Circulation: Heart Failure

ORIGINAL ARTICLE

# Two-Year Follow Up of the LATERAL Clinical Trial

## A Focus on Adverse Events

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**BACKGROUND:** The LATERAL trial validated the safety and efficacy of the thoracotomy approach for implantation of the HeartWare HVAD System, leading to Food and Drug Administration approval. We sought to analyze 24-month adverse event (AE) rates, including a temporal analysis of the risk profile, associated with the thoracotomy approach for the HVAD system.

**METHODS:** AEs from the LATERAL trial were evaluated over 2 years postimplant. Data was obtained from the Interagency Registry for Mechanically Assisted Circulatory Support database for 144 enrolled United States and Canadian patients. Temporal AE profiles were expressed as events per patient year.

**RESULTS:** During 162.5 patient years of support, there were 25 driveline infections (0.15 events per patient year), 50 gastrointestinal bleeds (0.31 events per patient year), and 21 strokes (0.13 events per patient year). Longitudinal AE analysis at follow-up intervals of <30 and 30 to 180 days, and 6 to 12 and 12 to 24 months revealed the highest AE rate at <30 days, with a decrease in total AEs within the first 6 months. After 6 months, most AE rates either stabilized or decreased through 2 years, including a 95% overall freedom from disabling stroke.

**CONCLUSIONS:** Two-year follow-up of the LATERAL trial revealed a favorable morbidity profile in patients supported with the HVAD system, as AE rates were more likely to occur in the first 30 days postimplant, and overall AE rates were significantly reduced after 6 months. Importantly, 2-year freedom from disabling stroke was 95%. These data further support the improving AE profile of patients on long-term HVAD support.

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**Key Words:** heart failure ■ morbidity ■ sternotomy ■ thoracotomy

The use of left ventricular (LV) assist devices (LVAD) to support patients with end-stage heart failure is growing. Historically, LVADs have been implanted via full midline sternotomy.[1,2] As LVAD technology evolved and devices became smaller, the trend to implant using a less invasive thoracotomy approach has increased, becoming the surgical strategy of choice at many centers.[3–6] The thoracotomy approach can be performed with optimal visualization of cardiac structures, even though incisions are smaller compared with conventional sternotomy.[7,8] The LATERAL trial has previously reported safety and efficacy of the thoracotomy implant technique of the HeartWare HVAD system (Medtronic, Minneapolis, MN) compared with conventional median sternotomy, by demonstrating noninferiority of 6-month survival on original device free from disabling stroke, transplanted or

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### WHAT IS NEW?

- The LATERAL trial is the first published multicenter clinical trial of a centrifugal flow ventricular assist device implanted via thoracotomy as bridge to transplant in patients with end-stage heart failure.

### WHAT ARE THE CLINICAL IMPLICATIONS?

- This analysis provides the first long-term outcomes of left ventricular assist device patients implanted via this innovative approach that may help reduce complications associated with sternotomy, including stroke, bleeding, and right heart failure, while shortening index hospital stay.
- Further understanding of the long-term adverse events profile of left ventricular assist devices will advance the field's knowledge to develop best practices for optimizing patient management and surgical techniques, improving outcomes, and therapy adoption.

### Nonstandard Abbreviations And Acronyms

| | |
|---|---|
| **AE** | adverse events |
| **BTT** | bridge to transplant |
| **DLI** | driveline infection |
| **EPPY** | events per patient year |
| **INTERMACS** | Interagency Registry for Mechanically Assisted Circulatory Support |
| **LV** | left ventricle |
| **LVAD** | left ventricular assist device |
| **QoL** | quality of life |
| **RHF** | right heart failure |
| **RV** | right ventricle |

explanted for recovery, as well as significantly reducing hospital stay.[8]

Despite the fact that the number of patients with heart failure continues to grow, there remains a paucity of donor hearts, creating longer wait times for heart transplantation. Additionally, with the newly revised United Network for Organ Sharing criteria,[9,10] stable LVAD patients awaiting heart transplant are lower on the priority listing, often extending LVAD support times rivaling destination therapy. As such, it is important to ensure that the adverse event (AE) profile of LVAD patients is low to ensure a good quality of life (QoL) with low long-term morbidity. We now present long-term data on patients implanted with the HVAD system via thoracotomy describing the AE profile through 2 years of support.

## METHODS

The study design of the LATERAL trial, including specific inclusion and exclusion criteria, was described previously.[8] Briefly, between January 15, 2015, and April 26, 2016, 144 HVAD implants were performed at 26 investigational sites via a lateral thoracotomy approach in bridge to transplant (BTT) patients. The LATERAL patient population was comparable to other BTT trials, including 33% with ischemic cardiomyopathy, 23% prior cardiac surgery, >80% Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles 1 to 3, 3.5% cardiogenic shock, 18.8% chronic kidney disease, and 4.9% prior stroke.[8,11]

The HVAD system was implanted via a left anterolateral thoracotomy with an upper hemi-sternotomy or a right anterior thoracotomy for outflow graft anastomosis to the ascending aorta. All implants were performed on cardiopulmonary bypass. All data were collected via the INTERMACS Registry database. Patients were followed for 2 years, or until device exchange, transplant, or death. The clinical data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedures.

### Data Collection and Statistical Analysis

In addition to primary end point and total hospital length of stay,[8] secondary end points of the LATERAL trial included major AE's (per INTERMACS Protocol 4.0 definitions), QoL, functional capacity, and survival. QoL was measured by Kansas City Cardiomyopathy Questionnaire and EuroQol EQ-5D. Functional status was measured by New York Heart Association functional class and 6-minute walk test.

Freedom from event analyses were performed using Kaplan-Meier methodology. Patients were censored from analysis at the time of original device exchange, explant, or death. AE comparisons of events per patient year (EPPY) across time intervals were performed using Poisson modeling. Events were considered clinically independent. Postimplant QoL and functional capacity measures were compared with baseline measures using paired *t* test at each time point. All statistical analyses were performed with SAS v.9.4 software (SAS Institute, Cary, NC). The study was conducted in compliance with Food and Drug Administration regulations for Good Clinical Practice and approved by each clinical site's institutional review board. All subjects or their authorized representatives provided informed consent.

## RESULTS

This report describes 2-year follow-up of the 144 BTT patients implanted with the HVAD pump using a thoracotomy approach between January 2015 and April, 2016 in the United States and Canada. At 2 years, 53.5% patients underwent heart transplantation, 2.1% were explanted for recovery, and 31.9% were alive on the original device. Seventeen deaths (11.8 %) were reported, the most common cause of death being neurological dysfunction (n=4, 2.8%), followed by right heart failure (RHF; n=3, 2.1%).

During the 2-year follow-up (162.5 patient-years), there were 25 driveline infections (DLI; 0.15 EPPY), 50 gastrointestinal bleeds (0.31 EPPY), one severe RHF event requiring right ventricular (RV) assist device (0.006 EPPY), and 21 strokes (0.13 EPPY), with 9 hemorrhagic (0.06 EPPY), and 12 ischemic (0.07

**Table 1. Summary of Adverse Events Occurring Through 24 mo**

| Adverse events | LATERAL trial (N=144) cumulative number of events (EPPY) | | | |
|---|---|---|---|---|
| | 30 days (11.8 PY) | 6 mo (62.4 PY) | 12 mo (105.5 PY) | 2 y (162.5 PY) |
| Bleeding | | | | |
| Requiring reoperation | 5 (0.42)* | 8 (0.13)* | 8 (0.08)* | 9 (0.06) |
| Requiring transfusion | 16 (1.36) | 38 (0.61) | 50 (0.47)* | 69 (0.42) |
| Gastrointestinal | 9 (0.76) | 24 (0.38) | 36 (0.34) | 50 (0.31) |
| Any device malfunction/failure† | 10 (0.85) | 20 (0.32) | 55 (0.52) | 69 (0.42) |
| Driveline infection | 2 (0.17) | 10 (0.16) | 15 (0.14) | 25 (0.15) |
| Stroke | | | | 21 (0.13) |
| HCVA | 3 (0.25) | 6 (0.10) | 8 (0.08) | 9 (0.06) |
| ICVA | 3 (0.25) | 6 (0.10) | 8 (0.08) | 12 (0.07) |
| TIA | 1 (0.08) | 5 (0.08) | 10 (0.09) | 13 (0.08) |
| Hepatic dysfunction | 1 (0.08) | 1 (0.02) | 1 (0.01) | 2 (0.01) |
| Renal dysfunction | 8 (0.68) | 15 (0.24) | 16 (0.15) | 18 (0.11) |
| Severe right heart failure requiring RVAD | 0 (0.00) | 1 (0.02)‡ | 1 (0.01)‡ | 1 (0.006)‡ |
| Cardiac arrhythmia | 38 (3.22) | 51 (0.82) | 57 (0.54) | 73 (0.45) |
| Ventricular arrhythmia | 25 (2.12) | 34 (0.54) | 38 (0.36) | 48 (0.30) |

EPPY indicates events per patient year; HCVA, hemorrhagic cerebrovascular accident; ICVA, ischemic cerebrovascular accident; PY, patient-years; RVAD, right ventricular assist device; and TIA, transient ischemic attack.

*Represents a statistically significant reduction when compared with bleeding requiring reoperation in the ADVANCE Bridge to Transplant + Continous Access Program trial over the same time period (represents a post hoc analysis).

†Any device malfunction/failure includes pump thrombus and any device component failure including peripheral components such as batteries, controllers, etc.

‡This difference is not significant ($P$=0.07) when compared post hoc to the ADVANCE BTT+CAP trial results.

EPPY; Table 1). Kaplan-Meier analysis of freedom from any stroke was 91% at 6 months, 88% at 1 year, and 82% at 2 years. Freedom from disabling stroke (modified Rankin Scale, >3) was 96% at 6-months and one-year and 95% at 2 years (Figure). There were 3 LVAD exchanges for thrombus in the first year (2.1%) and none between years 1 and 2.

We evaluated the 2-year longitudinal temporal AE profile over time intervals of <30 days, 30 to 180 days, 6 to 12 months, and 1 to 2 years postimplant (Table 2) to asses the overall AE burden. Stroke, bleeding, and cardiac arrythmia rates declined significantly after the first 30 days. After 6 months, most AE rates either stabilized or decreased. The hemorrhagic stroke rate between 1 and 2 years declined from 0.05 EPPY to 0.01 EPPY. There were no additional RHF episodes between 6 months through 2 years. An analysis of first-event-per-patient per category while on support, essentially a patient-based analysis, revealed a reduction or stabilization in the percentage of patients with a first-event after 6 months, except for DLI, which may be attributable to increased activity as highlighted by the functional capacity measures, and ischemic stroke and cardiac arrhythmia, all which declined initially with the larger ongoing support cohort, but were higher at 2 years (Table I in the Data Supplement). These first-event percentages may be skewed by the reduced patient cohort at 2 years postimplant due to the number of patients who were transplanted or explanted (≈55%) during the course of the study. Hence, the AE-based analysis with EPPY provides a clearer understanding of the AE burden or risk over time.

Patient self-reported QoL measured by Kansas City Cardiomyopathy Questionnaire showed a mean improvement of 18.1 through 24 months, with the EQ-5D Visual Analog Scale improving by an average of 30.1 points above baseline (Table 3). Both New York Heart Association functional class and 6-minute walk test showed improvement from baseline through 24 months. The majority of patients had New York Heart Association functional class IV at baseline (76.4%), whereas by 24 months postimplant, 46.7% were New York Heart Association functional class II. Mean 6-minute walk test increased from 76.7 meters at baseline to 151.7 meters at 24 months (Table 3).

## DISCUSSION

One of the biggest challenges with LVAD therapy is the AE burden, which greatly impacts overall perception and acceptance of mechanical circulatory support therapy in patients. Although the overall AE profile has greatly improved since earlier pulsatile devices, it remains high for this type of therapy. Despite advances in pump design and improved clinical management strategies, AEs still occur regularly in LVAD patients, with multifactorial risk factors.[12] According to the eighth Annual INTERMACS report, 60% of patients are rehospitalized at least once

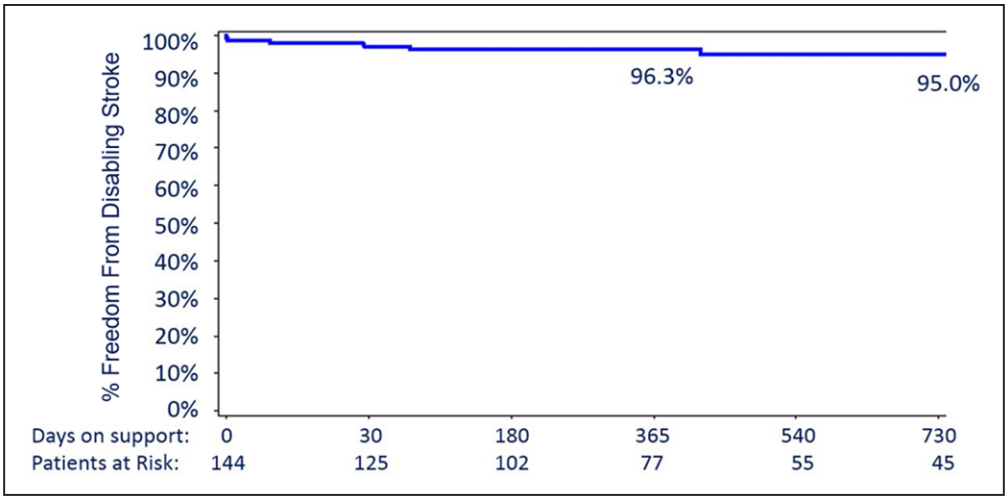


**Figure. Freedom from disabling strokes.**
A stroke is disabling if modified Rankin Scale (mRS) was 4 or 5 at 24 wk poststroke, the patient died within 24 wk of the stroke (mRS=6), or the 24-week mRS was missing and the latest recorded mRS was 4 or 5. Patients are censored at the first occurrence of transplant, device exchange to a different device, explant, or death.

by 6-months postimplant, with 1-year rehospitalization rates as high as 80%. Traditionally, stroke and multisystem organ failure were associated with early risk of death, while DLI, RHF, and gastrointestinal bleeding were associated with recurrent hospitalizations.[13] Patient comorbidities and their preexisting end-organ dysfunction have been postulated as leading to higher rates of AEs.[13,14] The current LATERAL trial reports favorable AE rates at 2-years (Table 1). Notably, those events which are typically problematic for LVAD patients, specifically stroke, severe RHF, and DLI, remained low at 2-years.

Maltais et al[15] described temporal trends in AE profiles over time in the HeartWare ADVANCE BTT+CAP cohort, showing that the total number of AEs occurring within the first 30 days postimplant was significantly higher compared with those occurring between 30 and 180 days (30.36 versus 5.34 EPPY, $P<0.0001$). Even at 1-year, overall AE rates continued to decrease and were considerably lower compared with the prior 5 months of support (5.34 versus 4.09 EPPY, $P<0.0001$). This trend could be attributed to the overall improvement in LVAD patient management postimplant. A longitudinal, temporal review of the AE rates for this study reveals AE rates following a similar trend of greatest risk early on, then considerably lower risk over increasing time on support (Table 2). Both studies also highlight the need for greater understanding of the early (<6 months) postimplant AE rates and related risk profiles, and the potential clinical management strategies to significantly ameliorate them.

Neurological complications can create some of the most devastating outcomes post-VAD implant. Stroke rates have been described in previous HeartWare studies.[6,11,16] Understandably, multiple factors contribute to the risk of developing stroke postimplant, including history of stroke and atrial fibrillation, showered thrombi, postoperative infection, and both sub- and supra-therapeutic

**Table 2. Longitudinal Temporal Analysis of Adverse Events (EPPY)**

| INTERMACS adverse events | ≤30 d, n=144, 11.8 PY | >30–180 d, n=140, 50.7 PY | *P* value ≤30 d vs >30–180 d | >180–365 d, n=102, 43.1 PY | *P* value >30–180 d vs >180–365 d | >365–730 d, n=75, 57.0 PY | *P* value >180–365 d vs >365–730 d |
|---|---|---|---|---|---|---|---|
| Bleeding | 1.53 | 0.51 | <0.001 | 0.39 | 0.45 | 0.39 | >0.99 |
| Requiring reoperation | 0.42 | 0.06 | 0.008 | 0.00 | 0.10 | 0.01 | >0.99 |
| Gastrointestinal | 0.76 | 0.30 | 0.03 | 0.28 | >0.99 | 0.25 | 0.84 |
| Cardiac arrhythmia | 3.22 | 0.26 | <0.001 | 0.14 | 0.25 | 0.28 | 0.20 |
| Driveline infection | 0.17 | 0.16 | >0.99 | 0.12 | 0.78 | 0.18 | 0.60 |
| Total stroke | 0.51 | 0.12 | 0.01 | 0.09 | 0.76 | 0.09 | >0.99 |
| Ischemic CVA | 0.25 | 0.06 | 0.09 | 0.05 | >0.99 | 0.07 | 0.71 |
| Hemorrhagic CVA | 0.25 | 0.06 | 0.09 | 0.05 | >0.99 | 0.01 | 0.58 |
| Severe right heart failure requiring RVAD | 0.00 | 0.02 | >0.99 | 0.00 | >0.99 | 0.00 | NE |

CVA indicates cerebrovascular accident; EPPY, events per patient year; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NE, not evaluable, no comparison of 0 vs 0; PY, patient year; and RVAD, right ventricular assist device.

**Table 3. Overall Quality of Life and Functional Capacity Measured Over 24 mo of LVAD Support**

| Assessment | Visit | LATERAL (N=144)* | *P* value† |
|---|---|---|---|
| KCCQ overall summary score | Baseline | 38±21 | N/A |
| | 6 mo | 64±18 | <0.001 |
| | 12 mo | 64±20 | <0.001 |
| | 24 mo | 55±24 | 0.002 |
| EQ-5D overall score | Baseline | 46±25 | N/A |
| | 6 mo | 71±20 | <0.001 |
| | 12 mo | 71±23 | <0.001 |
| | 24 mo | 72±20 | <0.001 |
| 6MWT (meters walked) | Baseline | 77±136 | N/A |
| | 6 mo | 225±223 | <0.001 |
| | 12 mo‡ | 210±209‡ | <0.001 |
| | 24 mo | 152±206 | 0.02 |

6MWT indicates 6-minute walk test; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; and N/A, not applicable.

*Data presented as mean±SD.

†Comparison to the baseline value using a paired *t* test >0 change.

‡Data from a single subject was excluded as an outlier (indicated >750 m, ±4500 m walked in 6 min).

levels of anticoagulation.[17–20] Findings have consistently shown that the risk for stroke post-LVAD implantation is highest immediately following LVAD implantation.[17–20] There has been some difficulty comparing stroke rates between devices due to the differences in patient populations as well as different INTERMACS stroke definitions.[21,22] INTERMACS version 4.0 definitions were used in the LATERAL trial and categorized strokes as either ischemic, hemorrhagic, or transient ischemic attacks. All types of stroke events carried a low event rate (Table 1), with 6.3% hemorrhagic (n=9, 0.06 EPPY) and 7.6% ischemic (n=12, 0.07 EPPY), with 13.2% overall stroke (n=21, 0.13 EPPY) at 2 years. Despite the potential devastating impact of stroke, LATERAL trial patients experienced a 95% 2-year freedom from disabling stroke. These data corroborate prior temporal analyses of stroke rates from the ADVANCE BTT CAP cohort, which also showed a substantially declining risk after 6 months to 1 year. This risk continued to decline over time, specifically between 180 days and 3 years.[15]

Multiple studies have described DLI in LVAD patients, with typical rates ranging from 10% to 25%.[23,24] In the INTERMACS database, continuous flow LVAD had a DLI rate of 1.31 per 100 patient months within the first 3 months postimplant (early) and 1.42 per 100 patient months occur after 3 months (late).[11] DLI rates reported in the LATERAL trial remain low (11.8%, 0.15 EPPY) at 2 years, which is superior to rates reported in the earlier HeartWare Advance BTT+CAP cohort (19.6%, 0.25 EPPY).[15]

RHF presents a challenge for LVAD patient management, occurring in up to 30% of patients postimplant and has been associated with high mortality rates.[24,25] Persistent RHF can be managed based on the acuity and severity of clinical symptoms. Medical management with inotropes may ameliorate less severe RHF, however, for acute severe RHF, a RV assist device may be needed. The rate of severe RHF requiring RV assist device in the LATERAL trial at 2-years was 0.006 EPPY (n=1). A temporal review of severe RHF rates compared with BTT+CAP (0.00 versus 0.33 EPPY respectively in the first 30 days) suggests there may be some benefit in performing LVAD implant via a less invasive, thoracotomy approach.[15] Furthermore, the overall bleeding events requiring rehospitalization were significantly less in thoracotomy-implanted patients as compared with the BTT+CAP sternotomy patients. A temporal review of overall bleeding events reveals that the greatest impact on event rates was in the first 30 days (1.53 versus 5.21 EPPY, respectively).[15]

The reduction in the incidence of early RHF and overall bleeding following thoracotomy may be attributable to the thoracotomy approach. The lateral approach respects the geometry of the LV and even more so the RV as partial opening of the pericardium may allow for less leftward interventricular septal shift, thereby preserving RV geometry[24,25] and RV ejection and function. Additionally, the thoracotomy approach may result in less surgical trauma and less overall surgical bleeding, reducing the need for blood transfusions and consequential RV dysfunction. With echocardiography confirmation, the lateral approach may also facilitate more precise inflow cannula placement since the heart is not lifted out of the cavity. Proper pump placement may reduce suction events and allow proper LV unloading, which may also help reduce strokes and avoid RV failure.

The analysis of overall QoL and functional capacity measures continues to reveal definite and sustained improvements. The Kansas City Cardiomyopathy Questionnaire, EQ-5D, and 6-minute walk test were all improved significantly from baseline, with sustained improvements through 2-years. This is important when considering the extended times on support for LVAD patients, especially since the revised United Network for Organ Sharing changes will likely result in longer support durations for BTT patients.

## Limitations

There are several limitations to this study. First, this was not a randomized trial comparing thoracotomy to median sternotomy. The original LATERAL trial was designed using a performance goal based on historical data to measure success. A more robust randomized trial might more clearly elucidate the differences and nuances in surgical approaches, including long-term AE profiles. Second, this trial was limited to a BTT population, which could be more representative of a younger patient cohort. Third, the surgeons participating in this study were experienced in the thoracotomy implant approach. For those

with less experience with minimally invasive thoracotomy surgery, there may be a learning curve before perfecting the approach. Lateral thoracotomy may not be suitable for all patients, particularly concurrent valvular procedures; therefore, it is crucial that there is a well-thought through surgical plan and appropriate patient selection before deciding whether thoracotomy is the best route for VAD implantation.

## CONCLUSIONS

Long-term follow-up of patients in the LATERAL trial reveals encouraging rates of AEs through 2-years, in particular low DLI, RHF, and strokes. A temporal analysis confirmed that the greatest risk of AEs occurs in the first 30 days through 6 months, with stabilizing or decreasing rates thereafter throughout the 2-years of follow-up. These data establish that HVAD therapy can be used in patients for longer support, with improving AE profiles. Understanding the changing risk profiles may help to decrease AE rates through targeted surgical and patient management strategies, thus improving overall LVAD patient outcomes.

## ARTICLE INFORMATION

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### Supplemental Materials

Supplemental Methods
Table I

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