Thrombosis Research 173 (2019) 65–70

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Bleeding and thrombotic events occur early in children on durable ventricular assist devices

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ARTICLE INFO

Keywords:
Ventricular assist device
Mechanical circulatory support
Pediatrics
Heart failure
Thrombosis
Bleeding

ABSTRACT

Introduction: Durable Ventricular Assist Devices (VADs) are increasingly used in children with end-stage heart failure. Major complications are bleeding and thromboembolism (TE). Our objective was to determine the timing, incidence and risk factors for bleeding and TE in children implanted with VADs.

Methods: This was a retrospective cohort of 8 years experience for children implanted with HeartWare HVAD and Berlin Heart EXCOR VADs at the Royal Children's Hospital, Melbourne.

Results: 44 patients were implanted with Berlin Heart EXCOR or HeartWare HVAD devices. Major bleeding occurred in 17 patients (39%), 7 (16%) experienced thromboembolic strokes, 13 (30%) required device exchange for TE, and 4 (9%) experienced arterial thromboembolism. Twenty-seven patients (61%) were transplanted, three (7%) recovered, and six (14%) remain on device when censored. Eight patients (18%) died on VAD, with leading causes being thromboembolic stroke and intracranial bleeding. The majority of bleeding events and thromboembolic events occurred while patients were on unfractionated heparin (bleeding 66%, TE 40.5%) or transitioning between heparin and warfarin (bleeding 22%, TE 38%). Majority of patients were on more than one antiplatelet agent at the time of a major bleeding (87%) or thromboembolic (89%) event.

Conclusions: The majority of bleeding and TE events occurring in children supported with durable VADs occur when they are on unfractionated heparin or transitioning to warfarin. Modifications to anticoagulation and monitoring in the early post-operative periods should be a research focus.

1. Introduction

Ventricular Assist Devices (VAD) are an increasingly utilized therapy for long-term support in pediatric end-stage heart failure (HF) patients. Durable VADs are artificial pumps designed to provide cardiac support for months to years, and are most often employed in children as a bridge-to-transplantation or as a bridge-to-recovery. The main devices used in children at present include the Berlin Heart EXCOR (BHE)

Abbreviations: aPTT, activated partial thromboplastin time; BHE, Berlin Heart EXCOR; HF, heart failure; INR, International Normalized Ratio; LMWH, Low Molecular Weight Heparin; PRBC, packed red blood cells; SD, standard deviation; TE, thromboembolism; UFH, unfractionated heparin; VAD, Ventricular Assist Device

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https://doi.org/10.1016/j.thromres.2018.11.019
Received 14 October 2018; Received in revised form 15 November 2018; Accepted 19 November 2018
Available online 22 November 2018
0049-3848/

(Berlin Heart AG, Berlin Germany) and HeartWare HVAD (HeartWare Inc., Framingham, MA, USA), with contemporary survival rates for patients on these devices ranging from 75% to 92% [1–4].

Two common complications of VAD use are thromboembolism (TE) and bleeding, despite the protocolized use of antiplatelet and anticoagulant therapies supported by consistent anticoagulation monitoring. Currently, the optimal antithrombotic therapy for children with VADs is unknown, with a lack of safety and efficacy studies in this clinical setting [5,6]. Pediatric VAD anticoagulation is particularly challenging as the hemostatic system of children is continuously maturing, a concept known as developmental hemostasis [5]. Although the rates of bleeding and TE are high, detailed investigation of the related anticoagulation for these events has not been carried out in a pediatric VAD cohort. The management strategies after an event are also lacking, despite this being a high-risk period for further bleeding and TE events.

Thus, this study aimed to address these knowledge gaps by evaluating the timing, incidence and associated anticoagulation or risk factors surrounding bleeding and TE events in children on VAD at the Royal Children's Hospital, Melbourne, Australia, as the National Pediatric Transplant Centre which cares for all Australian pediatric VAD patients.

2. Methods

This was a single-center retrospective chart review of children aged 0–18 years old implanted with a durable BHE or HeartWare HVAD VAD at the Royal Children's Hospital. The study period included all patients implanted from the hospital's first BHE VAD implantation in October 2009, until July 1, 2017. Clinical data were collected from the medical record of each patient, either from paper records or the hospital's recently implemented electronic medical records. All data was entered into the REDCap™ web based database specifically designed for this study. Patients requiring BHE or HeartWare VAD support, who were ≤18 years of age at the time of VAD implantation were included. Patients supported with only short-term centrifugal VAD devices were excluded. All patients were followed up for the duration of their VAD support period, or until end of study period (censored July 1st 2017). The 'general outcome' was determined when the child was taken off VAD therapy due to death, heart transplantation or ventricular recovery. Patient survival post-transplant was recorded until November 9th 2018.

Ethics approval was obtained from the Royal Children's Hospital, Melbourne (HREC 37047A) and Monash University Human Research Ethics Committee (project number: 8776). The need for consent was waived due to the negligible risk of the study and in the public interest. All data was de-identified for data analysis and publication purposes.

2.1. Outcomes assessment

Bleeding and TE events were determined from the time of durable VAD implantation to heart transplantation, explant or death depending or whichever was first. The definitions for bleeding and TE were determined a priori to ensure consistent categorization. Thrombotic events included: thromboembolic neurological events (thromboembolic stroke, transient ischaemic attack); arterial thrombosis (thrombosis in visceral organs or peripheral arteries); pump exchange (pump change due to fibrin or clot); and intracardiac thrombosis (thrombosis in the heart chambers). Major bleeding was defined as bleeding into a major organ (including intracranial hemorrhage) or requiring surgery or transfusion of packed red blood cells (PRBC) as follows:

- During first 7 days post implant
  - ≥ 50 kg: ≥4 units PRBC within any 24-hour period during first 7 days post implant
  - < 50 kg: ≥20 cm^3/kg PRBC within any 24-hour period during first 7 days post implant
- More than 7 days post implant
  - Any transfusion of PRBC

Thromboembolic neurological events and intracranial hemorrhage were diagnosed by Computerized Tomography scans. Minor bleeding was any other record of bleeding if the major bleeding definition was not met. Presence of fibrin in the pump or cannulas was also noted but not included as a TE event, if this did not trigger a pump head change. A number of clinical and laboratory variables were also recorded, including patient demographics, VAD-related variables, anticoagulation, hematological monitoring tests, and outcomes.

2.2. Statistical analysis

Data was analyzed using the Stata 14.0 statistical software package (StataCorp LLC, College Station, Tex). Figures were made using Stata 14.0 software.

Shapiro-Wilk test was utilized to assess normality of the baseline data (e.g. patient demographics, VAD-related characteristics). For descriptive statistics, discrete variables were reported as number or (%) for proportions. Continuous data were described as mean (standard deviation [SD]) for normally distributed data and median (interquartile range) for non-normally distributed data.

The numbers of clinical events of each type were stratified by VAD type, and event rates were calculated per 100 patient-months. In addition, time to first major bleeding or TE was plotted using the Kaplan-Meier estimate. Patients were censored at death, heart transplantation, VAD explantation due to recovery, and on 1st July 2017 for those who remained on device. Patient survival post-transplantation was also censored on the 1st July 2017.

Where appropriate, discrete categorical variable differences between children who experienced TE or bleeding and those who did not experience these events was determined by Fisher's exact test for contingency tables with an expected frequency of < 5 in a cell and by chi-squared test for larger contingency tables. Continuous variables were compared using the student *t*-test for normally distributed data and a Mann-Whitney *U* test for non-normally distributed data. Statistical significance for all analyses was considered when P-values < 0.05.

For analyses of potential associations with TE or bleeding, logistic regression with odds ratio and 95% confidence intervals (CI) was utilized. Variables were analyzed in a univariate model to identify potential significant associations (P-values < 0.05) and entered into multivariate models with age and VAD type to identify if there were any confounders between these associations. Due to a large number of comparisons, we adjusted the α level using a Bonferroni correction according to the number of variables tested. The significance level for statistical association was a P value < 0.0002 (Bonferroni correction factor 193).

3. Results

3.1. Patient characteristics

The study cohort consisted of 44 patients implanted with durable VADs (BHE, n = 34; HeartWare HVAD, n = 10). All patients met the study inclusion criteria and were included in the final study analyses. The characteristics of the cohort are presented in Table 1. Support was via a left VAD in 35 children (80%), a biventricular assist device in 5 (11%) and VAD for single-ventricle physiology in 4 children (9%). Three patients had primary biventricular assist device implantation and two patients had staged implants, with the right VADs inserted 22 and 29 days after the initial left VAD implantation.

The median (IQR) support time for patients was 78 days (36 to 144), with a total of 146 patient-months of follow-up. Majority of patients required VAD placement for bridge to transplantation (n = 37, 84%), followed by bridge to recovery (n = 7, 16%). The primary reason for

Table 1
Patient characteristics for children supported with Berlin Heart EXCOR or HeartWare HVAD ventricular assist devices at the Royal Children's Hospital from October 2009 to 1, July 2017.

Variables	No. (%) or median (IQR) or mean (SD)	
	Berlin Heart EXCOR (N = 34)	HeartWare HVAD (N = 10)
Age (years)	1.39 (0.53–4.12)	13.6 (± 2.5)
Body surface area (m^2)	0.49 (0.37–0.64)	1.49 (± 0.27)
Male	16 (47)	7 (70)
Cardiac diagnosis[a]		
Cardiomyopathy	29 (85)	10 (100)
CHD	2 (6)	1 (10)
Myocarditis	6 (18)	0
Single ventricle circulation	5 (15)	0
Stroke prior to implant	5 (15)	0
Previous cardiac transplant	1 (3)	2 (20)
Pre-operative ECMO	17 (50)	4 (40)
Mean duration (days, SD)	7.47 (± 3.86)	3.75 (± 1.4)
Pre-operative centrifugal VAD	17 (50)	1 (10)
Mean duration (days, SD)	6.76 (± 3.36)	4
Haemofiltration/dialysis, n (%)	3 (9)	0

CHD = congenital heart disease; ECMO = Extracorporeal Membrane Oxygenation; SD = standard deviation; IQR = interquartile range; VAD = ventricular assist device.

[a] Cardiac Diagnoses were not mutually exclusive and each patient could have had multiple diagnoses.

VAD insertion was acute decline in cardiac output (57%), followed by end stage heart failure requiring inotropic and ventilatory support (32%), cardiac arrest (4.5%), worsening tachyarrhythmia (4.5%), and decline in respiratory function (2%).

3.2. General outcomes

Thirty-eight children (86%) survived to 30-days after VAD implantation, including 10 (100%) Heartware and 28 (82%) BHE patients. 91% (32/35) of LVAD patients and 100% (5/5) of BiVAD patients survived to 30-days post-VAD implantation. Of the 44 children in the study, 27 (61%) survived to transplantation, and 3 (7%) were successfully weaned from the device following recovery. Twenty-five patients survived post-transplant. Two patients died post-transplant: one patient died five days post-transplant from TE stroke, and the other patient died six months post-transplant due to antibody mediated rejection. Eight (18%) patients died while on VAD support, resulting in a total of 10 (23%) deaths in the overall cohort. The primary causes of death during VAD support included TE stroke in 4, intracranial hemorrhage in 3, sepsis in 1, multi-system organ failure in 1, and ineffective VAD support in a single ventricle patient with restrictive ventricular physiology. Six patients (14%) were continuing support on VAD at the time of study cessation.

3.3. Bleeding and TE events

The overall incidence of major bleeding was 39% (95% CI, 24–55) and for TE was 41% (95% CI, 26–57). Table 2 illustrates the incidence of bleeding and TE events, respectively. Eight patients (18%) had both major bleeding and TE events, and 17 (39%) patients had no bleeding or TE events.

Table 3 illustrates the event rate per 100 patient-months with the overall number of events according to VAD type. The total number of patient-months of follow-up is 89 patient-months for BHE, 57 patient-months for HeartWare HVAD. There were no recognized venous TE events in the study cohort.

Figs. 1 and 2 depict the time to first major bleed or thrombotic event, respectively. Time to the first event is illustrated for the BHE (see Figs. 1a, 2a) and HeartWare HVAD (see Figs. 1b, 2b) sub-groups. This analysis demonstrates the likelihood of remaining free of events at any time after VAD implantation, with patients censored at death, heart transplantation or VAD explantation due to recovery. All figures have a steep drop in the initial post-operative period (i.e., within the first 30 days post-implantation) and plateau after approximately the 150-day mark.

3.4. Risk factors

Our statistical analyses of potential risk factors for bleeding and TE did not reveal any significant associations after adjusting P-values for Bonferroni correction ($P < 0.0002$). Variables tested included: sex, age at implantation, adolescent compared with non-adolescent, body surface area, cardiac diagnosis before VAD implantation (e.g. myocarditis, congenital heart disease), stroke prior to implantation, pre-VAD Extracorporeal Membrane Oxygenation, pre-VAD centrifugal VAD, Biventricular versus Univentricular VAD use, previous cardiac operations, haemofiltration, reason for device insertion, presence of implantable cardiac defibrillator, previous number of cardiac hospitalisations, VAD type, concomitant surgery during implantation, arrhythmia during VAD, and death while on VAD.

3.5. Antithrombotic therapy

Anticoagulation protocol varied with each device. For BHE patients the protocol involved unfractionated heparin (UFH) within 24 h of implantation. Patients transitioned to warfarin (target International Normalized Ratio [INR] 3–4) when oral intake was sufficient, and the patient was stable. For HeartWare HVAD patients, UFH was started within 24 h of implantation. Patients were transitioned to warfarin (target INR 2–3) when oral intake was sufficient and the patient was stable. In both BHE and HeartWare HVAD patients, LMWH was occasionally used as an interim bridge or as rescue therapy when the INR was low on warfarin.

In our study cohort, all children received UFH within the first 24 h after VAD implantation and 38 (86%) patients received warfarin. Twenty-four (55%) patients received LMWH, and we bridged 18 BHE patients on warfarin therapy with LMWH when the INR was < 2.7 and five Heartware HVAD patients when the INR was < 1.8 with doses of 0.5–1 mg/kg BD. Three patients received antithrombin supplementation, but antithrombin administration and monitoring is not routine as part of our anticoagulation protocol.

During the study period, the antiplatelet protocol for VAD patients included aspirin (5 mg/kg/day) alone for Heartware HVAD and in conjunction with dipyridamole (1–2 mg/kg/dose 3 times a day) or clopidogrel (0.2 mg/kg/day) for BHE, commencing at 6–24 h post-operatively once there is no bleeding. We do not conduct routine antiplatelet monitoring to test for antiplatelet response. In our cohort during the VAD support period, 42 patients (95%) received aspirin, 29 (66%) clopidogrel, 18 (41%) dipyridamole, and 7 (16%) tirofiban. Of the 42 patients who received aspirin, 23 (52%) started aspirin within the first 24 h postoperatively. Seven of the 18 patients (29%) who received dipyridamole were started on the medication within the first 24 h postoperatively. Tirofiban was used intermittently at a dose ranging from 0.1–0.4 μg/kg/min for patients with poor oral intake or concerns regarding the absorption of the regular antiplatelet agents.

Table 4 illustrates the antithrombotic agents a patient was receiving at the time of a bleeding or TE event. The majority of bleeding events (66%) and TE events (40.5%) occurred while the patient was on UFH as the only anticoagulant therapy. The transition period between UFH and warfarin is another time where bleeding (22%) and TE (38%) events occurred. Regarding antiplatelet use, 87% of major bleeding events and 89% of TE events occurred when the patients were on some form of an antiplatelet agent.

Of the 32 bleeding events, UFH was ceased in the 6 of 29 (21%) events and warfarin was ceased in 5 of 9 events (56%). Aspirin was

Table 2
Incidence of bleeding & thromboembolism events.

Outcome	Total N = 44, n	Incidence % (95% confidence interval)	Number of patients with more than one event	Maximum number of events per single patient	Total number of events
Minor bleed	11	25 (13, 40)	4	14	28
Major bleed	17	39 (24, 55)	6	4	32
Chest re-exploration	6	14 (5, 27)	2	3	9
ICH	3	7 (1, 19)	0	1	3
TE event	18	41 (26, 57)	8	5	37
TE neurological (stroke)	7	16 (7, 30)	1	3	9
Arterial thrombosis	4	9 (3, 22)	1	2	5
Device exchange	13	30 (17, 45)	5	3	12
Intracardiac thrombosis	1	2 (−)	0	1	1

ICH = intracranial hemorrhage; N/A = not applicable; TE = thromboembolism; TIA = transient ischaemic attack.

discontinued in 6 of 26 (23%) events, dipyridamole was discontinued in 1 of 9 (11%), and clopidogrel was discontinued in 2 of 8 (25%) events. Of the 37 TE events, three (8%) events resulted in the initiation or re-initiation of UFH and four events (11%) occurred on the day of warfarin initiation or re-initiation. Three TE events resulted in the initiation of clopidogrel and one event resulted in the initiation of aspirin.

3.6. Anticoagulation monitoring – HeartWare HVAD and BHE

No significant association could be identified between activated partial prothrombin time (aPTT) during UFH use or INR during warfarin use and the incidence of bleeding or TE.

4. Discussion

Pediatric VAD is an increasingly utilized option for HF, although device use carries an inherent risk of TE, which is mitigated by intensive anticoagulation therapy. This therapy can cause severe bleeding and requires careful monitoring. Additionally, the current pediatric VAD anticoagulation and antiplatelet protocols have been developed somewhat empirically and have not been extensively evaluated. The results of this study sought to provide knowledge specific to the timing of bleeding and TE events in the context of their anticoagulation therapy.

The major bleeding incidence in our study of 39% is within the previously reported incidences in pediatric VAD patients of 26–57% [2,3,7–10]. The incidence of chest re-exploration for bleeding (14%) is on the lower end of the reported range of 21–47% [9–13] and has significantly reduced compared to the 57% incidence we reported early in our experience [7]. Our incidence of TE stroke was 16% compared to previously reported incidences of 13–29% [2,10,13,14], and our device exchange was 30% compared to a reported 14–56% incidence [8,10,15,16].

Regarding device type, our HeartWare HVAD group had the lowest overall events rates for bleeding and TE with no requirement for device exchange, which is consistent with expectations for a continuous flow device. HeartWare HVAD is only implanted in older children (> 17 kg, body surface area > 0.7 m^2, age usually > 8 years old).

The majority of bleeding and TE events occurred within the first 30 days, suggesting that the initial post-operative period is the most crucial and complicated time for anticoagulation management. Whether the operative procedure itself or the immediate post operative care is the crucial factor remains unknown. The time period immediately post surgery likely means the patients have highest inflammatory activation pushing the haemostatic system towards clotting, and incomplete wound healing pushing the haemostatic system towards bleeding. These results are similar to Byrnes et al.'s and Cassidy et al.'s studies which reflect that majority of chest re-explorations occurred within the first month of support in which many patients had both bleeding and thrombotic complications [11,13]. A major challenge is the subsequent management of anticoagulation and antiplatelet therapy after a bleeding or TE event. Significant bleeding post-operatively and chest re-explorations for bleeding can potentially delay the commencement of anticoagulation and antiplatelet therapy, potentially predisposing the patient to TE events. The adjustment of antithrombotics post-complication is variable as illustrated by the cessation and addition of antithrombotics in our VAD population and may contribute to patients bouncing between bleeding and clotting. Further research to help establish an evidence-based protocol for antithrombotic therapy following a clinical event may be worthwhile.

The majority of bleeding events and TE events occurred when the patient was only on UFH and with warfarin initiation, correlating with the high frequency of events in the initial post-operative period and highlighting the issue of balancing UFH use in a high-risk period for bleeding and TE. The lack of data supporting a specific therapeutic range for UFH in this patient population, and the difficulties in accurate monitoring caused by attempting to obtain non-contaminated samples from central lines, may both be factors that contribute to this observation. The transition period between heparin and warfarin was another time where bleeding and TE events occur. Fourteen TE events occurred in the transition period as compared to seven bleeding events. This transition period may be complicated because of the difficulties in measuring the true cumulative anticoagulant effect of the multiple agents as distinct from their combined effect on the monitoring tests. While the aPTT is used to monitor UFH therapy and the INR used to monitor warfarin, each agent can affect both tests and hence assessing

Table 3
Event rate of major bleeding and thromboembolic events according to Ventricular Assist Device type.

Device	n	Event rate per 100 patient-months (overall number of events)								
		Death (%)	Bleeding				Thromboembolism				
			Overall	GIT	ICH	CR	Overall	Neurological	Arterial	Device	Intracardiac
Berlin Heart EXCOR	34	8 (23)	30 (27)	9.0 (8)	2.2 (2)	7.9 (7)	38 (34)	10 (9)	3.4 (3)	25 (22)	0
HeartWare HVAD	10	0	8.8 (5)	0	1.8 (1)	3.5 (2)	5.3 (3)	0	3.5 (2)	0	1.8 (1)

Arterial = arterial non-central nervous system thromboembolism; CR = chest re-exploration for bleeding; Device = device exchange due to thromboembolism; GIT = gastrointestinal bleeding, ICH = intracranial hemorrhage; Neurological = neurological thromboembolic event (including stroke, transient ischemic attack).

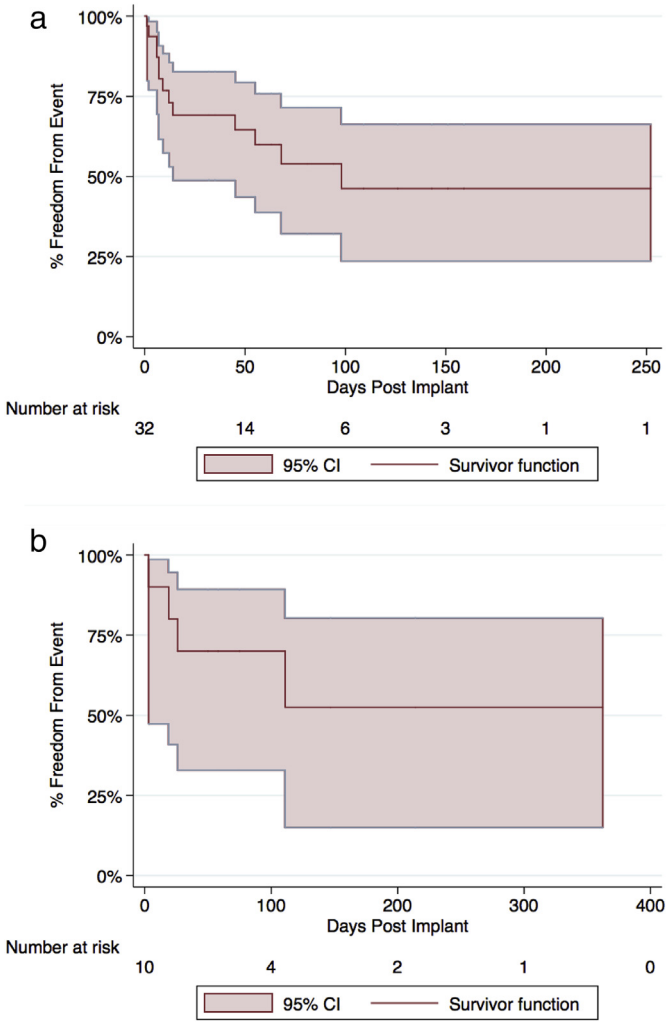

Fig. 1. a. Major Bleeding, time to first major bleeding event for Berlin Heart EXCOR patients.
b. Major Bleeding, time to first major bleeding event for HeartWare HVAD patients.

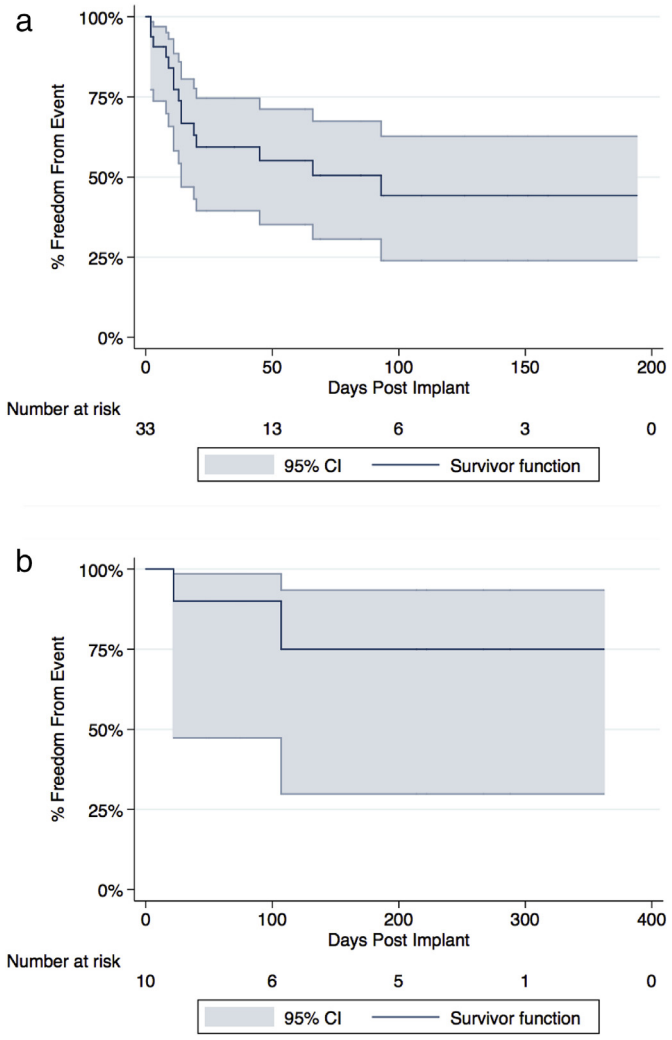

Fig. 2. a. Thromboembolic Events, time to first thrombotic event for Berlin Heart EXCOR patients.
b. Thromboembolic Events, time to first major thrombotic event for HeartWare HVAD patients.

the true anticoagulant effect during the transition period can be difficult. Delaying the time of transition until the patient is more generally stable may be a potential strategy for reducing the risk but further research is required.

Warfarin management is particularly challenging in children, especially in the infant age group [17]. Hence, LMWH has been a suggested alternative in children on VAD < 12 months old, as it can be given subcutaneously and lacks the risk of interference by diet or other medications [17]. The current target anti-Xa range of 0.8–1.1 units/mL is empiric and further study into establishing an optimal target anti-Xa range for VAD patients would be useful [18]. The impact on the bone density of longer-term high dose LMWH has not been established. However, this is likely increased in small infants because they are undergoing the maximal rate of bone growth.

Regarding antiplatelet agents, 87% of major bleeding events and 89% of TE events occurred when the patients were on some form of an antiplatelet agent. Some patients were receiving three antiplatelet agents at the time of a thrombotic event, questioning the effectiveness of the antiplatelet therapy in preventing TE. Currently there is no way to differentiate between poor absorption (many VAD patients have poor gut function especially early after implantation), or true drug resistance. The effect of antiplatelet agents on the VAD hemostatic system should be evaluated given that the platelets in VAD children may respond differently, and there is currently no standardized measure for determining antiplatelet response. A previous study by Steiner et al. [8] utilized monitoring tests such as TEG and platelet mapping for monitoring antiplatelet activity, and illustrated a difference in antiplatelet monitoring results between patients with and without bleeding or neurological outcomes in the setting of VAD in children. However, Rosenthal et al. showed no benefit to monitoring over weight based dosing in terms of bleeding and thrombotic outcomes including stroke [19]. Future prospective study of coagulation and platelet parameters in pediatric VAD patients could assist in providing a more comprehensive understanding of how the coagulation system functions in these complex children.

Although knowledge of the overall incidence and timing of bleeding and TE events provides a sense of the burden of these complications, different adverse events have different impacts on mortality and morbidity for each patient. The presence of neurological complications has been associated with a reduced quality of life in children on VAD as a bridge-to-transplant compared to children who underwent heart transplantation without VAD support [22]. In a cohort of 50 pediatric VAD patients, patients with a greater improvement in functional status during VAD support and fewer adverse events were more likely to have successful bridge to transplantation [4]. Future evaluation of the lasting effects of bleeding and TE events in larger cohorts would be useful for

Table 4
Antithrombotic therapy at the time of bleeding and thromboembolic events in patients on ventricular assist devices.

	Major Bleeding event (n = 32, %)	Thromboembolic Event (n = 37, %)
Anticoagulants		
Single agent		
UFH	21 (66)	15 (40.5)
LMWH	0	0
Warfarin	2 (6)	5 (13.5)
UFH & LMWH	1 (3)	1 (3)
UFH & warfarin	7 (22)	14 (38)
LMWH & warfarin	0	2 (5)
No agent	1 (3)	0
Antiplatelet agents		
Single agent	9 (28)	4 (11)
Aspirin	8 (25)	2 (5)
Dipyridamole	0	0
Clopidogrel	0	1 (3)
Tirofiban	1 (3)	1 (3)
Dual agents	19 (59)	26 (70)
Aspirin & dipyridamole	9 (28)	4 (11)
Aspirin & clopidogrel	7 (22)	17 (46)
Aspirin & tirofiban	2 (6)	5 (14)
Clopidogrel & tirofiban	1 (3)	0
Triple agents	0	3 (8)
Aspirin, dipyridamole, clopidogrel	0	2 (5)
Aspirin, clopidogrel, tirofiban	0	1 (3)
No antiplatelets	4 (13)	4 (11)

LMWH = Low Molecular Weight Heparin; UFH = unfractionated heparin.

understanding the consequences of VAD on morbidity in pediatric patients.

4.1. Study limitations

Our study is limited by its retrospective nature, limitation to a single center, and the multiple changes in clinical practice and protocols within the study period. Data may be missing in chart reviews, and the free-text format in medical charts can be difficult to interpret. Other limitations of the study design include the small patient numbers, and that the data collector was not blind to the study aims. The size of our retrospective cohort may have been inadequately powered to detect significant potential risk factors for bleeding and TE.

5. Conclusions

In summary, this is the first specific evaluation of bleeding and TE events evaluated in the context of the associated antithrombotic therapies. The outcomes and features associated with bleeding and thrombotic events in this pediatric VAD population provide an opportunity to refine the anticoagulation and antiplatelet protocols. A significant knowledge gap still exists in the understanding of the effectiveness and optimal monitoring strategies for antithrombotic therapies. As more patients are placed on pediatric VADs, and the devices improve, further evaluation of different practices to reduce bleeding and TE rates can be evaluated. Continued monitoring of complications and evaluation of management protocols is vital for ensuring the best outcomes in this rapidly developing practice.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

All authors report that they have no relationships relevant to the contents of this paper to disclose.

Acknowledgements

None.

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