Circ J 2017; 81: 213–219
doi:10.1253/circj.CJ-16-0942

Higher Body Mass Index Increases Risk of HeartMate II Pump Thrombosis But Does Not Adversely Affect Long-Term Survival

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Background: Obesity has been correlated with various adverse events in patients who receive left ventricular assist devices (LVAD). In this study, we sought to further characterize the role of obesity in this patient population.

Methods and Results: We performed a retrospective analysis of 164 patients implanted with a HeartMate II from August 2008 to December 2014. Patients were categorized into 2 BMI groups based on WHO guidelines: BMI 18.5–30 kg/m^2 (n=99) and BMI >30 kg/m^2 (n=65). Patient demographics, adverse outcome and long-term survival were compared between the 2 groups. For any outcome associated with BMI groups, we performed a Cox regression to identify confounding comorbidities. Preoperative demographics and comorbidities were similar. Patients with BMI >30 were younger (P=0.01) and had a higher incidence of type 2 diabetes (P=0.01). While rate of pump thrombosis was higher among patients with BMI >30 (P=0.02), overall survival at 2 years did not differ. The most common cause of death was hemorrhagic stroke in the obese group. On multivariable cox regression analysis, BMI was an independent risk factor of pump thrombosis.

Conclusions: Higher BMI does not reduce survival after VAD implantation but it does appear to increase the risk of pump thrombosis. Further studies to characterize the role of BMI in survival and thrombosis rates are warranted.

Key Words: Chronic heart failure; Thrombosis; Ventricular

More than one-third of the US population is now considered to be obese, defined as body mass index (BMI) >30.[1,2] The increasing prevalence of obesity in the USA and worldwide poses a significant public health concern given that obesity is a major risk factor for increased mortality and heart failure (HF).[3] End-stage HF may eventually require more invasive therapy such as continuous-flow left ventricular assist device (CF-LVAD) therapy or heart transplant (HT).[4] Of the approximately 15,000 patients who have been implanted with LVAD to date, the estimated prevalence of obesity is >30%.[5–8]

While obesity has been associated with decreased survival in HT patients, several large retrospective studies have suggested that increased BMI does not adversely affect survival after CF-LVAD implantation. The association between obesity and VAD-related complications, however, lacks consensus in literature.[5–8] Studies have reported various associations between increased BMI and outcomes such as pump thrombosis, post-discharge bleeding, increased frequency and duration of hospitalization, and infection – but these reports have varied.[9,10] In the present large continuous CF-LVAD cohort, we sought to evaluate the influence of obesity status on overall survival and complication rates, specifically that of pump thrombosis, following implantation. Anticoagulation profiles and device parameters were analyzed in detail to better assess the correlation between pump thrombosis and increased BMI. Furthermore, we analyzed the patterns of change in BMI over the course of VAD therapy and the implications for outcome.

Methods

Patient Selection

The Institutional Review Board of the University of Pennsylvania approved this study. We reviewed the institution's VAD database and analyzed those who underwent

Received September 19, 2016; revised manuscript received November 10, 2016; accepted November 21, 2016; released online December 22, 2016 Time for primary review: 46 days

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ISSN-1346-9843

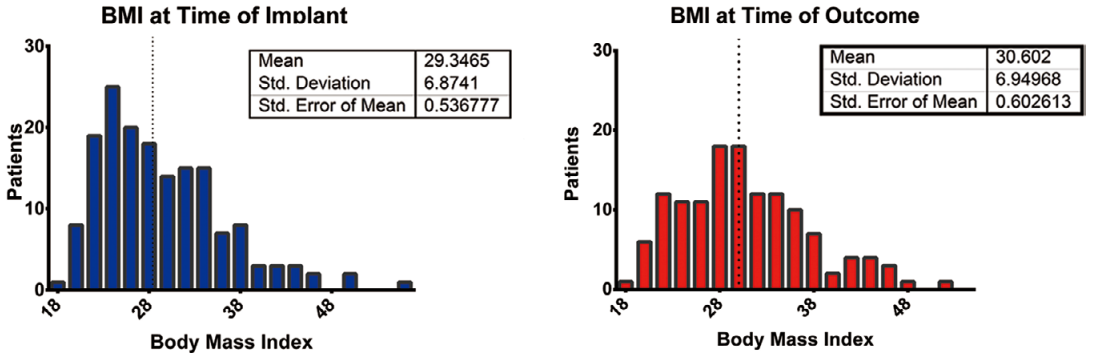

Figure 1. Body mass index distribution in the left ventricular assist device cohort at time of discharge and at outcome.

Table 1. Patient Characteristics

	Group 1 (BMI 18.5–30 kg/m²) (n=99)	Group 2 (BMI >30 kg/m²) (n=65)	P-value
Demographics			
Age (years)	64 (54–74)	57 (52–70)	0.01*
Male	83 (84)	51 (78)	0.38
Caucasian	47 (47)	31 (48)	1.00
Bridge to transplant	25 (25)	25 (38)	0.08
INTERMACS			1.00
1	14 (14)	10 (15)	
2	47 (47)	25 (38)	
3	23 (23)	21 (32)	
4	13 (13)	6 (9)	
Comorbidities			
Ischemic cardiomyopathy	49 (49)	30 (46)	0.41
Hypertension	63 (64)	38 (58)	0.51
Pulmonary hypertension	39 (39)	15 (23)	0.02*
Diabetes mellitus	36 (36)	41 (63)	0.001*
Chronic obstructive pulmonary disease	19 (19)	14 (22)	0.74
Smoking	45 (45)	21 (32)	0.09
Renal failure on dialysis	6 (6)	8 (12)	0.17
Chronic renal insufficiency	39 (39)	24 (37)	0.93

Data given as median (IQR) or n (%). *P<0.05. BMI, body mass index; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

HeartMate II LVAD (Thoratec Corp., Pleasanton, CA, USA) implantation as bridge to transplant (BTT) or destination therapy (DT) from August 2008 to December 2014. The patients were then stratified into 2 BMI groups based on the definition of obesity proposed by the World Health Organization and National Institute of Health guidelines: BMI 18.5–30 kg/m² and BMI >30 kg/m². Patients with BMI <18.5 kg/m² were excluded from this study. As per the management guidelines, patients were started on Aspirin 81 mg and warfarin with a target international normalized ratio (INR) of 2.5±0.5 immediately postoperatively. INR, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured prior to discharge and at the time of outcome-defining events (transplant, device exchange, explantation and death). Anticoagulation and antiplatelet therapy were stopped in the event of bleeding, and were resumed upon resolution of the bleeding source. Primary outcome was defined as immediate postoperative, 1-year and 2-year survival.

Variable Selection

Patient demographics and comorbidities previously associated with LVAD outcomes such as hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), end-stage renal disease, pulmonary hypertension, and smoking were included. Perioperative as well as postoperative characteristics including device parameters, anticoagulation regimen and adverse events were analyzed. Adverse events included moderate-severe right ventricular (RV) failure (defined as receiving inotropic therapy or

Table 2. Device Parameters and Anticoagulation Profiles

Parameters at discharge	Group 1 (BMI 18.5–30 kg/m²) (n=99)	Group 2 (BMI >30 kg/m²) (n=65)	P-value
Laboratory values			
WBC (×10⁹/L)	8.5±4.8	8.8±3.6	0.59
Creatinine (mg/dL)	1.5±0.8	1.5±0.6	0.61
Total bilirubin (umol/L)	1.4±1.0	1.3±0.6	0.38
LVAD parameters			
Flow (L/min)	4.9±0.9	5.5±1.0	0.001*
Speed (rpm)	9,020±450	9,320±530	0.002*
Pulsatility index	5.2±1.0	5.1±1.1	0.6
Power (Watts)	5.8±0.8	6.6±1.4	0.001*
Anticoagulation			
Aspirin	78 (95)	48 (98)	1.0
INR†	2.2 (0.6)	2.4 (0.7)	0.13
PT (s)†	23.8 (6.6)	25.4 (6.8)	0.11
aPTT (s)†	39.1 (9.0)	39.5 (7.0)	0.85
Platelets (×10⁹/L)†	300 (135)	296 (148)	0.84
Anticoagulation at time of event			
Aspirin	78 (95)	48 (98)	1.0
INR†	2.1 (1.0)	2.1 (0.9)	0.94
PT (s)†	23.2 (11.0)	23.2 (9.0)	1.0
aPTT (s)†	39.7 (16.7)	39.3 (11.6)	0.90
Platelets (×10⁹/L)†	196 (80)	213 (77)	0.12

Data given as mean±SD, n (%) or †median (IQR). *P<0.05. aPTT, activated partial thromboplastin time; BMI, body mass index; INR, international normalized ratio; LVAD, left ventricular assist devices; PT, prothrombin time; WBC, white blood cells.

inhaled pulmonary vasodilators for >7 days or requiring RVAD support[11]), reintubation rates, gastrointestinal bleed, stroke including transient ischemic attack, postoperative renal failure, pump thrombosis, and driveline infection requiring oral or IV antibiotic therapy. Postoperative renal failure was classified as the need for hemodialysis. The diagnosis of pump thrombosis was made by visual, bench-top confirmation by the operating surgeon during device explantation and/or confirmed by bench top analysis of the pump after explant. Composite as well as cause-by-cause mortality were compared.

Statistical Analysis

All data analysis was performed using GraphPad Prism, version XML6 (GraphPad Software, La Jolla, CA, USA) and Stata 13.0 (StataCorp, College Station, TX, USA). Patient characteristics, perioperative characteristics, and adverse outcomes were compared between the 2 groups on univariable analysis. Continuous variables are reported as mean±SD, non-parametric variables are reported as median (IQR) and were compared using Kruskal-Wallis test for non-normally distributed data. Categorical variables were reported as count and percent, and were compared using chi-squared test. Fisher's exact test was used if the sample size were not sufficiently large. Kaplan-Meier survival at 30 days, 1 year and at 2 years was compared using log-rank test between the 2 groups. Those outcomes with P<0.2 on univariable Cox regression analysis for pump thrombosis were entered into multivariable Cox regression. We utilized the Hosmer-Lemeshow test for goodness of fit. For all analyses, P<0.05 was considered significant.

Results

Patient Characteristics

Between August 2008 and December 2014, 166 patients underwent HeartMate II implantation. Of the total, 65 patients were categorized as obese (BMI >30 kg/m²) and 99 patients were not (BMI 18.5–30 kg/m²). Two patients had BMI <18.5 kg/m² and were excluded. BMI distribution at the time of device implant is given in **Figure 1**.

Average duration of LVAD support was 472±523 days. Patients with BMI >30 kg/m² were younger (64±16.9 years, P=0.011) and consisted of a greater percentage of BTT candidates. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) class distribution between the 2 groups was similar. Pulmonary hypertension was more common in the normal BMI group (P=0.023) and DM was more common in the BMI >30-kg/m² group (P=0.001). There were no significant differences in the percentage of chronic lung disease, hypertension and smoking. Preoperative renal function, defined as creatinine level prior to LVAD implantation, was similar between the groups (**Table 1**).

Device parameters including flow (5.5±1.0 vs. 4.9±0.9 L/min, P=0.001), speed (9,320±530 vs. 9,020±450 RPM, P=0.002) and power (6.6±1.4 vs 5.8±0.8 Watts, P=0.001) were significantly higher in the BMI >30-kg/m² group. Anticoagulation regimen and INR were similar between the 2 groups at the time of discharge and at the time of event (**Table 2**). Time to therapeutic INR after VAD implantation did not differ between the BMI >30 and BMI <30 groups, respectively (median, IQR: 9, 6 days vs. 9, 8 days).

Table 3. Peri- and Postoperative Characteristics

	Group 1 (BMI 18.5–30 kg/m²) (n=99)	Group 2 (BMI >30 kg/m²) (n=65)	P-value
CPBT (min)†	83 (41)	77 (50)	0.23
Blood product transfusion			
Red blood cells (units)†	3 (7)	4 (13)	0.97
Fresh frozen plasma (units)†	0 (4)	1 (0)	0.31
Platelets (units)†	0 (1)	4 (1)	0.28
Time to extubation (days)†	3 (6)	2 (6)	0.42
ICU LOS (days)†	6.5 (8)	7 (14)	0.71
Total hospital LOS (days)†	21.5 (19)	21 (28)	0.92
Survival to discharge	82 (83)	49 (75)	0.32
Adverse outcomes			
RV failure	11 (11)	9 (14)	0.63
Reintubation	20 (20)	10 (15)	0.44
Gastrointestinal bleed	12 (12)	9 (14)	0.75
Ischemic stroke	6 (6)	7 (11)	0.28
Pump thrombosis	10 (10)	16 (25)	0.02*
Driveline infection	5 (5)	4 (6)	0.74
Surgical exploration for bleeding	24 (24)	11 (17)	0.26

Data given as n (%) or †median (IQR). *P<0.05. BMI, body mass index; CPBT, cardiopulmonary bypass time; ICU, intensive care unit; LOS, length of stay; RV, right ventricular.

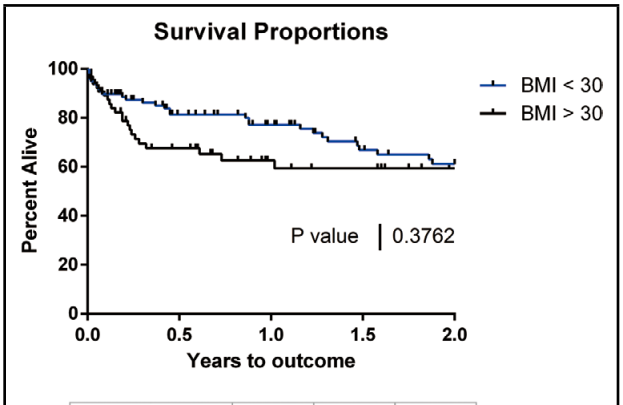

Figure 2. Kaplan-Meier survival curves stratified by body mass index (BMI) cut-off of 30.

Perioperative and Postoperative Outcomes

Perioperative characteristics and outcomes were similar between the 2 groups (**Table 3**). The rates of RV failure, stroke, gastrointestinal bleed, renal failure, and driveline infection were similar between the 2 groups. Of note, the BMI >30 group had a significantly higher rate of pump thrombosis compared with the normal BMI group (n=16, 25% vs. n=10, 10%, respectively, P=0.02; **Table 3**). Increased BMI did not adversely affect patient survival at 2 years after LVAD implantation (61.2% vs. 59.4% at 2 years, P=0.38), but patients with BMI >30 kg/m² did have a higher risk of mortality during the early (1 year) postoperative course (percent alive, mean±SE: 61.5±6.4% vs. 77.5±4.4%, P=0.035; **Figure 2**). When analyzed by various causes of mortality, a higher percentage of deaths in the BMI >30-kg/m² group was attributable to hemorrhagic stroke than in the normal BMI cohort (n=9, 14% vs. n=5, 5%, P=0.08; **Table 4**). Death due to hemorrhagic stroke tended to occur early on in the BMI >30-kg/m² group (median, IQR: 80, 120 days).

All variables that had P<0.2 on univariate analysis of pump thrombosis (BMI, INR, VAD speed, pulsatility index and COPD) were included in the Cox regression model. BMI (OR, 1.13; 95% CI: 1.03–1.25; P=0.014) was a significant predictor (**Table 5**). The Hosmer-Lemeshow test was non-significant (P=0.62) signifying appropriate goodness of fit.

As a cohort, there was a significant increase in BMI over the course of the VAD therapy (1.4±3.9, P<0.001). When stratified by initial BMI, the BMI in the non-obese group increased significantly (+2.1±3.4, P<0.001), while the obese group remained weight neutral. There was no association between change in BMI and incidence of adverse outcomes or survival.

Discussion

In this study, we investigated the role of BMI on postoperative outcome and survival. The principal findings are: (1) higher BMI does not adversely affect long-term survival after LVAD implantation, but it does appear to lead to a higher proportion of early (<1 year) postoperative mortality; and (2) obesity is an independent risk factor for pump thrombosis.

VAD therapy is a life-saving intervention for patients with end-stage HF.[4,12] Although longevity on device support has improved drastically over the past decade, frequent complications resulting in readmissions has highlighted the importance of optimizing patient selection.[13–17] Financially and ethically, there has also been increased pressure to ensure evidence-based allocation of scarce health-care

Table 4. Fatal Outcomes and Cause of Death

Fatal outcomes	Group 1 (BMI 18.5–30 kg/m²) (n=99)	Group 2 (BMI >30 kg/m²) (n=65)	P-value
During admission for LVAD implantation	17 (17)	16 (25)	0.32
Total deaths	35 (35)	21 (32)	1.00
Cause of death			
Sepsis	10 (10)	6 (9)	1.00
Cardiogenic shock	4 (4)	3 (5)	1.00
Ischemic stroke	1 (1)	1 (1)	1.00
Hemorrhagic stroke	5 (5)	9 (14)	0.08
End-organ failure	5 (5)	0 (0)	0.16
Intraoperative death	2 (2)	0 (0)	1.00
Pump thrombosis	1 (1)	1 (2)	1.00
Other	7 (7)	2 (3)	0.32

Data given as n (%). BMI, body mass index; LVAD, left ventricular assist device.

Table 5. Univariate and Cox Regression Analysis of Pump Thrombosis

	Univariate			Cox regression	
	Control (n=138)	Pump thrombosis (n=26)	P-value	OR (95% CI)	P-value
Demographics					
Age (years)†	60 (23)	61 (14)	0.78		
Male	113 (81)	21 (84)	0.75		
Caucasian	68 (45)	15 (60)	0.29		
INTERMACS class 1	21 (16)	3 (12)	0.80		
Comorbidities					
Ischemic cardiomyopathy	69 (50)	10 (40)	0.83		
Hypertension	85 (61)	16 (64)	0.79		
Pulmonary hypertension	46 (33)	8 (32)	0.88		
Diabetes mellitus	64 (46)	13 (52)	0.58		
Chronic lung disease	23 (17)	10 (40)	0.01*	3.16 (0.86–11.64)	0.084
Smoking	58 (42)	8 (32)	0.36		
Chronic renal insufficiency	51 (37)	12 (48)	0.32		
Creatinine (mg/dL)†	1.4 (0.63)	1.3 (0.61)	0.21		
BMI at implant (kg/m²)†	28.6 (6.5)	33.2 (7.8)	0.01*	1.13 (1.03–1.25)	0.014
BMI at event (kg/m²)	29.7	35.4	0.01*		
INR at discharge†	2.22 (0.57)	2.49 (0.58)	0.05*	1.65 (0.58–4.69)	0.35
INR at event	2.11	2.24	0.36		
WBC (×10⁹/L)†	8.6 (4.4)	8.8 (4.4)	0.78		
Platelets (×10⁹/L)†	296 (99)	308 (104)	0.61		
Total bilirubin (umol/L)†	1.4 (0.9)	1.4 (0.8)	0.91		
Albumin (g/L)†	3.3 (0.6)	3.5 (0.5)	0.14	2.50 (0.69–9.13)	0.17
Delta BMI	1.42	1.32	0.96		
ECHO_LVEDD (mm)†	6.8 (1.0)	6.6 (1.1)	0.39		
VAD parameters					
Speed (RPM)†	9,100 (520)	9,290 (380)	0.06	1.00 (0.99–1.00)	0.10
Flow (L/min)†	5.1 (1.0)	5.3 (0.8)	0.36		
Pulsatility index†	5.1 (0.9)	5.6 (1.2)	0.1	0.44 (0.16–1.18)	0.10
Power (Watts)†	6.1 (1.2)	6.3 (1.2)	0.49		

Data given as n (%) or †median (IQR). ECHO_LVEDD, ECHO left ventricular end-diastolic dimension. Other abbreviations as in Tables 1,2.

resources to patients who will benefit most both in terms of increased longevity and preserved quality of life.

Obesity has become a variable of interest in the process of optimizing patient selection for mechanical circulatory support due to its alarming prevalence in the general population as well as its association with adverse cardiovascular outcomes after cardiac transplantation.[18,19] Several large-scale retrospective studies have investigated patient survival after LVAD implantation stratified by initial BMI. Butler et al, despite having hypothesized that obesity

would have a negative impact, found that it was actually protective among their LVAD patients, thus coining the phrase, "risk factor paradox".[20] Several studies since then, the largest of which used data from 896 HeartMate II trial patients, also showed no decrease in survival among obese LVAD patients as far out as 3 years after implantation.[5–7]

Although obesity has not been found to adversely affect survival, it has been linked with a number of VAD-related complications. A large study by Boyle et al identified BMI as an independent risk factor for post-discharge bleeding, ischemic stroke and pump thrombosis.[9] A subsequent INTERMACS study corroborated the increased risk of pump thrombosis among patients with a higher BMI.[10] Higher risk of infection, respiratory failure and overall increase in re-hospitalization rates has also been described.

The present findings, which were derived exclusively from HeartMate II patients, were consistent with published literature in that higher BMI did not change the perioperative or 2-year survival in patients undergoing LVAD implantation. We did find, however, that patients with BMI >30 kg/m^2 had a precipitous drop in survival during the early (<1 year) postoperative period compared with the normal BMI group despite having similar INTERMACS profiles, prevalence of comorbidities, and perioperative characteristics (**Table 1**).

The reasons for this are surely multifactorial, but part of the explanation in the present cohort may be due to the earlier and increased occurrences of pump thrombosis and fatal hemorrhagic stroke in the BMI >30 cohort: pump thrombosis was more than twice as common among obese patients than in non-obese patients despite similar antiplatelet/anticoagulation regimen and therapeutic levels (INR, PT) both at the time of discharge and at the time of pump thrombosis (**Table 2**). Multivariable analysis also identified increased BMI as the only independent risk factor. Although prior studies have observed that obese patients require larger doses of warfarin and more time to achieve therapeutic INR compared with normal weight patients, in the present study there was no difference in the 2 groups' subtherapeutic duration (data not shown). Similar to what has been reported, we also observed that patients with BMI <30 kg/m^2 tended to gain weight while patients with BMI >30 kg/m^2 remained weight neutral over the duration of the study, but did not find any correlations with adverse outcomes.[21]

The mechanism of obesity leading to increased risk of pump thrombosis is not yet understood, but 2 major hypotheses have been proposed. From a physical standpoint, obese patients have a higher risk of developing blood clots due to decreased level of activity and increased stasis. Their body habitus may also interfere with optimal pump placement or remodeling. From a physiological standpoint, morbid obesity has been shown to alter hematologic profiles by increasing the level of clotting factors in the blood as well as by impeding fibrinolytic pathways. Moreover, platelets from obese individuals have been reported to have a higher propensity to aggregate at baseline, and even after aspirin therapy.[22,23] Further studies on how BMI alters the body's coagulative function are warranted to potentially prevent the increased rate of pump thrombosis.

The present study also compared the various causes of death between the 2 groups, which has not been previously studied. We found that fatal hemorrhagic stroke was more than twice as common in the BMI >30-kg/m^2 group than in the normal BMI group, although it did not reach statistical significance. In fact, hemorrhagic stroke was the most common cause of death in the BMI >3,030-kg/m^2 group despite elevated pump thrombosis rates, which further complicates the task of titrating anticoagulation therapy with regard to obesity status for patients with LVAD. The BMI >30-kg/m^2 group did require significantly higher VAD speed, flow and power, which likely reflects the need for higher cardiac output among obese patients when optimizing the pump settings for adequate hemodynamic support and ventricular unloading. This may have resulted in greater shear stress and exacerbated von Willebrand factor deficiency.[24] Further investigation into this association may shed more light on the mechanism of increased bleeding risk in obese patients.

The present study had several limitations. First, it is a single-institution retrospective study. Second, there are inherent limitations to analyzing anticoagulation data due to varied adherence and monitoring among patients, and response to warfarin. Increasing the frequency of INR monitoring for future analysis of time in therapeutic range may be of value. Last, although BMI at both extremes was of interest in the present study, we were unable to identify sufficient underweight (BMI <18.5) patients for meaningful analysis.

In conclusion, BMI >30 kg/m^2 does not affect long-term survival after LVAD implantation. We did note, however, that these patients have elevated early (<1 year) risks of pump thrombosis, hemorrhagic stroke and ultimately death. This preliminary analysis supports the conventional belief that obesity should not be an absolute contraindication to LVAD implantation, but it does suggest that a more in-depth hematological work-up may assist with patient selection, inform postoperative anticoagulation strategies and ultimately mitigate the risk of bleeding and thrombotic complications.

Disclosures

M.A.A. is a consultant for Thoratec Corp. P.A. is a principal investigator for the ENDURANCE, MOMENTUM III and LATERAL Clinical Trial.

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