Risk factors for thromboembolic events in pediatric patients with ventricular assist devices

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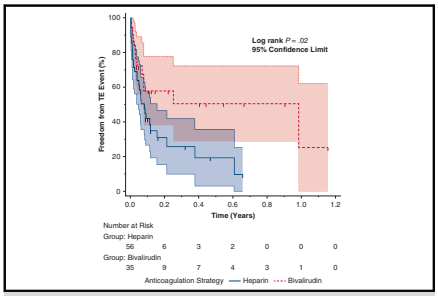
ABSTRACT

Objective: Pediatric patients on ventricular assist devices (VAD) are at risk of thromboembolic (TE) complications. Our objective was to identify factors associated with TE events, including the role of initial anticoagulation strategy and device type in the pediatric VAD population.

Methods: This was a retrospective, single-center review (2005-2022) of children who were implanted with paracorporeal pulsatile (PP), paracorporeal continuous (PC), or a combination of devices. Patient- and device-related factors were collected. Kaplan-Meier survival analysis was performed to determine freedom from TE. Cox proportional hazard analysis was conducted to look for factors associated with TE events.

Results: Ninety-five patients included with a median age of 0.9 years (interquartile range, 0.3, 5.4); median weight of 8.4 kg (interquartile range, 4.5, 17.8), and 63.2% with noncongenital heart disease. Device breakdown included 47.4% PC, 24.2% PP, and 23.2% combination of devices. Initial anticoagulation was either heparin (61.5%) or bivalirudin (38.5%). In Kaplan-Meier analysis, unadjusted freedom from a TE event was significantly greater in those who received bivalirudin as their initial anticoagulation strategy ($P = .02$) and PP VADs ($P = .02$). In multivariate analysis, initial anticoagulation strategy with bivalirudin (hazard ratio, 0.30; 95% confidence interval, 0.12-0.75, $P = .01$) was associated with a reduced hazard of TE events, whereas PC device strategy was found to be associated with an increased hazard (hazard ratio, 2.78; 95% confidence interval, 1.12-6.88, $P = .03$).

Conclusions: This study suggests that PC device strategy and heparin as an initial anticoagulation strategy are associated with increased hazard of TE events. Further research is required to understand the interaction between device type and initial anticoagulation strategy. (JTCVS Open 2024;20:132-40)



Freedom from TE event based on initial anticoagulation strategy.

CENTRAL MESSAGE

This study suggests that a paracorporeal pulsatile device strategy and bivalirudin as an initial anticoagulation strategy are associated with increased freedom from thromboembolic events.

PERSPECTIVE

Pediatric patients on ventricular assist devices (VAD) are at-risk of thromboembolic (TE) complications. TE events are one of the most significant adverse events that contribute to morbidity and mortality in pediatric patients on VAD support. This study suggests that type of VAD and choice of initial anticoagulation strategy can impact the hazard of TE events post-implantation.

Ventricular assist devices (VADs) are important tools in managing pediatric heart failure and are primarily used as a bridge to transplant or myocardium recovery. VADs have improved survival to transplant. Despite the lifesaving benefits of VADs, there is ongoing risk of morbidity and mortality.[1-3] Thromboembolic (TE) events are one of the

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Abbreviations and Acronyms

AT = antithrombin
CHD = congenital heart disease
CI = confidence interval
CRRT = continuous renal-replacement therapy
CVA = cerebrovascular accident
DTI = direct thrombin inhibitor
HR = hazard ratio
IQR = interquartile range
KM = Kaplan-Meier
PC = paracorporeal continuous
Pedimacs = Pediatric interagency registry for mechanical circulatory support
PP = paracorporeal pulsatile
TE = thromboembolic
TIA = transient ischemic attack
VAD = ventricular assist device

most significant adverse events that contribute to morbidity and mortality in pediatric patients on VAD support.[1,4-7] VAD-associated TE events include pump thrombosis, neurologic changes related to cerebrovascular accident (CVA), and transient ischemic attack (TIA).[1,8] An early North American trial of the Berlin Heart EXCOR (Berlin Heart Inc) in 2012 showed TE stroke events in 29% of patients.[9,10]

Pump thromboses are significant complications that contribute to morbidity.[11] Pump thrombosis has been reported as high as 18% in patients on paracorporeal pulsatile (PP) devices with significant intercenter variability with TE events associated with readmissions to the intensive care unit.[12,13]

The past decades of collective circulatory support experience have led to advancements and innovation in pediatric VAD care. A recent study of the Advanced Cardiac Therapies Improving Outcomes Network showed that rates of stroke between 2018 and 2021 decreased to 14% in PP devices.[14] With changes to management strategies, specifically the introduction of direct thrombin inhibitors (DTIs) such as bivalirudin for initial anticoagulation, there is need for additional analysis to determine the factors that affect the risk of TE events. With this in mind, we designed our study to analyze the factors associated with TE events, including the role of initial anticoagulation strategy and device type in the pediatric VAD population.

METHODS

This was a retrospective, single-center review of all pediatric patients on paracorporeal ventricular assist devices implanted at the Stollery Children's Hospital (Edmonton, Alberta, Canada) between 2005 and 2022. The research ethics board waived the need for patient informed consent and granted approval for use of data associated with this study (Pro00091553) on May 21, 2019. Patient demographics, pre-VAD characteristics, and VAD-related characteristics were collected (Table 1). Adverse events related to TE events including CVA, TIA, and pump thrombosis were collected over the patient's duration of VAD support. Data were managed using REDCap (Research Electronic Data Capture) tools hosted at the University of Alberta (Edmonton, Alberta, Canada). REDCap is a secure, web-based software platform designed to support data capture for research studies.[15]

All clinical laboratory values were collected within 1 week before VAD implant. Initial anticoagulation strategy, defined as the first anticoagulant initiated after device implantation, was recorded. Anticoagulation and antiplatelet strategy were recorded at the time of TE event. Device strategy and type, including both PP (Berlin Heart EXCOR) and paracorporeal continuous (PC) device types (CentriMag/PediMag; Abbott) were recorded. Patients who transitioned from PC to PP devices were classified as having a combination of support. Patients who were not classifiable according to the previously mentioned device strategies were classified as "other." All patients who experienced TE events were identified. Pump thrombosis was defined as the clot development with visible fibrin in the paracorporeal pump requiring device exchange as assessed by the VAD physicians at our site. TE strokes and TIA were recorded according to the definitions laid out by the Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs).[16] Era of implantation was defined by year of VAD support with the earlier era encompassing those implanted between 2005 and 2014 and later era including those implanted between 2015 and 2022. Management of patients did not vary significantly over the 17-year period, with the exception of the anticoagulation strategy. From 2005 to 2014, patient anticoagulation was managed according to the Edmonton Protocol.[17] In 2015, initial anticoagulation strategy was switched to bivalirudin (The Medicines Company) with a single antiplatelet agent.

Statistical Analysis

Data were analyzed and displayed descriptively as the median with interquartile range (IQR) (25th, 75th) for continuous data and as a frequency with percentages for categorical data. Comparisons were made between groups anticoagulated with heparin and bivalirudin, as well as between 3 categories of device strategies. The Kruskal-Wallis one-way analysis of variance test was used to assess group differences for continuous variables, whereas the χ^2 or the Fisher exact test was used to assess differences between categorical variables. For all analyses, a 2-tailed P value of $< .05$ was defined as statistical significance. Univariate Cox proportional hazard analysis was conducted to identify variables with increased hazard for TE events. Variables with $P < .1$ on the basis of on univariate analysis were selected, and device strategy and initial anticoagulation strategy were forced into the model as the result of their clinical significance. Variables identified in the Cox multivariate analysis were assessed for multicollinearity. Kaplan-Meier (KM) survival analysis was performed to determine freedom from TE event on the basis of initial anticoagulation strategy and device type with log-rank analysis used to identify significant differences. Pairwise comparisons were made between PC and PP and PC and the combination group. Therefore, we used a Bonferroni correction, with the threshold for significance set at $P < .025$. SPSS, version 28.0 (IBM Corp) was used for statistical analyses.

RESULTS

Demographics

A total of 95 patients were included in this analysis, with a median age of 0.9 years (IQR, 0.3, 5.4) with a male predominance (55.8%). Median height at time of implant was 72.0 cm (IQR, 55.5, 107.5) and median weight was 8.4 kg (IQR, 4.5, 17.8). In terms of diagnosis and etiology of heart failure, our sample was found to be predominantly

TABLE 1. Demographic and clinical characteristics dichotomized by initial anticoagulation strategy

Variable	Initial anticoagulation strategy, n (%) or median (IQR)			
	Overall (n = 95)	Heparin* (n = 56)	Bivalirudin (n = 35)	*P* value
Demographics				
Age, y	0.9 (0.3, 5.4)	2.6 (0.2, 8.9)	0.6 (0.3, 1.2)	.08
Sex, male	53 (55.8)	32 (57.1)	18 (51.4)	.67
Weight, kg	8.4 (4.5, 17.8)	11.0 (4.1, 22.0)	6.7 (4.9, 9.1)	.08
Height, cm	72 (55.5, 107.5)	88.0 (55.3, 124.5)	65.0 (56.5, 76.3)	.045
Diagnosis				.82
Non-CHD	60 (63.2)	36 (64.3)	21 (60.0)	
CHD	35 (36.8)	20 (35.7)	14 (40.)	
Period of VAD implant				<.001
2005-2014	52 (54.7)	47 (83.9)	1 (2.9)	
2015-2022	43 (45.3)	9 (16.1)	34 (97.1)	
Preimplant factors				
ECMO (yes)	51 (53.7)	28 (50.0)	20 (57.1)	.53
CRRT (yes)	18 (18.9)	11 (19.6)	6 (17.1)	1.0
CRP	25 (26.3)	14.3 (3.8, 14.3)	44.9 (6.1, 72.0)	.63
eGFR	84 (54.8, 107.6)	79.8 (44.0, 105.7)	86.0 (67.0, 109.0)	.23
Bilirubin, μmol/L	20 (13.0, 55.0)	24.0 (14.0, 57.0)	16.0 (10.0, 27.0)	.023
Urea, mmol/L (CRRT excluded)	5.6 (4.0, 8.3)	6.0 (4.0, 13.7)	5.0 (4.0, 7.4)	.08
ALT, μmol/L	23.5 (16.0, 67.0)	30.5 (15.0, 104.5)	18.5 (16.0, 31.0)	.09
AST, μmol/L	56.0 (29.0, 170.0)	73.0 (40.0, 173.0)	38.0 (25.0, 58.0)	.013
Treatment factors				
Cannulation strategy				.012
LVAD	62 (65.3)	31 (55.4)	29 (82.9)	
RVAD	12 (12.6)	8 (14.3)	4 (11.4)	
BiVAD	21 (22.1)	17 (30.4)	2 (5.7)	
Type of VAD				<.001
PC	45 (47.4)	25 (44.6)	20 (57.1)	
PP	23 (24.2)	18 (32.1)	1 (2.9)	
Combination of devices	22 (23.2)	8 (14.3)	14 (40.0)	
Other	5 (5.3)	5 (8.9)	–	

IQR, Interquartile range; *CHD*, congenital heart disease; *VAD*, ventricular assist device; *ECMO*, extracorporeal membrane oxygenation; *CRRT*, continuous replacement renal therapy; *CRP*, C-reactive protein; *eGFR*, estimated glomerular filtration rate; *ALT*, alanine transaminase; *AST*, aspartate aminotransferase; *LVAD*, left ventricular assist device; *RVAD*, right ventricular assist device; *BiVAD*, biventricular assist device; *PC*, paracorporeal continuous; *PP*, paracorporeal pulsatile. *Initial anticoagulation strategy data missing on 4 patients.

noncongenital (63.2%), with cardiomyopathy being the most common diagnosis (36.8%). More than one half (53.7%) of the population was on extracorporeal membrane oxygenation preimplant and 18.9% were on continuous renal-replacement therapy (CRRT). In terms of device strategy, 47.4% of patients were supported on an isolated PC VAD, 24.2% on an isolated PP VAD, and 23.2% on a combination of support, with 5.3% classified as other. Most patients were on a heparin-first (61.5%) anticoagulation strategy, with the remaining 38.5% on bivalirudin. Table 1 outlines the patient demographics and preimplant laboratory test values.

Table 1 compares the demographics and clinical characteristics between those treated with initial heparin versus bivalirudin strategy. This comparison shows that the patients treated with the initial bivalirudin strategy were shorter ($P = .045$), with lower preimplant bilirubin values ($P = .023$) and aspartate aminotransferase values ($P = .013$) compared with those with the heparin-first strategy. The distribution of devices was also different, primarily driven by a greater proportion of patients with a combination of devices in those treated with bivalirudin and lower proportion of patients with a biventricular assist device compared with the heparin group.

When analyzing group differences by device strategy (Table 2), we found sex to be significantly different, with an isolated PP strategy having a male predominance of 78.3% when compared with the other 2 device strategies ($P = .037$). There were significant differences in diagnosis, with the PC group having a greater proportion of congenital heart disease (CHD) compared with the other 2 groups ($P = .008$). Preimplant characteristics also differed, with CRRT more frequently used before PC implant compared with the other strategies ($P = .013$) and with a greater

TABLE 2. Demographics and clinical characteristics based on VAD strategy

Variable	Device strategy, n (%) or median (IQR)				
	Overall (n = 90)	PC (n = 45)	PP (n = 23)	Combo (n = 22)	*P* value
Demographics					
Age, y	0.9 (0.3, 5.7)	0.5 (0.1, 5.7)	2.4 (0.5, 13.6)	0.8 (0.6, 3.1)	.13
Sex, male	52 (57.8)	25 (55.6)	18 (78.3)	9 (40.9)	.037
Weight, kg	8.4 (4.4, 8.4)	6.3 (3.9, 17.6)	11.5 (5.7, 38.9)	8.5 (6.4, 11.1)	.15
Height, cm	71.5 (55.0, 108.0)	65.0 (53.0, 109.0)	84.0 (59.0, 156.0)	70.5 (64.0, 91.0)	.21
Diagnosis					.008
Non-CHD	58 (64.4)	22 (48.9)	18 (78.3)	18 (81.8)	
CHD	32 (35.6)	23 (51.1)	5 (21.7)	4 (18.2)	
Period of VAD implant					<.001
2005-2014	47 (52.2)	20 (44.4)	21 (91.3)	6 (27.3)	
2015-2022	43 (47.8)	25 (55.6)	2 (8.7)	16 (72.7)	
Preimplant factors					
ECMO (yes)	49 (54.4)	29 (64.4)	9 (39.1)	11 (54.4)	.14
CRRT (yes)	18 (20.0)	15 (33.3)	3 (13.0)	–	.004
CRP	22.6 (4.7, 71.3)	31.2 (6.1, 74.8)	7.8 (1.6, 40.9)	47.5 (8.9, 122.2)	.18
eGFR	84.0 (51.8, 108.3)	90.5 (55.0, 107.6)	62.0 (38.0, 110.5)	85.0 (64.0, 106.0)	.57
Bilirubin, μmol/L	19.0 (12.0, 55.0)	26.5 (15.5, 56.0)	22.5 (13.0, 76.0)	14.0 (8.5, 19.5)	.013
Urea, mmol/L (CRRT excluded)	5.5 (4.0, 8.3)	5.0 (3.2, 8.3)	6.5 (3.5, 13.6)	5.4 (4.0, 7.5)	.51
ALT, μmol/L	24.0 (16.0, 67.)	23.0 (15.0, 55.0)	50.0 (19.0, 138.5)	18.0 (16.0, 30.0)	.14
AST, μmol/L	57.0 (29.0, 170.0)	63.0 (33.0, 174.0)	74.0 (31.5, 167.5)	40.5 (27.0, 106.0)	.51
Treatment factors					
Cannulation strategy					.11
LVAD	59 (65.6)	28 (62.2)	15 (65.2)	16 (72.7)	
RVAD	11 (40.7)	9 (20.0)	–	2 (9.1)	
BiVAD	20 (22.2)	8 (17.8)	8 (34.8)	4 (18.2)	
Initial anticoagulation strategy*					<.001
Heparin	51 (59.3)	25 (55.6)	18 (94.7)	8 (36.4)	
Bivalirudin	35 (40.7)	20 (44.4)	1 (5.3)	14 (63.6)	

VAD, Ventricular assist device; *IQR*, interquartile range; *PC*, paracorporeal continuous; *PP*, paracorporeal pulsatile; *CHD*, congenital heart disease; *ECMO*, extracorporeal membrane oxygenation; *CRRT*, continuous replacement-renal therapy; *CRP*, C-reactive protein; *eGFR*, estimated glomerular filtration rate; *ALT*, alanine transaminase; *AST*, aspartate aminotransferase; *LVAD*, left ventricular assist device; *RVAD*, right ventricular assist device; *BiVAD*, biventricular assist device. *Initial anticoagulation strategy data missing on 4 patients.

bilirubin value also seen in this group ($P = .13$). Lastly, initial anticoagulation strategy did vary by device strategy, with those in the PP group having a greater proportion of patients receiving heparin ($P < .001$).

TE Events

One half (50.5%) of the patients in this cohort experienced at least 1 TE event while on VAD support. Across the cohort, the median time to a first TE event was 14 days (IQR, 4.3, 30.8). Fifty-seven percent (n = 32) of patients with heparin as the initial anticoagulation strategy had a TE event, whereas 37% of patients with bivalirudin as the initial anticoagulation strategy had a TE event. At the time of CVA or TIA, 38.5% of patients were on an anticoagulant only, and 61.5% were on anticoagulant and antiplatelet therapy. The most common regimen at the time of CVA or TIA was heparin alone (23.1%), followed by bivalirudin alone (15.4%). Anticoagulants paired with antiplatelet therapy, including aspirin, dipyridamole, and dual antiplatelet therapy, made up the remaining distribution at approximately 7.7% each. At the time of pump thrombosis, 66.7% were on an anticoagulant only and 33.3% were on anticoagulation and antiplatelet therapy. The most common regimen at the time of event was heparin only (48.7%), followed by bivalirudin only at 17.9% and bivalirudin and aspirin at 12.8%. Of the patients on a combination of support, 53.8% experienced their first TE event on the initial PC device and 46.2% on the later PP device.

KM analysis on the basis of initial anticoagulation strategy revealed an increased freedom from TE event in patients initially anticoagulated with bivalirudin compared with heparin ($P = .02$) (Figure 1). However, there was no significant difference identified when stratified by device strategy ($P = .12$) (Figure 2). There was a significant difference in freedom from TE events between those with a PC and PP VAD ($P = .02$) but not between those with a PC

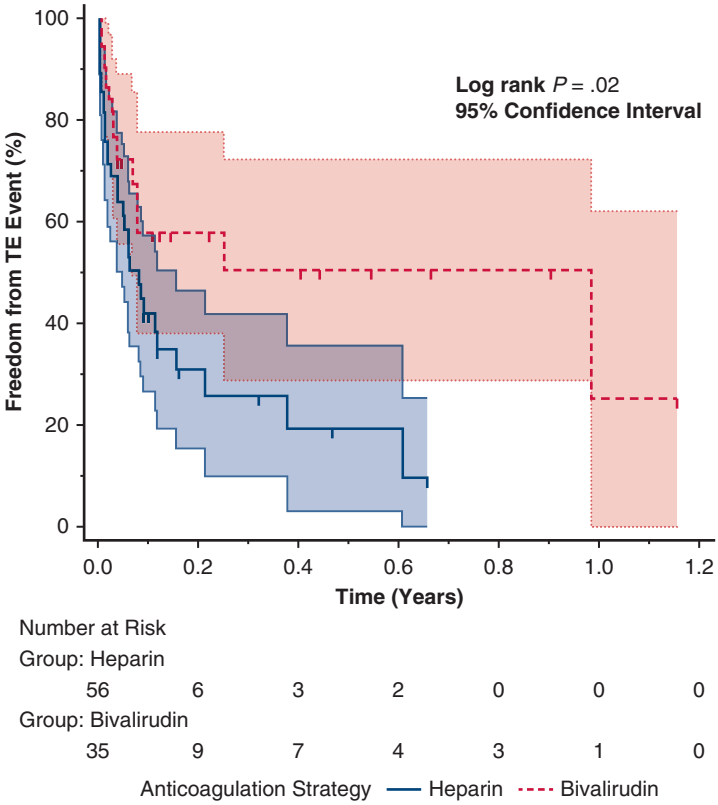

FIGURE 1. Freedom from thromboembolic (*TE*) event based on initial anticoagulation strategy, 95% confidence interval.

VAD and on a combination of support ($P = .03$) (data not shown). See Figure 3 for a graphical abstract of the study.

Cox proportional hazard analysis results are provided in Table 3. The multivariate model revealed that patient height was found to be associated with a 2% decreased hazard of TE events of per centimeter increase in height (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.97-0.99, $P \leq .001$). Device strategy, specifically isolated PC VAD, was found to have a significant increased hazard of TE events (HR, 2.78; 95% CI, 1.22-6.88, $P = .03$) when compared with an isolated PP device strategy. Combination of support and other device strategy was not associated with an increased hazard of TE events compared with an isolated PP device strategy. Lastly, initial anticoagulation strategy was an independent predictor for increased hazard of TE events, with a bivalirudin-first strategy found to be protective in comparison to a heparin-first strategy (HR, 0.30; 95% CI, 0.12–0.75; $P = .01$). Assessment of multicollinearity revealed variance inflation factor values of <3, indicating that there is no confounding multicollinearity.

DISCUSSION

Although TE events have historically plagued the care of pediatric patients supported with paracorporeal VADs, our study highlights that these complications are not universal across all management strategies. With a bivalirudin-first strategy and the use of PP pumps, the hazard for TE events can be reduced. Previous studies examining risk factors for TE events in patients on VAD have been predominately focused on adult patients, with this study being one of the first to highlight specific risk factors in pediatrics.[7]

Initial anticoagulation strategy after VAD implantation is an important consideration in VAD management, given that most TE events occur early after VAD initiation. Since the early 2000s, the primary choice of initial antithrombotic strategy has been unfractionated intravenous heparin infusion followed by use of aspirin and dipyridamole, with eventual transition to enoxaparin or heparin. Beginning in the 2010s, centers began to shift to the use bivalirudin and other DTIs, with the addition of an antiplatelet (eg, aspirin) as an antithrombotic regimen for pediatric patients supported on paracorporeal devices.[18] Bivalirudin had been previously employed as a means of treating pump thrombosis at our center, but its use expanded to include initial anticoagulant.[11] Bivalirudin's effect may be secondary to more favorable times to target levels, decreased risk of bleeding, and a more stable pharmacologic profile because of its direct action on thrombin.[11,19,20]

Changes in patient management, notably the shift to DTIs, is also cited as a contributor to the reduction in ischemic stroke incidence in the Advanced Cardiac

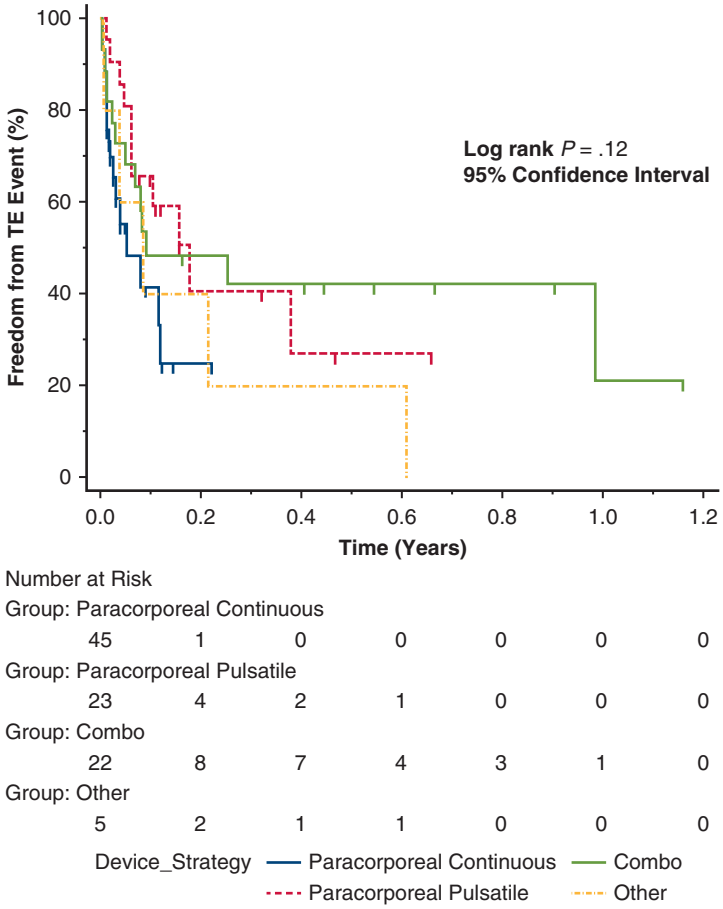

FIGURE 2. Freedom from thromboembolic (*TE*) event based on device strategy, 95% confidence interval.

Therapies Improving Outcomes Network study cohort.[14,21] A 2021 study of CVA in Pedimacs found that later era from 2017 to 2019 was associated with a decreased hazard of stroke, but the authors did not isolate anticoagulation strategy as significant variable.[1] Our findings further support this by demonstrating that bivalirudin is protective against TE events and this is independent of other patient characteristics. This relative benefit of bivalirudin may not only be related to the aforementioned factors but also to its mechanism of action. Bivalirudin inhibits thrombin directly without the need for antithrombin (AT) as a cofactor. This is important, as the plasma level of AT in pediatric patients is reduced up to 50% at birth and does not normalize until 6 months of age, perhaps limiting the effectiveness of AT-dependent anticoagulants such as heparin.[12,22,23] In addition, bivalirudin importantly has thrombolytic properties, as it has been shown to act on clot-bound thrombin.[24] Although it is likely that changes in anticoagulation strategy over time account for the difference in CVA incidence, our multivariate model did not identify era of implantation as an independent factor. This may be related to overlap between management strategies, notably the continued use of heparin as initial anticoagulation strategy for several patients in the early years of the second era between 2015 and 2016.

In our study, an isolated PC device strategy was shown to increased hazard of TE events. In clinical practice, device strategy selection of PC versus PP is based on patient factors and clinical needs of the patient. PC VADs are indicated for short-term support after surgical intervention, for specific cardiac lesions and when dialysis or an oxygenator is required.[17] PP VADs, such as the Berlin Heart, are used in smaller children and for patients who are expected to spend additional time on circulatory support while awaiting transplant or myocardium recovery.[16] The timing of conversion from a PC to PP device depends on a number of factors that have been previously reported by Sughimoto and colleagues.[17] The advantages of pulsatile flow for improved end-organ perfusion, rates of ventricular recovery, and reduction of gastrointestinal bleeding is documented in the VAD literature.[17,25] In terms of TE events, a recent review of Pedimacs demonstrated decreased freedom from ischemic stroke in PC devices in KM analysis. and our findings support this finding.[26] The differences in etiology of heart failure, greater incidence of preimplant CRRT, and increased bilirubin levels in the PC group compared with

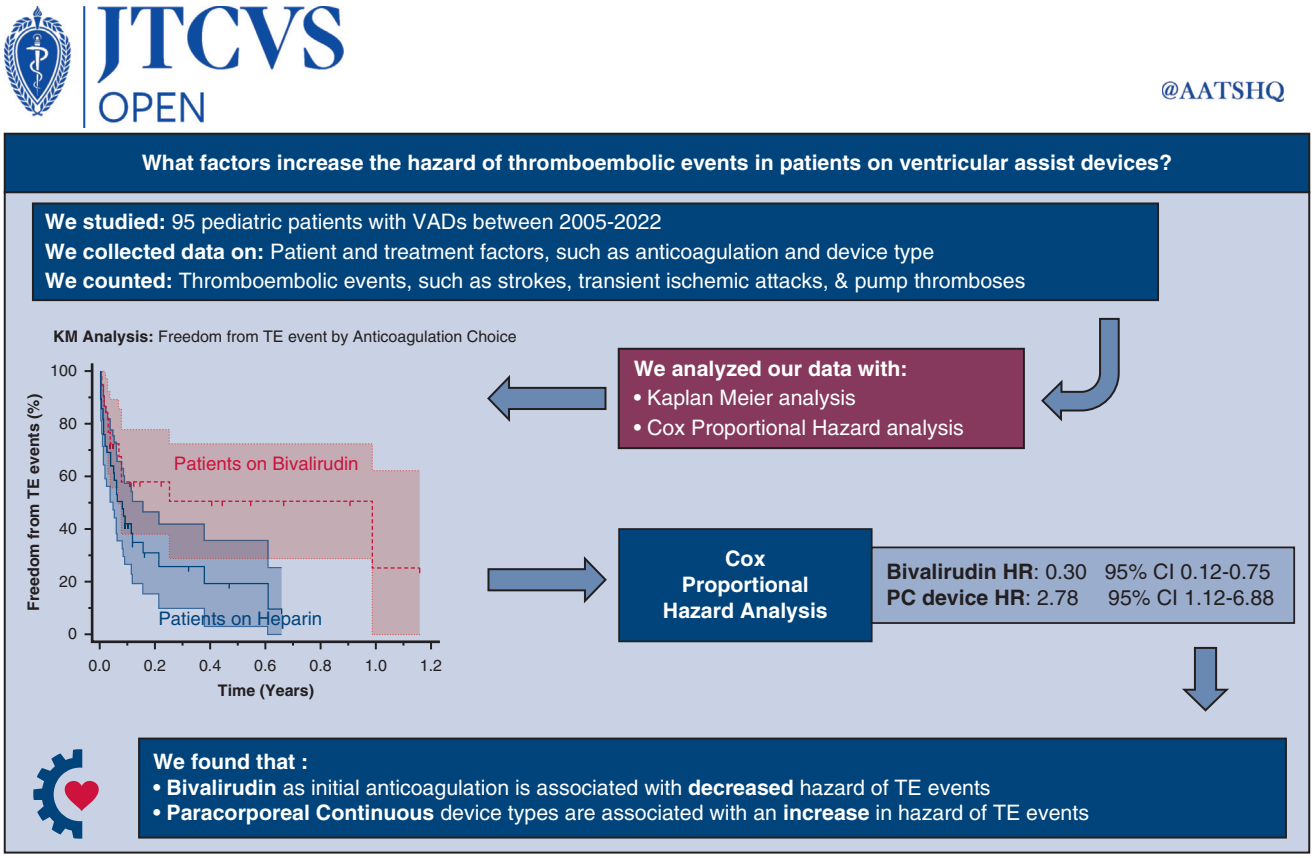

FIGURE 3. Graphical abstract. *VAD*, Ventricular assist device; *KM*, Kaplan-Meier; *TE*, thromboembolic event; *HR*, hazard ratio; *CI*, confidence interval; *PC*, paracorporeal continuous.

the PP group attest to the varied clinical situations of these patient groups. In addition, the greater proportion of heparin use in the PP group is reflective of the era with more PC and combo VADs being used in the later era. These characteristics were accounted for in the multivariable analysis.

Patient factors such including demographics, height, weight, and preimplant diagnosis were considered in our analysis. Increasing height was found to being significantly associated with a reduction in hazard of TE events. Interestingly, weight was not found to be significant in our analysis, given the expected association between increased height and increased weight. A recent study of the Pedimacs registry by Kwiatkowski and colleagues[27] showed that patients less than 20 kg were more likely to have a CVA than larger patients. Generally, smaller patients have more difficult venous access, are more likely to have had previous operations, are less mobile, and have smaller cannulas and pump sizes, all of which may contribute to TE events.[27]

In our study, no significant associations were found between etiology of myocardial dysfunction and TEs. This is an interesting finding, given the known hazard association between CHD and TE events in the non-VAD population.[28-30]

TABLE 3. Cox proportional hazard analysis, final model

Variable	β	Hazard ratio	95% CI	*P* value
Height	−0.02	0.98	0.97-0.99	<.001
Type of VAD (PP as reference)				
PC	1.02	2.78	1.12-6.88	.03
Combo	0.25	1.29	0.45-3.65	.64
Other	−1.04	0.35	0.11-1.18	.09
Initial anticoagulation (heparin as reference)				
Bivalirudin	−1.20	0.30	0.12-0.75	.01

CI, Confidence interval; *VAD*, ventricular assist device; *PP*, paracorporeal pulsatile; *PC*, paracorporeal continuous.

A retrospective case control study by Fox and colleagues[29] found that CHD is associated with a 19-fold risk of ischemic stroke. It is however unclear how these factors are modulated by hemodynamics and exposure to exogenous materials in VADs. This relationship between CHD and hemostatic abnormalities is discussed in a recent review by Ghbeis and colleagues,[12] but there is limited understanding of how the coagulation cascade in patients with CHD interacts with VADs.

Limitations

Our study is limited by its retrospective design, its single-center nature, and relatively small sample size when compared with multicenter studies. Despite the use of a multivariable model, there is still the potential for confounding as the result of variables not examined or potentially changed over time. This can only be addressed with a larger sample size and the incorporation of matching.

CONCLUSIONS

These analyses demonstrate increased hazard of TE events in patients managed with heparin compared with patients managed with bivalirudin and in patients with a PC device strategy. Although other studies have shown associations between bivalirudin and decreased incidence of TE events, this multivariate study has demonstrated the independent significant clinical benefits of DTIs in this patient population. Investigations into time to anticoagulation targets and the thrombolytic properties of bivalirudin will be required to fully understand the mechanisms underlying these advantages. Furthermore, additional research is required to determine how specific anticoagulation strategies interact with various device types.

Conflict of Interest Statement

H.B. reported consultant for Abbott. D.H.F. reported consultant, Bridge to Life; and founder, Tevesol Inc. J.C. reported unrestricted grant from Abbott; and medical monitor, Pumpkin Trial. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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