HMII group (11.7% compared with 19%), which is perhaps attributable to differences in antithrombotic treatment strategies. While in the MOMENTUM study all HMII patients received warfarin with an INR target of 2.0–3.0 together with a daily dose of aspirin (81–325 mg), our HMII patients only received warfarin with a target range of 2.0–2.5 without aspirin. It should also be noted that 15 of our HM3 recipients were on a reduced anticoagulant regimen due to involvement in studies focused on this kind of therapy.¹²

It should be also noted that the absolute PI value was lower in patients with LVAD than in individuals with physiological pulsatile flow.²⁶ However, even relatively small change of low PI might be sufficient to trigger clinical events in pre-existing anatomical and/or functional impairment of (micro) vasculature including cerebral vessels. In addition, AI@75 can be modified by a different pattern of pulsatility in LVAD recipients. However, despite AI@75 values are not fully comparable between LVAD recipients and patients presenting with physiological pulsatility, we can reasonably assume that analyses comparing differences between groups of LVAD recipients are quite reliable.

Despite the above mentioned limitations, this study is, to our knowledge, one of the first to describe the impact of the pulsatility index on deaths and cerebrovascular events in a relatively high number of LVAD recipients combined with a parallel study of arterial stiffness. Our data show the potential of an available and easily applicable imaging method for assessing the risk of death and cerebrovascular events in LVAD recipients.

Conclusions

According to our observations, carotid pulsatility measured by duplex ultrasound may be a strong predictor of death and cerebrovascular events in LVAD recipients.

Conflict of interest

Zuzana Tucanova is a recipient of grants and non-financial support from Abbott, Inc. Peter Ivak is a recipient of grants, personal fees, and non-financial support from Abbott, Inc. and serves as a consultant and overall PI for CARMAT, S.A. Ivan Netuka is a recipient of grants, personal fees, and non-financial support from Abbott, Inc.; serves as a consultant and overall PI for CARMAT, S.A.; and is a board member, stockholder, consultant, overall PI, and recipient of grants,

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information.

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