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Antithrombotic Therapy in a Prospective Trial of a Pediatric Ventricular Assist Device

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Efficacious ventricular assist device (VAD) support in pediatric patients depends on successful antithrombotic management. The experience with antithrombotic management for the EXCOR Pediatric VAD Investigational Device Exemption (IDE) study is described. All 68 children in North America enrolled in the IDE study from May 9, 2007 to December 10, 2010 are included. The Edmonton Anticoagulation and Platelet Inhibition Protocol was provided for management guidance. Monitoring parameters, drug dosing, targeted serious adverse events, and pump changes were reviewed. Major bleeding occurred in 43% of all subjects with most events occurring within 14 days of implantation. Bleeding events were probably/definitely related in 24% to antithrombotic management. Neurologic events occurred in 28% of subjects and were probably/definitely related in 9% to antithrombotic therapy intensity. Most neurologic events occurred between 4 and 30 days postimplantation and sporadically thereafter. Pump change occurred in 56% of subjects. Use of an antithrombotic protocol for enrolled subjects was possible in this multicenter study. Incidence of significant bleeding and thromboembolic events was acceptable when balanced against life-saving benefits of VADs. Further studies are needed to optimize the antithrombotic management of this patient population. *ASAIO Journal* 2016; 62:719–727.

Key Words: anticoagulation, ventricular assist device, pediatric, hemostasis

Heart failure in children results in either mortality or heart transplant in 46% within 5 years of diagnosis.[1] Although survival posttransplant has increased to approximately 87% at 3 years,[2] donor availability is limited and many children die on waiting lists.[2] Mechanical circulatory support can provide a bridge to heart transplant in life-threatening heart failure. Ventricular assist devices (VADs) have been increasingly utilized to extend the time of support to transplant in adults. The Berlin Heart EXCOR Pediatric VAD (EXCOR) IDE study (cohorts 1 and 2) demonstrated a significantly higher bridge to transplant or wean rate as compared with historical matched extracorporeal membrane oxygenation (ECMO) controls. However, the use of VAD support in children requires successful hemostasis and thrombosis management, balancing the risk of thromboembolic complications with potential life-threatening bleeding.[3] To optimize EXCOR patient management, the Edmonton Anticoagulation and Platelet Inhibition Protocol (protocol), an antithrombotic management guideline, was developed for the EXCOR Investigational Device Exemption (IDE) study. This study evaluates protocol use within the EXCOR study as follows: 1) outcomes using a predetermined management strategy; 2) features associated with thromboembolism or hemorrhage; and 3) future management modifications to limit morbidity and mortality.

Materials and Methods

In the EXCOR IDE study (a prospective, multicenter, single-group cohort study, 17 pediatric cardiac center study in the United States and Canada), a total of 68 subjects ≤16 years of age, who weighed 3–60 kg and had two ventricle circulation, severe heart failure, and were on the cardiac transplant waiting list, were recruited. The full inclusion/exclusion criteria details are described in the published study summary.[4,5] Cohort 1 included children less than 0.7 m^2, and cohort 2 children at least 0.7 m^2 but less than 1.5 m^2. In addition, following planned study recruitment, subjects continued to be recruited into cohort 1, known as continued access cohort, and are included in this analysis.[4–6]

The protocol for the EXCOR study was developed after literature review and expert opinion, incorporating modulation of both coagulation and platelet function.[7] The protocol is a detailed guideline for anticoagulation and antiplatelet therapy using standard management of anticoagulant (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH] and warfarin) and thromboelastography (TEG, Haemonetics, Braintree, MA) results to modify therapy. Protamine is used to reverse heparin effect after cardiopulmonary bypass for VAD implantation. When bleeding is minimal at 24–48 hours postimplantation, UFH is started, titrating to an antifactor Xa (anti-Xa) level

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0.35–0.5 units/ml and corresponding partial thromboplastin time (PTT) 1.5–2.5 times the subject's baseline. Thromboelastography is obtained before implantation, immediately after implantation, and then at least every 24 hours. The UFH is adjusted to maintain a TEG Kaolin R-time between 8 and 15 minutes. At 48 hours, antiplatelet therapy is generally started; dipyridamole is begun at 4 mg/kg/day if the patient is stable and meets specific laboratory parameters (platelets > 40,000/ul, TEG Maximum Amplitude obtained with citrated kaolin with heparinase (MA_{CKH}) > 56 mm). After chest tube removal, acetylsalicylic acid (aspirin, ASA; 1 mg/kg/day divided twice daily) is initiated according to TEG/Platelet Mapping parameters if the MA_{CKH} remains >72 mm, ADP Net G> 8 (calculated from the product of the baseline G_{CKH} and [100% – % adenosine diphosphate (ADP) inhibition/100]), and arachidonic acid (AA) % inhibition is <70% compared with the standard activator line in the TEG Platelet Mapping assay. Long-term anticoagulation for stable patients ≤12 months of age includes transitioning from UFH to LMWH (enoxaparin 1.5 mg/kg every 12 hours if ≤3 months old, 1 mg/kg every 12 hours if >3 months) with goal anti-Xa 0.6–1.0 units/ml. In children >12 months, long-term oral anticoagulation with warfarin is started at 0.2 mg/kg/day and titrated to maintain an international normalized ratio (INR) 2.7–3.5. Subjects were occasionally transitioned back to UFH from LMWH or warfarin if they were medically unstable or bridging to/from an invasive procedure. Anticoagulant (UFH/LMWH/warfarin) and antiplatelet (dipyridamole/ASA) doses were subsequently adjusted according to the protocol (**Figure 1**). Study sites were instructed to follow the protocol, however, physicians could diverge to provide best care.

Monitoring data from the primary (PTT, INR, anti-Xa) and secondary (TEG and platelet mapping [AA % inhibition and ADP NetG]) laboratory tests and drug dosages from preestablished time points at 1, 2, 4, 6 weeks, and 3 months and at the time of serious adverse event (SAE) were reviewed. Monitoring data were included and analyzed when the subjects were on the associated anticoagulation or antiplatelet medication. Testing for underlying prothrombotic predisposition was recommended preimplantation and included Protein C, Protein S, Factor V Leiden, Prothrombin 20210 defect, and heparin-induced thrombocytopenia.

An independent committee adjudicated all SAEs using definitions within INTERMACS (United States national registry for mechanical circulatory support device therapy) established *a priori*.[8] Targeted events reviewed included major bleeding, neurologic events, major infection, and pump changes for suspected thrombus. Thromboembolic and hemorrhagic events were reviewed for relatedness to the protocol management.

Summary statistics are presented as medians and ranges or number with percentage. Demographic characteristics were compared using the χ^2 test or Fisher's exact test where appropriate, for categorical variables and the Kruskal–Wallis test for continuous variables.

The IDE study protocol was approved by the Institutional Review Board at each site, and written informed consent was obtained for all subjects.

Results

There were 24 subjects in cohort 1 with an additional 20 subjects in the continued access cohort and 24 subjects in cohort 2. Analysis demonstrated significant differences in the medians of age, height, weight, and body surface area between cohort 1 and continued access subjects *versus* cohort 2 as expected, because cohort 2 subjects were larger by definition. However, all other demographic and preimplant variables as summarized in **Table 1** were not significantly different between cohorts, and therefore these groups were combined for this review. Potential age-related differences were explored for certain medications (UFH, LMWH, and warfarin).

Management

Medication doses at scheduled follow-ups are presented in **Figure 2**. Unfractionated heparin, LMWH, and antiplatelet agent dosages were widely variable. Too few subjects received warfarin to reliably determine a typical/generalizable dose range (only 4–11 subjects at prespecified reporting times). Median UFH dose decreased beyond 2 weeks of implantation, whereas LMWH and warfarin increased. Median dose of antiplatelet agents increased over time. Age-related dose differences were demonstrated in subjects receiving UFH who were <12 and ≥12 months (30.0 *vs*. 23.0 unit/kg/hour; $p < 0.001$).

Medication doses were compared between subjects implanted with a left ventricular assist device (LVAD) and biventricular assist devices (BVAD). Median doses were higher in subjects with a BVAD for UFH (30 *vs*. 23 unit/kg/hour; $p = 0.005$) and ASA (6.8 *vs*. 2.8 mg/kg/day; $p = 0.002$) only.

Monitoring

Monitoring data were collected at the specified follow-up points (**Figure 3**). Overall, the prespecified monitoring data for all agents were 83% complete. Low-molecular-weight heparin anti-Xa was in protocol target range 54%, and UFH anti-Xa and UFH PTT were in protocol target range 32% at reported follow-up visits. Dipyridamole ADP NetG and ASA AA % inhibition were in protocol target range 31% and 28%, respectively. Monitoring parameters achieved target range by 2 weeks postimplantation for 35% of UFH anti-Xa, 46% of UFH PTT, and 62% of LMWH anti-Xa values. Compared with BVAD subjects, LVAD subjects had higher median UFH PTTs (61.5 *vs*. 49 second, $p = 0.018$) and ASA AA % inhibition (72 *vs*. 53%, $p = 0.022$) despite lower median UFH (23 *vs*. 30 unit/kg/hour, $p = 0.005$) and ASA doses (2.8 *vs*. 6.8 mg/kg/day, $p = 0.002$).

Prespecified monitoring data were not uniformly collected at the time of events but was obtained for 74% of the requested studies. Overall, 40% of all monitoring values for all agents were within the target range.

Events

Laboratory values were compared in subjects with and without events. Sequential occurrence of events and relatedness of event to antithrombotic management is summarized below.

Major Bleeding Events

Major bleeding events occurred in 43% of subjects with 24% of the events adjudicated to be probably/definitely related to protocol medication. Subjects with major bleeding events had monitoring values for anticoagulant medications above the recommended protocol target range only 22% of the time, ASA AA % inhibition above target range 25% of the time, and never below

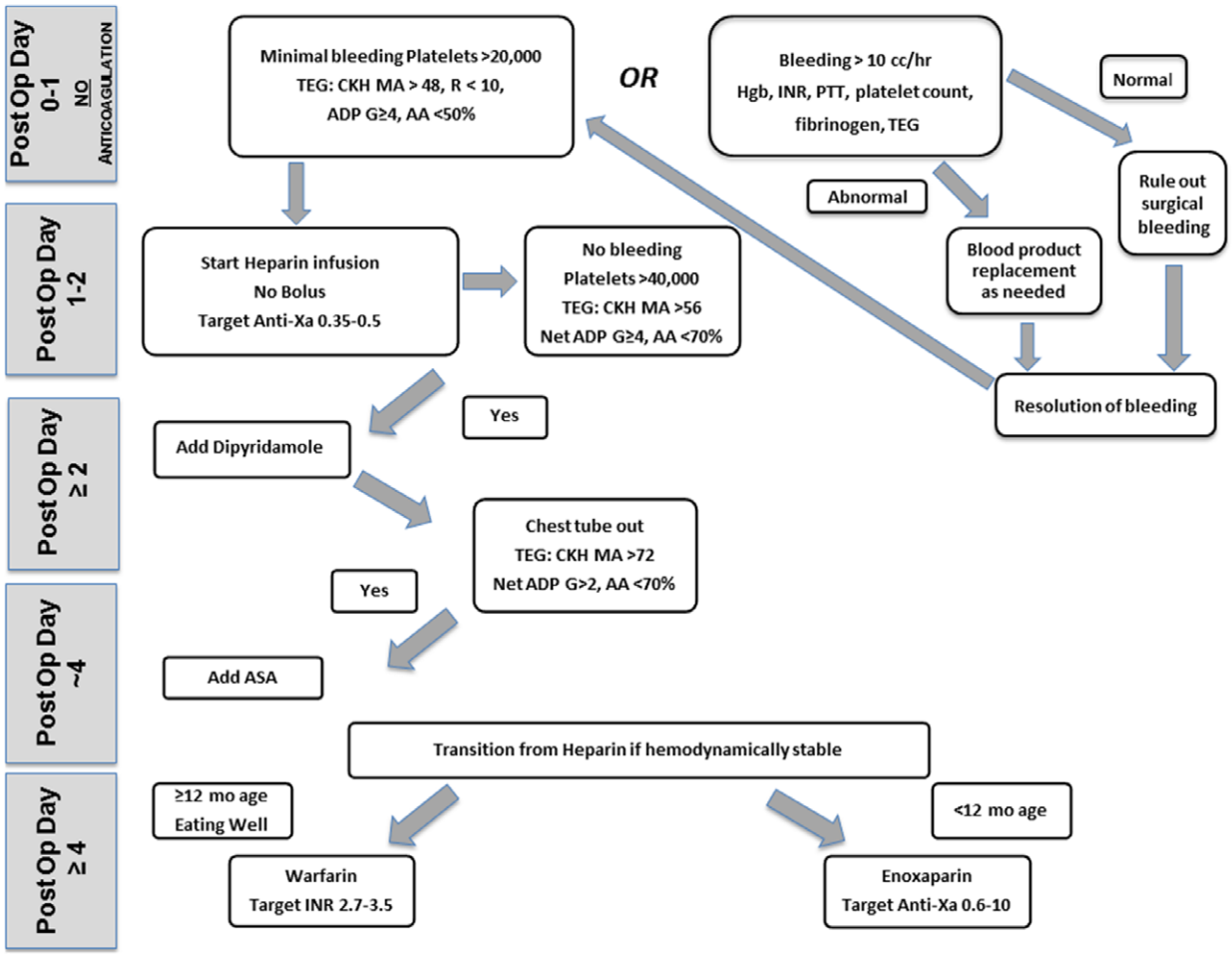

Figure 1. Anticoagulation and Platelet Inhibition Protocol (Edmonton Protocol). Bleeding or clotting issues recurring during therapy are addressed in an individualized manner dependent on etiology and laboratory and clinical parameters. Hgb, hemoglobin; INR, international normalized ratio; PTT, partial thromboplastin time; TEG, thromboelastography.

the protocol target range for dipyridamole ADP NetG. Comparison of overall median laboratory values between subjects who had major bleeding events to those who did not showed significantly higher median ASA AA % inhibition (81 *vs*. 69, $p = 0.033$) and dipyridamole ADP NetG (5.6 *vs*. 3.1, $p = 0.005$). The majority of subjects were on both anticoagulant and antiplatelet therapy at the time of the event. Initial bleeding events post implantation occurred on day 0–2 and day 3–4 in eight and seven subjects, respectively. Overall, 10% of subjects experienced subsequent neurologic dysfunction and 19% a subsequent pump change.

Neurologic Events

Neurologic events occurred in 28% of subjects and were adjudicated to be probably/definitely related to protocol medication in 9%. Subjects had monitoring values below the recommended target range in 78% for UFH anti-Xa, 17% for LMWH anti-Xa, 29% for ASA AA % inhibition, and above target range in 50% of dipyridamole ADP NetG. Comparison of median values between subjects with and without neurologic events showed statistical differences in UFH anti-Xa (0.30 *vs*. 0.39, $p = 0.010$), LMWH anti-Xa (0.6 *vs*. 0.8, $p = 0.013$), and antiplatelet monitoring (dipyridamole ADP NetG 5.8 *vs*. 4, $p = 0.002$; ASA AA% inhibition 88 *vs*. 63, $p < 0.001$), however, medians for the subjects with events were within the target range except for UFH anti-Xa. Subjects were on no antithrombotic medications or anticoagulation alone in nine cases, anticoagulation and one antiplatelet agent in five, and anticoagulation and two antiplatelet agents in 14 cases. Neurologic events followed a pump change in only 10% of subjects experiencing both events. Most neurologic events occurred day 4–30 and only sporadically thereafter. Only two subjects had their neurologic event within the first 4 days postimplantation. Both hemorrhagic strokes occurred in LVAD subjects at 18 and 56 days post ischemic stroke.

Major Infection

Major infection occurred in 50% of subjects. Monitoring values for anticoagulation agents were below target range 60% of the time, below protocol target range for ASA AA % inhibition 39% of the time, and above protocol target range for dipyridamole ADP NetG 19% of the time. Parameters showed statistically lower median UFH anti-Xa (0.3 *vs*. 0.39, $p = 0.024$), higher median dipyridamole ADP NetG (5.27 *vs*. 2.9, $p = 0.005$), and higher median ASA AA % inhibition (88 *vs*. 52, $p < 0.001$) in subjects with major infection. Only median UFH anti-Xa was below the desired

Table 1. Demographic and Implant Variables

Variable	IDE Study n = 68 [Cohort 1, n = 24 Cohort 2, n = 24 Cohort 1 CAP, n = 20]
Age (months), median [range]	25.1 [1.0–191.8]
Height (cm), median [range]	85.9 [50.0–171.0]
Weight (kg), median [range]	12.1 [3.0–58.1]
BSA (m^2), median [range]	0.53 [0.20–1.66]
Female gender	34 (50.0%)
INTERMACS profile 1	30 (44.1%)
Primary diagnosis	
Congenital heart disease	10 (14.7%)
Dilated cardiomyopathy	43 (63.2%)
Hypertrophic cardiomyopathy	1 (1.5%)
Restrictive cardiomyopathy	2 (2.9%)
Myocarditis	12 (17.7%)
Preimplant ECMO	18 (26.5%)
Previous cardiac surgery	15 (22.1%)
Stroke before implant	2 (2.9%)
Active infection at time of implant	3 (4.4%)
Device type:	
LVAD	42 (61.8%)
BVAD	26 (38.2%)
Support time on device (days), median [range]	42.0 [0–192]
Outcome: successfully transplanted/weaned	62 (91.2%)
Death or unsuccessful wean	6 (8.8%)

Unsuccessful wean is weaned subject that dies or has unacceptable neurologic outcome within 30 days of wean (n = 1).

BSA, body surface area; BVAD, biventricular assist device; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device.

target range. At the time of infection event, 31 subjects were on no antithrombotic medication or anticoagulation alone, 38 on an anticoagulant and two antiplatelet agents, three on two anticoagulants and two antiplatelet agents, and two subjects on two antiplatelet agents alone. Overall, 16% experienced a subsequent neurologic event, and 28% experienced a pump change.

Pump Changes Because of Suspected Thrombosis

Pump changes occurred in 56% of subjects. Monitoring values at the time of the change were below the recommended target range 38% of the time for anticoagulants and 40% for ASA AA % Inhibition and below protocol target range 27% of the time for dipyridamole ADP NetG. Comparing subjects with and without pump changes showed significantly higher median LMWH anti-Xa (0.8 *vs*. 0.6, $p = 0.007$) and significantly lower median dipyridamole ADP NetG (4.2 *vs*. 6.2, $p = 0.002$) for subjects with pump changes. Pump changes followed a major bleeding event 19% of the time and followed major infection 28% of the time; 10% of the subjects experienced a subsequent neurologic event. Only four pump changes occurred by day 4. Pump changes were not defined as a study SAE or centrally adjudicated.

Distribution of the 75 pump changes in 38 subjects included 21 with one change, three with two changes, and 14 with three or more changes with most occurring in LVADs (64%). Of the 14 subjects with three or more pump changes, 71% were LVAD only. Subjects with three or more pump changes experienced a disproportionate SAEs, including 21 major infections in 10 subjects (71%; 8 events occurring before initial pump change), nine neurologic events in six subjects (43%), and seven major bleeding events in five subjects (36%). These subjects were supported with the EXCOR longer (median 108 *vs*. 35 days), and their median time to first pump change was earlier than those with fewer changes (median 10 *vs*. 15 days).

Two of the 59 subjects with positive preimplant ELISA heparin-induced thrombocytopenia assays both experienced multiple SAEs or pump changes; confirmatory testing was not collected in the study. Despite protocol recommendations, other procoagulant testing was inconsistently obtained.

Death Because of Thrombosis

Of the five deaths in the study cohort, four were related to thrombotic events (3 stroke, 1 pulmonary embolism), three of whom had BVAD implants.

Discussion

United States Food and Drug Administration approval for the EXCOR partially depended on demonstration of acceptable thromboembolic or hemorrhagic risk-benefit balance. Adult VAD management is challenged by these complications,[9] but no standardized guidelines for antithrombotic management exist. Pediatric VAD patients are similarly challenged,[3] thus the protocol was developed to minimize thromboembolic or hemorrhagic SAEs in neonatal and pediatric patients treated with the EXCOR. In this study, adherence with the protocol was demonstrated by the overall monitoring medians largely achieving target range within 1–2 weeks of implantation although antiplatelet agent effects remained variable. This protocol is unique as the first successful multi-institutional attempt to standardize antithrombotic management of pediatric extracorporeal support.

Antithrombotic management varied by age and across time with broad dosing ranges for all antithrombotic agents (**Figure 2**). The maximum reported dosage of UFH (76 unit/kg/hour) highlights the need to monitor and individualize patient dosing, incorporating circuit volume, degree of coagulation activation, overall higher UFH dosing attributed to variable formulation, or potency.[10] Warfarin management is especially difficult in children,[11] thus administration in patients <12 months was not recommended. Low-molecular-weight heparin median doses in <3 month old subjects are consistent with recently revised dosing recommendations.[12] The AA % inhibition and ADP NetG were used to determine the initiation and modification of antiplatelet agent dosing. Multiple factors (*e.g.*, concomitant medications, cardiopulmonary bypass effects, prior ECMO course, continued bleeding) influence these test parameters. Dipyridamole and ASA dose ranges increased across all ages with increasing duration of EXCOR support, perhaps related to protocol titration or indicating progressive inflammation, vasculopathy, or other accrued events destabilizing hemostasis. Both agents were occasionally dosed higher than generally prescribed, likely because of pharmacologic complexity in this population, lack of pediatric formulation for oral agents requiring local compounding, and enteral absorption inconsistency. However, despite these higher dose ranges, monitoring values did not always achieve target range. This

protocol finding informs potentially increased dosing recommendations in the future.

Serious adverse events were adjudicated to be unrelated to protocol medications in the majority of the cases. This is evidenced by median monitoring parameters at time of major bleeding within the target range, with a statistically higher ADP NetG that would not be consistent with bleeding. Half of the subjects with a bleeding event had their first episode within 4 days of implantation and remained at a higher risk for a subsequent bleeding event over their EXCOR course. When bleeding starts within days post implantation after initiation of anticoagulation, it is possible that raw surfaces or poor tissue integrity present after difficult or repeat dissections may be susceptible to rebleeding with introduction of UFH. Other factors may also contribute to early bleeding such as hypothermia, postimplantation fibrinolysis (demonstrated to be increased in adult studies), persistent coagulopathy, abnormal von Willebrand multimers, residual functional platelet abnormalities, or inadequate postimplantation heparin reversal. Ideally, postimplantation pharmacologic anticoagulation is initiated only when minimal bleeding is evident; bleeding may thus delay the

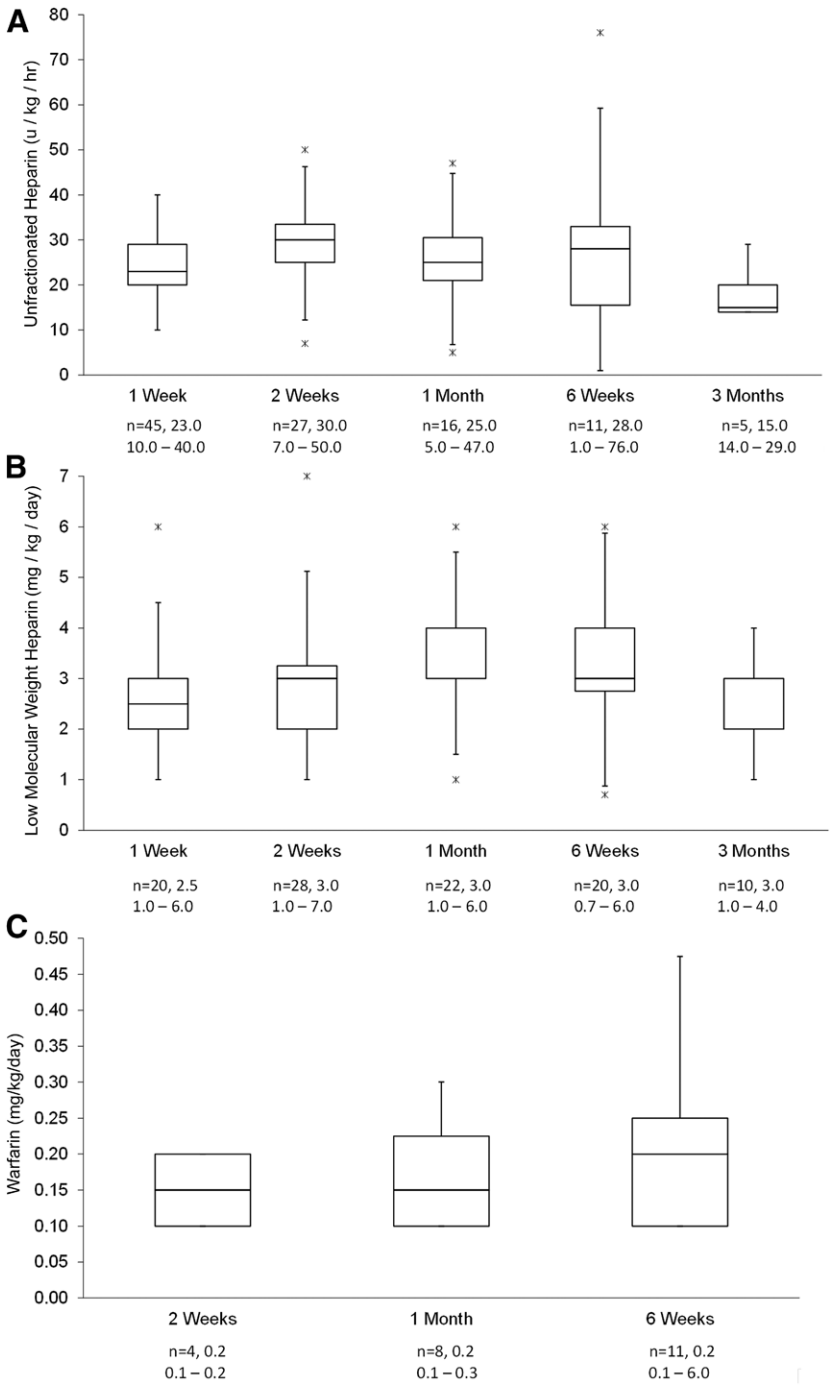

Figure 2. Medication dosages for scheduled follow-ups. Median ±2 SD with "*" as farthest outliers. **A**: Unfractionated heparin; **B**: low molecular weight heparin; **C**: warfarin; **D**: dipyridamole; and **E**: aspirin.

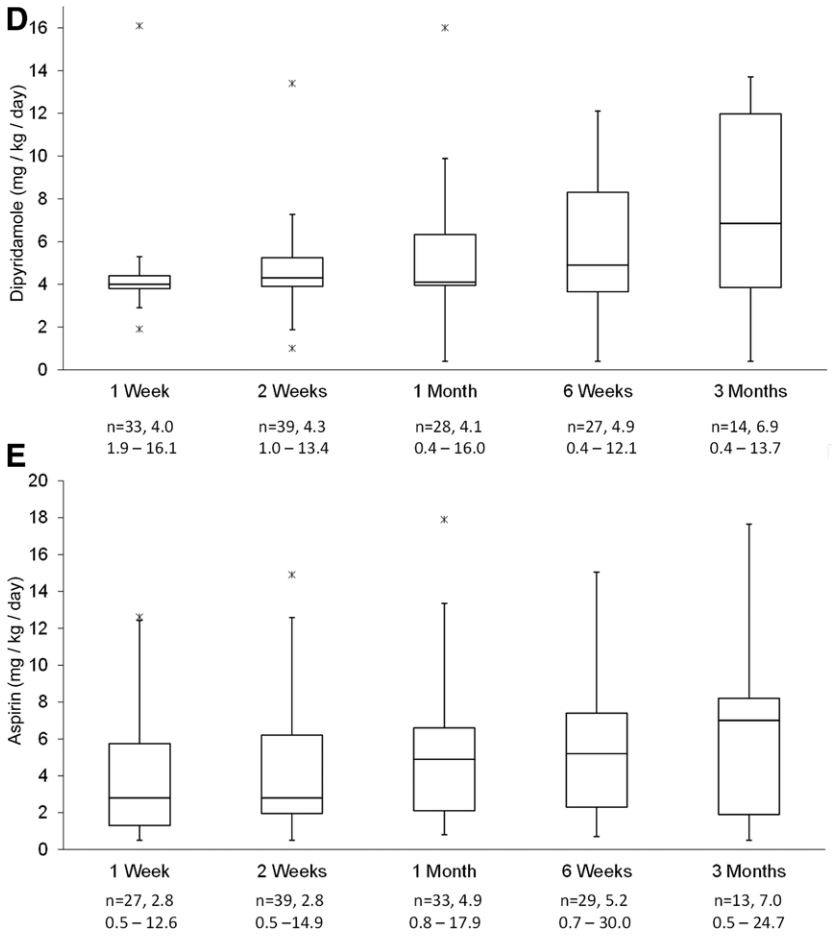

Figure 2. Continued.

commencement and escalation of antithrombotic therapy, predisposing the patient to subsequent SAEs. However, the impact of surgical or postimplantation bleeding on protocol initiation and adherence cannot be fully assessed because of lack of complete systematic data collection, including bleeding characteristics at the time of UFH initiation. In future studies, collection of complete clinical data with concurrent complete hemostatic testing may provide more insight into early bleeding post implantation.

Neurologic events occurred in 28% of subjects with three-quarters occurring within 4 weeks of implantation and the rest occurring sporadically thereafter. Events occurred despite median monitoring values being largely in target ranges, with half the subjects on anticoagulants as well as two antiplatelet agents. This timing and lack of clear association with specific medication use suggests that the first month postimplantation is a period of extreme hemostatic instability and vulnerability to thromboembolic complications.

The relation of infection and inflammation to thromboembolic events is not a novel association. EXCOR implantation is associated with significant and prolonged C-reactive protein elevation,[13] suggesting that ongoing inflammation is highly associated with the development of thrombosis. Most common of the sequential SAE associations was the occurrence of pump change after major infection (28%), reinforcing the likely impact of inflammatory and prothrombotic contribution of immune response during an EXCOR course. Hemostatic perturbations from baseline frequently precede major infection and could be indications for proactive interventions.[14]

Pump change guidelines were not established *a priori* because of the complexity of the decision-making process, producing challenges assessing protocol effectiveness. Pump changes occurred in 56% of subjects with subjects undergoing three or more pump changes having disproportionate SAEs and longer support duration. The monitoring data suggest that there is manipulation of therapy occurring around the pump change. This complication could be more specifically addressed in future protocol modifications.

Serious adverse events experienced with other types of VADs, such as the HeartWare VAD (HVAD), are of variable incidence in comparison to the EXCOR. Miera's series in seven patients (6–16 years) included six with dilated cardiomyopathy and one with congenital heart disease. There were no thromboembolic events in 480 days of accumulated support.[15] However, in his series of 13 younger patients (3.7–10.5 years) <1 m^2 with 61% primary diagnosis of cardiomyopathy/myocarditis, the group had 23% early bleeding and 15% late bleeding events (38% total) along with two (15%) patients with thromboembolic neurologic events and four with (31%) pump thrombosis.[16] Peng *et al*.[17] series of 12 patients were 3.7–17 years, three < 5 years, all but one of whom had cardiomyopathy. Anticoagulation was begun 24 hours after implantation and only when surgical bleeding was <1 ml/kg/hour

for three consecutive hours. Two patients experienced device thrombosis but no neurologic events, two patients required mediastinal reexploration for bleeding and clot removal, and two patients developed ischemic bowel, with one death.[17] The mechanical features and intrathoracic placement of the HVAD are potentially advantageous in terms of reducing thromboembolic complications. However, the Berlin patients reported in this paper included a broad range of patient sizes and a larger proportion of both congenital cardiac disease and infectious diagnoses, which may impact SAEs and outcomes. A larger, adequately powered prospective trial stratifying by patient size and initial diagnosis and using standardized Pedi-MACS SAE definitions would be needed to properly perform VAD comparisons.[18]

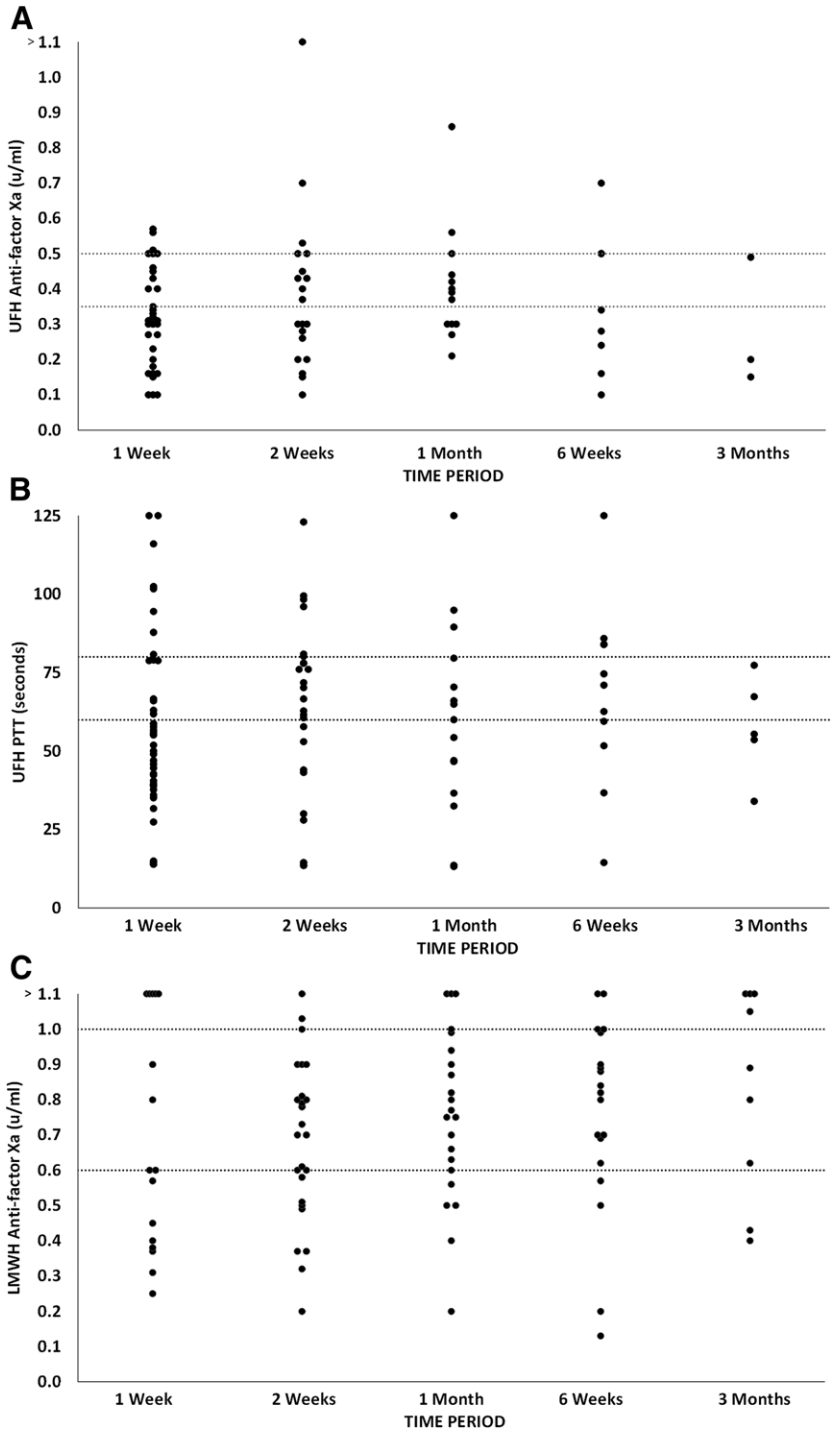

Figure 3. Monitoring values for scheduled follow-ups. **A**: UFH anti-factor Xa; (**B**) UFH PTT; (**C**) LMWH anti-factor Xa; (**D**) warfarin INR; (**E**) dipyridamole ADP Net G; (**F**) ASA AA% inhibition. Dotted lines indicate protocol target ranges. AA, arachidonic acid; ASA, acetylsalicylic acid; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PTT, partial thromboplastin time; UFH, unfractionated heparin.

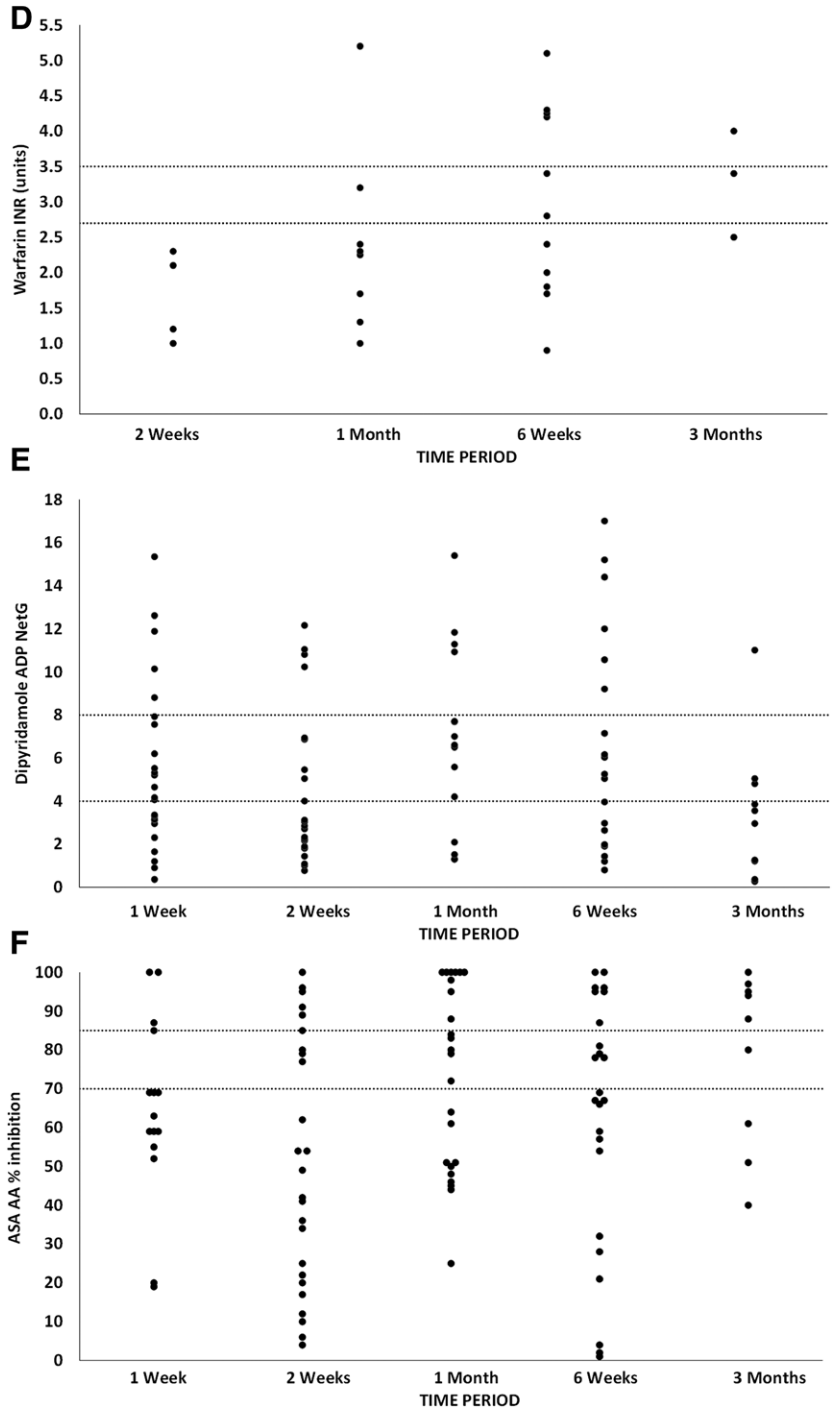

Figure 3. Continued.

Limitations of this study are largely consequences of prespecified laboratory data collection dates and on the day of an SAE or pump change, with inexact timing relative to the actual onset of the event. More comprehensive predetermined data collection design could facilitate more precise protocol evaluation. Aberrant monitoring values can occur from sampling, contamination and timing errors.[19] Additionally, TEG tracings were not centrally reviewed, and results can be misinterpreted, especially with rising activator lines from inflammation, heparin-activated platelets, or other factors[20] and contribute to inappropriate antiplatelet dose titration resulting in increased risk of SAEs. Preexisting procoagulant states and definitive heparin-induced thrombocytopenia testing were not uniformly investigated, which could provide more insight into mechanisms of SAE.

In summary, this is the first multi-institutional standardization of antithrombotic management in EXCOR pediatric patients. The outcomes and features associated with thromboembolism

and hemorrhage provide an opportunity to refine the protocol to reduce thromboembolic complications. The incidence of stroke (28%) and major bleeding (43%) and the four deaths attributed to thrombosis may be decreased by protocol revisions. Consideration could be given to earlier initiation of ASA with more rapid upward dose titration or use of agents with alternative mechanisms of action. Additionally, different methods of monitoring antiplatelet effect could be considered. Unique infant and toddler developmental hemostasis issues, including LMWH dosing, were not fully incorporated into the protocol[11]; earlier therapeutic anti-Xa levels may improve protection from thrombotic events. The association between pump changes with prior major bleeding and infection suggests continuing interplay of complex factors that alter hemostatic and thrombotic balance, including inflammation. The use of anti-inflammatory agents may decrease thrombotic events, but further study is required, as only a single center report demonstrating the association of decreased SAEs with anti-inflammatory therapy has been published.[21] Finally, consequences of surgical and postimplantation hemostasis potentially delay commencement and escalation of antithrombotic therapy, potentially predisposing the patient to subsequent SAEs.

The incidence of significant thromboembolic and hemorrhagic SAEs was deemed acceptable when balanced against the life-sustaining benefit of the EXCOR resulting in FDA approval of the EXCOR. Although the majority of the SAEs were not adjudicated to be related to the protocol, improvement of event-free survival may result from modifications of the protocol. It is critical that future guidelines are prospectively designed, have clearly defined objectives, use the same definitions of SAEs (PediMACS definitions[18]), and collect comprehensive monitoring data with predetermined analysis plans to optimize future antithrombotic modifications.

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