Incidence of Driveline Infections and Sepsis in a Contemporary HVAD Population

Nahush A. Mokadam MD, Georg Wieselthaler MD, Edwin McGee, Jr. MD, Mary Jacoski MS, Joseph Rogers MD, and Francis Pagani MD, PhD

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Disclosures

Nahush A. Mokadam MD: Consultant- Medtronic, Abbott, Carmat, SynCardia

Georg Wieselthaler MD: Consultant - Medtronic

Edwin McGee MD: Consultant - Medtronic

Mary Jacoski MS: Medtronic - Employee

Joseph Rogers MD: None

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ENDURANCE, ENDURANCE SUPPLEMENTAL and LATERAL: sponsored by Medtronic (formerly HeartWare Inc.)

Background

- Major infections remain a significant adverse event and increased risk for complications including stroke and pump thrombosis[1].
- Downstream results following major infection include increased burden of cost, complications, and risk of death for patients[2].
- An increased understanding of major infections is important as use of LVADs for DT continues to rise[3].

1. Kirklin, et al. 2017. *J Heart Lung Transplant.*
2. Slaughter, et al. 2011. *J Card Surg.*
3. Fukunaga, et al. 2018. *Curr Opin Cardiol.*

Background

BTT HVAD (ADVANCE), DLI & Sepsis

- In the ADVANCE BTT trial with HVAD, within 6 months of implantation DLI and sepsis occurred in 12.1% and 11.4% of patients, respectively[4].
- The follow-up ADVANCE BTT and CAP trial showed a DLI and sepsis infection rate within 6 months of 16.9% and 17.2%, respectively[5].

4. Aaronson, et al. 2012. *Circulation.*
5. John, et al. 2014. *J Heart Lung Transplant.*

Background

HVAD trials since ADVANCE

ENDURANCE[6]

Prospective, randomized, controlled, unblinded, multicenter trial comparing the safety and efficacy of HVAD to HMII in end-stage heart failure patients who did not qualify for heart transplant. Enrollment included 446 patients who were assigned, in a 2:1 ratio, to the HVAD or the HMII control (**296 HVAD System**, 149 HMII).

LATERAL[8]

Prospective, single-arm, multicenter, IDE study to evaluate the thoracotomy implant technique of the HVAD system in advanced heart failure patients. Enrollment included a total of 158 patients with **144 patients** included in the study population.

ENDURANCE Supplemental[7]

Prospective, randomized, controlled, unblinded, multicenter trial to prospectively determine the effectiveness of a blood pressure management strategy on neurological injury in patients receiving the HVAD System compared to HMII (control). Enrollment included a total of 465 patients in the intent-to-treat population (**308 HVAD System**, 157 HMII).

6. Rogers, et al. 2017. *N Engl J Med.*
7. Milano, et al. 2018. *JACC Heart Fail.*
8. McGee, et al. 2019. *J Heart Lung Transplant.*

Purpose

To assess the morbidity and mortality of driveline infections and sepsis in the HVAD population using pooled data from the ENDURANCE, ENDURANCE Supplemental, and LATERAL trials.

Methods

Post-hoc analysis of all HVAD patients enrolled in ENDURANCE, ENDURANCE Supplemental, and LATERAL trials combined (n=748)

- Patients who experienced driveline infection (DLI), sepsis, and neither event.
- Baseline characteristics and six-minute walk test were analyzed 2 years post-HVAD implant
- Survival was compared between all 3 infection groups across 2 years post-HVAD implant.

Results – DLI and Sepsis with HVAD

DT HeartWare™ HVAD™ System, DLI & Sepsis

- **ENDURANCE trial (DT1) with HVAD (PY: 410.1)**
  - DLI: 0.26 EPPY*
  - Sepsis: 0.15 EPPY
- **ENDURANCE Supplemental trial (DT2) with HVAD (PY: 454.9)**
  - DLI: 0.12 EPPY
  - Sepsis: 0.22 EPPY
- **LATERAL trail with HVAD (PY: 162.5)**
  - DLI: 0.15 EPPY
  - Sepsis: 0.02 EPPY

** EPPY = events per patient year*

Results – DLI and Sepsis with HVAD

Combined

DT1 + DT2 + LATERAL with HVAD (n=748, PY: 1027.5)

- DLI: n=188 (25.1%), 0.18 EPPY
- Sepsis: n=137 (18.3%), 0.16 EPPY
- Neither: n= 461 (61.6%)

Baseline Characteristics

Characteristic	DLI (n=188)	Sepsis (n=137)	Neither (n=461)	p-value DLI vs Neither	p-value Sepsis vs Neither
Age (years)	61.7 +/- 11.9	65.7 +/- 10.2	61.0 +/- 12.4	0.51	**<0.0001**
BMI (kg/m^2)	28.4 +/- 6	27.6 +/- 5.4	27.3 +/- 5.7	**0.03**	0.58
Creatinine (umol/L)	122.6 +/- 38.2	129.6 +/- 42.8	121.4 +/- 49.7	0.77	0.08
Sex (Female)	19.2%	15.3%	16.1%	0.36	0.89
Race (White)	69.2%	76.6%	72.0%	0.50	0.32
Etiology (Ischemic)	52.7%	62.8%	48.8%	0.39	**0.005**
Diabetes History	41.5%	51.1%	35.4%	0.15	**0.001**
Afib History	44.7%	56.2%	47.9%	0.49	0.10
Stroke History	20.4% (19/93)	18.3% (15/82)	12.06%	**0.01**	0.09
Hypertension History	67.6%	70.8%	55.3%	**0.005**	**0.002**
Intermacs 1	3.8%	2.9%	4.1%	1.00	0.62
Intermacs 2	30.6%	28.7%	31.1%	1.00	0.60
Intermacs 3	43.7%	43.0%	43.5%	1.00	0.92
Intermacs 4-7	22.0%	21.8%	21.3%	0.92	0.91
6MWT (m)	130.6 +/- 142.9	109.0 +/- 122.3	136.7 +/- 138.1	0.61	**0.03**
CPB (mins)	83.1 +/- 39.3	96.0 +/- 48.6	84.3 +/- 46.9	0.76	**0.01**

Legend: BMI: body mass index; Afib: atrial fibrillation; 6MWT: six-minute walk test; CPB: cardiopulmonary bypass

Multivariate analysis indicates that history of hypertension is a risk factor for developing DLI (HR 1.5, p=0.006)

- DLI patients had larger BMI, more likely to have a history of stroke, and more likely to have a history of hypertension than patients without DLI or sepsis
- Sepsis patients were older, were more likely to have ischemic HF, more likely to be diabetic, more likely to have a history of hypertension, had shorter 6MWT at baseline, and longer CBP times than patients without DLI or sepsis

Adverse Events

Adverse Event	DLI (n=188) PY: 331.35	Sepsis (n=137) PY: 191.61	Neither (n=461) PY: 579.23	p-value	
				DLI vs Neither	Sepsis vs Neither
Bleeding	0.72	1.60	1.12	**<0.0001**	**<0.0001**
GI Bleed	0.44	0.96	0.60	**0.002**	**<0.0001**
Infection, Localized Non-Device	0.60	1.29	0.85	**<0.0001**	**<0.0001**
Stroke	0.23	0.30	0.27	0.30	0.47
ICVA	0.14	0.11	0.18	0.27	**0.048**
HCVA	0.08	0.19	0.09	0.91	0.001
Any suspected Pump Thrombosis	0.11	0.10	0.15	0.11	0.14
RHF requiring RVAD	0.01	0.02	0.02	0.07	0.78
Renal Dysfunction	0.07	0.30	0.11	0.08	**<0.0001**
Respiratory Failure	0.14	0.47	0.24	**0.0004**	**<0.0001**

Legend: GI: gastrointestinal; ICVA: ischemic cerebrovascular accident; HCVA: hemorrhagic cerebrovascular accident; RHF: right heart failure; RVAD: right ventricular assist device

- DLI patients had lower rates of major bleeding including GI bleeding, infections other than DLI or sepsis, and respiratory failure through 2 years than patients without DLI or sepsis
- Sepsis patients had greater rates of major bleeding including GI bleeding, infections other than DLI or sepsis, renal dysfunction, and respiratory failure but lower rates of ICVA through 2 years than patients without DLI or sepsis

Adverse Events following DLI and Sepsis

	Driveline Infection 110 events within 6 months*		Sepsis 99 events within 6 months*	
Adverse Event	%	Mean time to event (months)	%	Mean time to event (months)
Major Infection	24.5%	2.1	15.3%	1.5
Major Bleeding	13.8%	1.2	13.9%	1.6
GI bleeding	8.5%	1.3	7.3%	1.4
Neurological Dysfunction	4.3%	2.6	5.1%	1.9
Pump Thrombus	3.2%	1.4	2.2%	1.0
Cardiac Arrhythmia	2.7%	2.1	6.6%	1.5
Respiratory Failure	0.5%	2.0	10.9%	0.1
RHF requiring RVAD	0.5%	0.7	0.0%	0.0
Renal Dysfunction	0.0%	0.0	7.3%	0.3

*First event after driveline infection or sepsis

Relationship between DLI and Sepsis

Event Sequence	Patients	Events	Patients w/ multiple DLI prior to Sepsis	Average # DLI for patients with >1	Median, range first DLI to first Sepsis (days)	Sepsis Within 30 days of DLI	Sepsis Within 60 days of DLI
DLI prior to Sepsis	27	45	8	3.7 (2-8)	370, range 6-1760	2	3

Event Sequence	Patients	Events	Patients w/ multiple Sepsis prior to DLI	Average # Sepsis for patients with >1	Median, range first Sepsis to first DLI (days)	DLI Within 30 days of Sepsis	DLI Within 60 days of Sepsis
Sepsis prior to DLI	11	12	1	2	357, range 87-1476	0	0

Multivariate analysis indicates that DLI is a risk factor for developing sepsis (HR 2.3, $p<0.0001$).

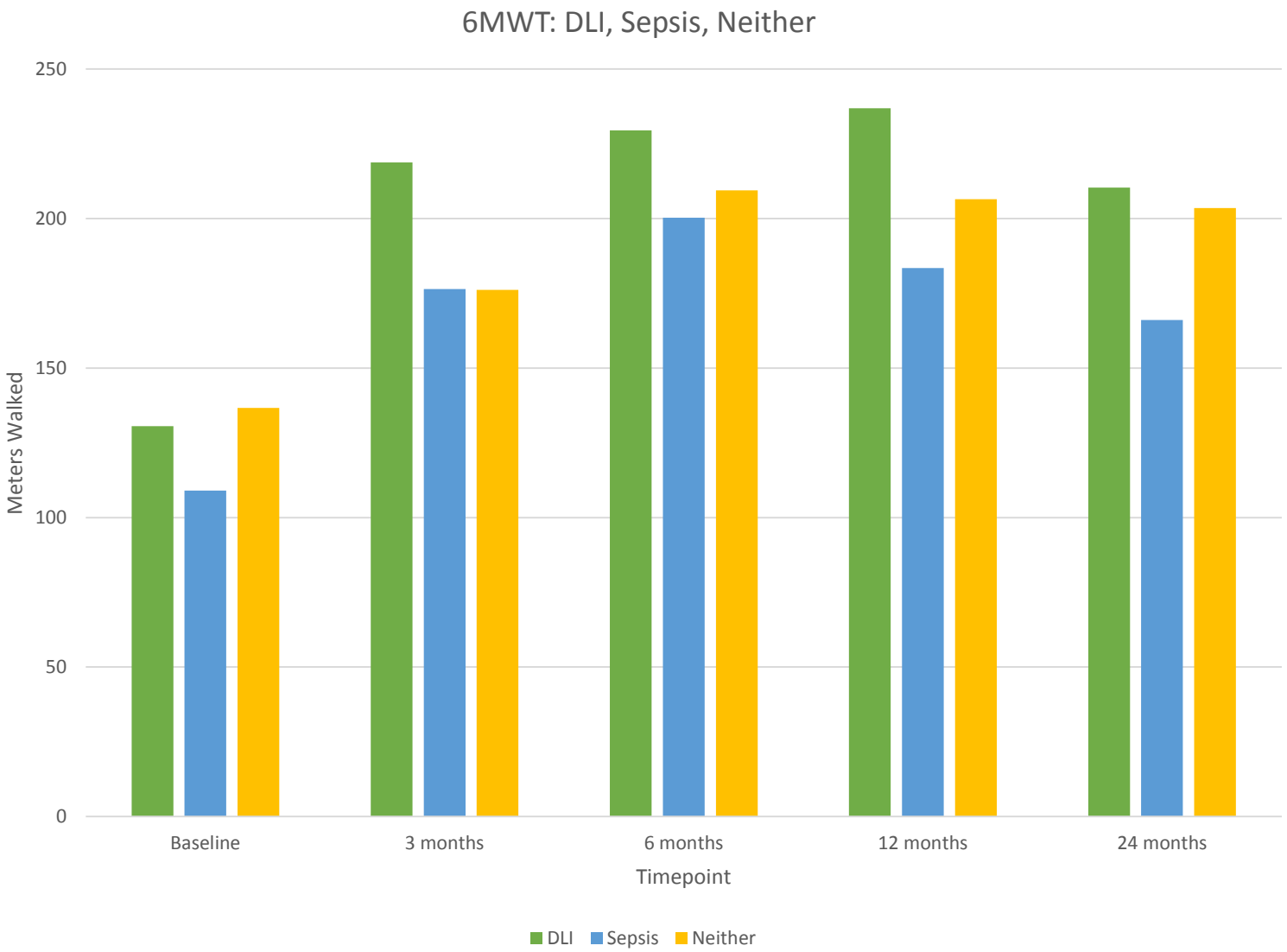
Sepsis was not a risk factor for developing DLI

Relationship between Sepsis and HCVA

Event Sequence	Patients	Events	Patients w/ Multiple Sepsis prior to HCVA	Average # Sepsis for patients with >1	Median, range first Sepsis to first HCVA (days)	HCVA Within 30 days of Sepsis	HCVA Within 60 days of Sepsis
Sepsis prior to HCVA	18	21	3	2	266.5, range 1-1751	4	6

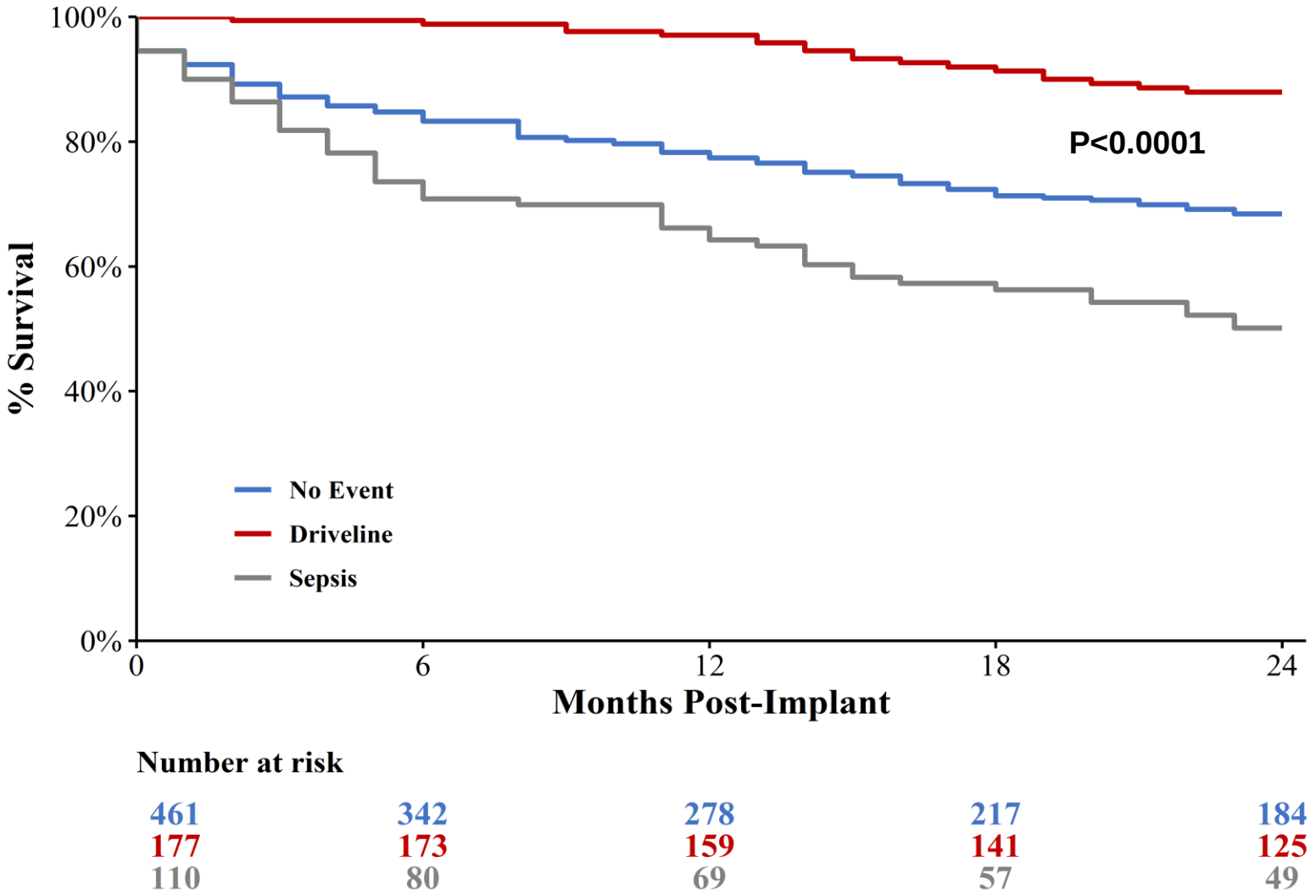
Multivariate analysis indicates that sepsis is not a risk factor for developing HCVA

Six-minute walk test



At 3 months, DLI patients had significantly longer 6MW than both Sepsis (p=0.03) and Neither (p=0.008)

Patient Survival



Time to death following first:
DLI: 19.8 ± 13.1 months
Sepsis: 9.2 ± 13.3 months

Conclusions

- The incidence of sepsis remains stable in the HVAD population.
- Risk factors for sepsis include ischemic etiology, diabetes, history of hypertension and CPB.
- Driveline Infection increases risk of developing sepsis
- While sepsis is a risk factor for mortality, the occurrence of DLI does not have an adverse effect on survival.

Limitations

- Retrospective review
- Combination of BTT and DT patients
- Different trial designs limit analyses on combined cohorts due to differences in collected data

THANK YOU

email: Nahush.Mokadam@osumc.edu
Twitter: @NahushMokadam

THE OHIO STATE UNIVERSITY
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