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Impact of a modified anti-thrombotic guideline on stroke in children supported with a pediatric ventricular assist device

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BACKGROUND: Stroke is the most feared complication associated with the Berlin Heart EXCOR pediatric ventricular assist device (VAD), the most commonly used VAD in children, and affects 1 in 3 children. We sought to determine whether a modified anti-thrombotic guideline, involving more intense platelet inhibition and less reliance on platelet function testing, is associated with a lower incidence of stroke.

METHODS: All children supported with the EXCOR at Stanford from 2009 to 2014 were divided into 2 cohorts based on the primary anti-thrombotic guideline used to prevent pump thrombosis: (1) the Edmonton Anti-thrombotic Guideline (EG) cohort, which included children implanted before September 2012 when dual anti-platelet therapy was used with doses titrated to Thromboelastrography/PlateletMapping (TEG/PM); and (2) the Stanford Modified Anti-thrombotic Guideline (SG) cohort, which included children implanted on or after September 2012 when triple anti-platelet therapy was used routinely and where doses were uptitrated to high, weight-based dosing targets, with low-dose steroids administered as needed for inflammation.

RESULTS: At baseline, the EG ($N = 16$) and SG ($N = 11$) cohorts were similar. The incidence rate of stroke in the SG cohort was 84% lower than in the EG cohort (0.8 vs 4.9 events per 1,000 days of support, $p = 0.031$), and 86% lower than in the previous Investigational Device Exemption trial ($p = 0.006$). The bleeding rate was also lower in the SG cohort ($p = 0.015$). Target doses of aspirin, clopidogrel and dipyridamole were higher (all $p < 0.003$), with less dosing variability in the SG cohort than in the EG cohort. There was no difference in adenosine diphosphate inhibition by TEG/PM, but arachidonic acid inhibition was higher in the SG cohort (median 75% vs 39%, $p = 0.008$).

CONCLUSIONS: Stroke was significantly less common in pediatric patients supported with the Berlin Heart EXCOR VAD using a triple anti-platelet regimen uptitrated to high, weight-based dosing targets

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as compared with the dual anti-platelet regimen titrated to PM, and without a higher risk of bleeding. Larger studies are needed to confirm these findings.
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The Berlin Heart EXCOR pediatric ventricular assist device (VAD) is the most commonly used VAD in children.[1,2] The single most feared complication associated with use of the Berlin Heart EXCOR VAD is stroke.[1–7] In the Investigational Device Exemption (IDE) study of the EXCOR, stroke occurred in 1 in 3 children and was the leading cause of death. It is uncertain whether the risk of stroke is fixed and inherent to the pump's older pulsatile design utilizing polyurethane valves[4,8] where most visible clots form (Figure 1), or whether the risk could be modifiable by altering the anti-thrombotic regimen used during Berlin Heart EXCOR support.

The primary anti-thrombotic guideline for the EXCOR (also known as the Edmonton Anti-thrombotic Guideline, EG) consists of 1 anti-coagulant (enoxaparin or warfarin) and 2 platelet inhibitors (aspirin and dipyridamole) that are actively dose-adjusted according to data from PlateletMapping (PM), a platelet function companion assay to Thromboelastography (Haemonetics Corporation, Braintree, MA).[1,9] Although the EG is widely regarded as a groundbreaking development in pediatric mechanical circulatory support anti-coagulation, 3 potential limitations have been identified in light of the high stroke rate observed in the trial. First, thromboembolic strokes significantly outnumbered hemorrhagic strokes, suggesting that the overall hemostatic "set point" for the EG may be targeted too low to prevent clots consistently.[1,2,7] Second, clinical confidence in PM was undermined by the perception of a weak correlation between the dose of anti-platelet therapy and the PM results. Third, studies based on data from Arkansas suggested that the thrombosis risk could be decreased by prophylactic administration of low-dose steroids in the setting of systemic inflammation.[10]

In 2012, we formally revised our institutional anti-thrombotic therapy guideline to address these potential limitations. The overall impact of this modified guideline on the risk of stroke in EXCOR recipients is unknown. Thus, the specific aim of this study was to determine whether our modified anti-thrombotic guideline is associated with a reduction in stroke rate in EXCOR recipients without a simultaneous increase in bleeding. The broader purpose of our study was to improve the safety and survival of children with advanced heart failure supported with the Berlin Heart EXCOR pediatric VAD, the most commonly used VAD in children in the United States.[11]

Methods

Study population

All children <18 years of age implanted with a Berlin Heart EXCOR pediatric VAD at Stanford University between January 2009 and June 2014 were included in our investigation. The study dates were chosen based on when there was consistent use of either the EG (before September 2012) or the Stanford Anti-thrombotic Guideline (SG) (September 2012 or after) in all EXCOR recipients (Table 1). Patients

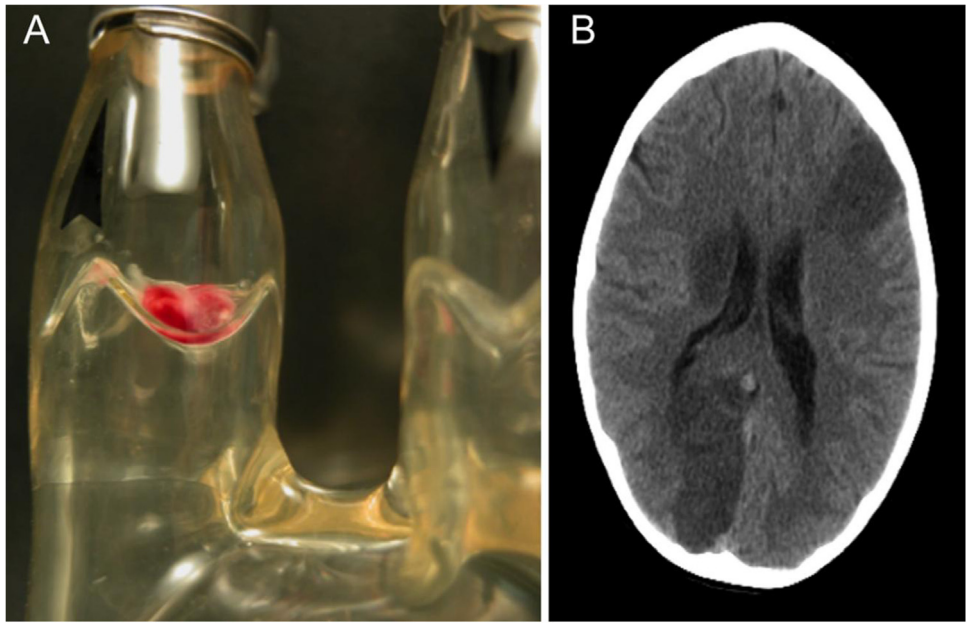

Figure 1 (A) Thrombus located on the outflow valve of a Berlin Heart EXCOR pediatric LVAD. (B) Computed tomography image of a child with embolic stroke on EXCOR support.

Table 1 Comparison of Anti-thrombotic Therapy Targets in the Edmonton and Stanford Anti-thrombotic Guidelines for the Berlin Heart EXCOR Pediatric VAD

	Edmonton Guideline	Stanford Guideline
Anti-coagulant	Enoxaparin (anti-Xa 0.6 to 1.0)	Same
Aspirin	Titrated to AA inhibition of >70% by TEG/PM	Titrated to a weight-based dose of 30 mg/kg/day (maximal dose 2,000 mg/day)
Dipyridamole (Persantine)	Titrated to an ADP Net G[a] 4 to 8 or ADP inhibition >70% by TEG/PM	Titrated to a weight-based dose of 15 mg/kg/day
Clopidogrel (Plavix)	No recommendation	0.2 mg/kg/day (starting) titrated to a fixed dose of 1 mg/kg/dose once daily
Prednisone	No recommendation	As needed for fibrinogen >600 mg/dl or other signs of inflammation (fever, rise in CRP)[b]

AA, arachidonic acid; ADP, adenosine diphosphate; C-reactive protein; IDE, Investigational Device Exemption (study); INR, international normalized ratio; PM, PlateletMapping; TEG, Thromboelastography; VAD, ventricular assist device.

[a]Net G is calculated by subtracting the percent inhibition of ADP from 100%, dividing by 100, and multiplying the value by the baseline G from the citrated specimen activated with kaolin in the presence of heparinase.

[b]Anti-platelet therapy and steroids titrated primarily to achieve an M_A value of between 55 and 65 mm using a citrated specimen activated with kaolin in the presence of heparinase.

were excluded if they were implanted before 2009 ($N = 8$) to avoid introducing an era bias related to a device learning effect that would favor later-term results. All patients were followed from the time of EXCOR implant until explantation or the day of last observation on June 30, 2014.

The SG

The modified SG addressed the perceived weaknesses of the EG by: (1) adding a third platelet inhibitor, clopidogrel; (2) eliminating PM and replacing it with high, weight-based dosing targets of each platelet inhibitor; and (3) administering low-dose prednisone as needed for signs of inflammation (Table 1). The anti-platelet medications were introduced sequentially, in the following order: aspirin, then dypyridamole, then clopidogrel. Each was uptitrated to target before adding the next agent. The guideline did not specify in detail how clinicians should respond to bleeding episodes, but our practice during this period was to briefly interrupt anti-thrombotic therapy for major bleeding episodes (requiring transfusion or surgical intervention), and then to reintroduce therapy after hemostasis was assured, uptitrating rapidly back to the previous level.

Study hypothesis, definitions and outcome measure

To evaluate the effectiveness of the SG in preventing stroke, we tested the hypothesis that, among children supported with the EXCOR, those managed according to the SG had a lower incidence of stroke compared with children managed according to the EG at Stanford. We also tested the hypothesis against a second comparator group, the EXCOR IDE study cohort, for which published event rates are available where a multicenter cohort was treated using the EG.[1,2,12] The primary safety hypothesis was that, among children supported with the EXCOR, those managed according to the SG had a non-inferior rate of bleeding serious adverse events compared with children at Stanford managed according to the EG. We also tested the hypothesis against the published rate of bleeding events in the EXCOR IDE cohort.

Serious adverse events, including stroke, systemic thromboembolism and bleeding, were defined according to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS Protocol Version 3.0) criteria.[11] In these definitions, strokes were categorized as follows:

1. Ischemic stroke: an event that persisted for >24 hours or was associated with infarction on an imaging study.
2. Hemorrhagic stroke: an event that persisted for >24 hours or was associated with parenchymal hemorrhage or hemorrhagic infarction on an imaging study.

INTERMACS profiles were defined according to the classification proposed by Stevenson.[12] Race/ethnicity data were analyzed based on family report. Glomerular filtration rate (GFR) was estimated using the modified Schwartz formula,[13] and was categorized as normal ($\geq$90 ml/min/1.73 m^2), severely decreased (GFR <30 ml/min/1.73 m^2) or moderately decreased for all values in between. Invasive hemodynamic support at transplant was analyzed using previously described categories: VAD; extracorporeal membrane oxygenation (ECMO); ventilator; or none of the above.[14]

TEG/PM parameters, including the maximum amplitude (M_A), percent inhibition to arachidonic acid (%AA inhibition) and percent inhibition to adenosine diphosphate (%ADP inhibition), were reported according to the manufacturer's definitions,[15] and were performed using citrated specimens with kaolin as the activator in the presence of heparinase, unless specified otherwise. Secondary analyses included testing whether rates of stroke or systemic thromboembolic event differed between the 2 groups, whether the target doses of anti-platelet medicines were different, and whether the TEG/PM values were different at the target doses. Target anti-platelet doses were defined as the final dose of each medicine, and TEG/PM values were defined as the average of the last 3 TEG/PM values performed on device support once the target dose of anti-platelet medicines had been achieved. Anti-Xa levels were defined analogously, as the last 3 levels measured at least 48 hours before device removal (in case there was a deliberate dose adjustment made in anticipation of the procedure).

Statistical analysis

Summary statistics for the study groups were presented as median (Quartile 1 to Quartile 3) or number (%) when appropriate. Patients' characteristics across study groups were compared using the chi-square test or Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. The incidence rates of stroke, bleeding, pump exchange and total complications were computed in the EG and SG cohorts, and incidence rate ratios (SG:EG) with 95% confidence intervals were calculated and significance assessed using a 1-sided exact test.

Adverse events in the SG cohort were also compared with the IDE trial data using the same method.[1,9,12]

Results

Between January 2009 and March 2014, 27 children underwent implantation of a Berlin Heart EXCOR pediatric VAD as a bridge to heart transplant at Stanford. Of these, 16 (59%) patients were implanted before September 2012 when the EG was used, whereas 11 (41%) were implanted after September 2012 when the SG was used as the anti-thrombotic guideline. The baseline characteristics of the study cohort are summarized in Table 2. There were no significant baseline differences between the EG and SG cohorts except for the proportion of patients who were INTERMACS Level 1 at implantation, which was 75% for the EG cohort, as compared with 27% for the SG cohort ($p = 0.01$). Baseline brain imaging was obtained in 15 of 16 patients in the EG cohort, and 10 of 11 in the SG cohort ($p = 0.78$).

Overall patient survival before and after heart transplant

Children in the EG cohort were supported for a total duration of 1,220 days (63 [range 31 to 111] days), after which 69% were transplanted, 25% died or deteriorated and 6% recovered. Children in the SG cohort were supported for a total duration of 1,279 days (121 [62 to 190] days), after which 64% were transplanted, 9% died or deteriorated, 9% recovered and 18% were still on support when the study was closed. In the EG cohort, there were 4 deaths (1 hypoxemia, 1 sepsis, 1 multi-system organ failure and 1 withdrawal of support after overwhelming neurologic injury). In the SG cohort, there was 1 death (hemorrhagic shock), which occurred at 48 hours after implantation, in a patient who had

Table 2 Baseline Characteristics of the Study Cohorts Guideline

	Total cohort ($N = 27$)	Edmonton Guideline ($N = 16$)	Stanford Guideline ($N = 11$)	p-value
Age (months)	19.1 (14.4 to 37.1)	19.0 (15.3 to 41.6)	19.1 (13.9 to 25.4)	0.60
Age categories				0.97
<1 year	5 (19%)	3 (19%)	2 (18%)	
≥1 year	22 (81%)	13 (81%)	9 (82%)	
Weight (kg)	7.1 (5.7 to 8.9)	6.8 (5.6 to 9.9)	7.3 (6.3 to 9.3)	0.98
Weight category				0.59
<5 kg	3 (11%)	1 (6%)	2 (18%)	
5 to 9 kg	17 (63%)	11 (69%)	6 (55%)	
>10 kg	7 (26%)	4 (25%)	3 (27%)	
Female gender	15 (56%)	10 (63%)	5 (46%)	0.38
Blood type O	11 (41%)	8 (50%)	3 (27%)	0.15
Cardiac diagnosis				0.40
Dilated cardiomyopathy	14 (52%)	10 (63%)	4 (36%)	
Congenital heart disease	8 (30%)	4 (25%)	4 (45%)	
Other	5 (18%)	2 (12%)	3 (19%)	
Support type				0.95
LVAD	17 (63%)	10 (63%)	7 (64%)	
BiVAD	10 (37%)	6 (38%)	4 (36%)	
EXCOR pump size				0.95
10 ml	17 (63%)	10 (63%)	7 (64%)	
25/30 ml	10 (37%)	6 (37%)	4 (36%)	
Pump:patient size ratio (stroke volume/m^2)	36 (32 to 43)	36 (34 to 40)	38 (30 to 49)	0.89
Total bilirubin (mg/dl)	0.6 (0.4 to 1.2)	0.7 (0.5 to 2.2)	0.4 (0.4 to 0.8)	0.13
Serum creatinine (mg/dl)	0.5 (0.3 to 0.6)	0.5 (0.3 to 0.5)	0.4 (0.3 to 0.6)	0.29
GFR (ml/min/1.73 m^2) categories[a]				0.81
Normal (≥90)	8 (29%)	4 (25%)	4 (36%)	
Moderately decreased (30 to 89)	16 (59%)	10 (63%)	6 (55%)	
Severely decreased (<30)	2 (7%)	2 (13%)	1 (9%)	
INTERMACS level at implantation				0.01
1	15 (56%)	12 (75%)	3 (27%)	
2	11 (41%)	4 (25%)	7 (64%)	
3	1 (4%)	—	1 (9%)	
Intubated at time of Implant	19 (70%)	10 (62%)	9 (82%)	0.28

All values defined at the time of EXCOR implant unless otherwise noted. Data presented as median (Quartiles 1 to 3) or as frequency (%). BiVAD, biventricular assist device; CHD, congenital heart disease; CrCl, creatinine clearance; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device.

[a]CrCl categories defined using the modified Schwartz equation.

not had any anti-coagulation administered. There were 2 post-transplant deaths in the EG cohort (16 and 310 days) and none in the SG cohort. Thus, the 30-day post-transplant survival was 82% in the EG cohort, and 100% in the SG cohort ($p = 0.20$). The median duration of support was 63 (31 to 111) days in the EG cohort and 121 (62 to 189) days in the SG cohort, which was not significantly different, likely due to large intra-group variability ($p = 0.14$). After heart transplantation, the median duration of mechanical ventilation was 2 days for each cohort ($p = 0.93$). The median length of stay after heart transplantation was 21 days for the EG cohort and 20 days for the SG cohort ($p = 0.65$).

Stroke

There were 6 strokes in the EG cohort and 1 in the SG cohort, all of which were ischemic. In the EG cohort, the clinical presentation of stroke was: hemiparesis ($n = 1$); altered sensorium ($n = 2$); seizure ($n = 1$); and clinically silent ($n = 2$, incidental findings during head computed tomography). In the SG cohort, the single stroke patient presented with hemiparesis. As summarized in Table 3, the incidence rate of stroke in the SG cohort was 84% lower than in the EG cohort ($p = 0.031$). Similarly, stroke was significantly less common in the SG cohort than in the IDE trial cohort, in which there were 17 events in 2,787 days of support (6.0 events per 1,000 days of support),[1,9,12] with an incidence rate ratio of 0.13 (0.02 to 0.70, $p = 0.006$).

Other adverse events, including bleeding and pump changes

There was only 1 systemic thromboembolism (not central nervous system) in the EG cohort and none in the SG cohort. As also summarized in Table 3, bleeding events were more common in the EG cohort, with an incidence rate of 18.8 per 1,000 days of support compared with 8.6 for the SG cohort ($p = 0.015$). There were twice as many pump changes in the EG cohort than in the SG cohort (33.6 vs 16.4 per 1,000 days of support; $p = 0.003$). Despite the use of steroids in the SG cohort, the number of infections did not differ between the groups, with a median of 2 for the EG cohort and 1 for the SG cohort ($p = 0.31$).

Doses of platelet inhibitors and TEG/PM findings

As depicted in Figure 2, the median target doses of aspirin, clopidogrel and dipyridamole were all significantly higher (4.4, 3.7 and 2.3 times higher, respectively) with substantially less variability in dosing between patients in the SG cohort compared with the EG cohort. At target values, the percent inhibition to arachadonic acid was significantly higher in the SG cohort than in the EG cohort ($p = 0.008$), although inhibition to adenosine diphosphate (ADP) was similar ($p = 0.55$; Figure 3). There was a no significant difference in median M_A for the citrated kaolin specimen with heparinase (66 mm for SG vs 60 mm for EG, $p = 0.15$; Figure 3). With respect to enoxaparin, the median anti-Xa level in the EG cohort was 0.74 and 0.73 in the SG cohort ($p = 0.71$ between cohorts).

Discussion

In this study, we found that use of a modified anti-thrombotic guideline, consisting of triplet anti-platelet therapy titrated to high, weight-based target doses—rather than values derived from TEG/PM—combined with prophylactic steroids as needed for inflammation was associated with a substantially lower incidence of stroke and device-related thromboembolism compared with usual care. We also found that the frequency of bleeding adverse events, defined according to standard pediatric INTERMACS criteria, was not higher with triple platelet therapy. In fact, the rate of bleeding was actually lower in the modified guideline, which remains unexplained, although it is possible that it may reflect improvements in surgical technique. Finally, we found that the total doses of aspirin, clopidogrel and dipyridamole were significantly higher—with much less variability in dosing among patients. Although the percent arachidonic acid inhibition by PM was higher, other TEG/PM values did not differ between the cohorts. Anti-Xa levels were similar between the groups, despite a change in heparin potency during this time period.

It is important to note that the results of this investigation are necessarily preliminary, insofar as they describe results from a single-center practice. We cannot definitively link the reduction in stroke rate to any particular component of the guideline. Indeed, it is possible that some or all of the

Table 3 Serious Adverse Event Rates by Anti-thrombotic Guideline[a]

	Edmonton Guideline ($N = 16$)	Stanford Guideline ($N = 11$)	Incidence rate ratio (SG:EG)	p-value
Ischemic stroke	6 (4.9)	1 (0.8)	0.16 (0.03 to 1.0)	0.031
Hemorrhagic stroke	0	0	NA	NA
Systemic thromboembolism	1 (0.8)	0	—	—
Bleeding	23 (18.8)	11 (8.6)	0.46 (0.23 to 0.92)	0.015
Pump exchanges	41 (33.6)	21 (16.4)	0.49 (0.29 to 0.82)	0.003
All serious adverse events	71 (58.1)	34 (30.5)	0.52 (0.36 to 0.77)	<0.011

IDE, Investigational Device Exemption trial; NA, not applicable.

[a]Data are presented as the number of events followed by the incidence rate per 1,000 days of support in parentheses, unless otherwise specified. Incidence rate ratios are SG:EG, with 95% confidence intervals in parentheses. Serious adverse events are defined according to the original pediatric INTERMACS definitions. Data are based on 1,220 days of support in the SG cohort and 1,279 in the SG cohort.

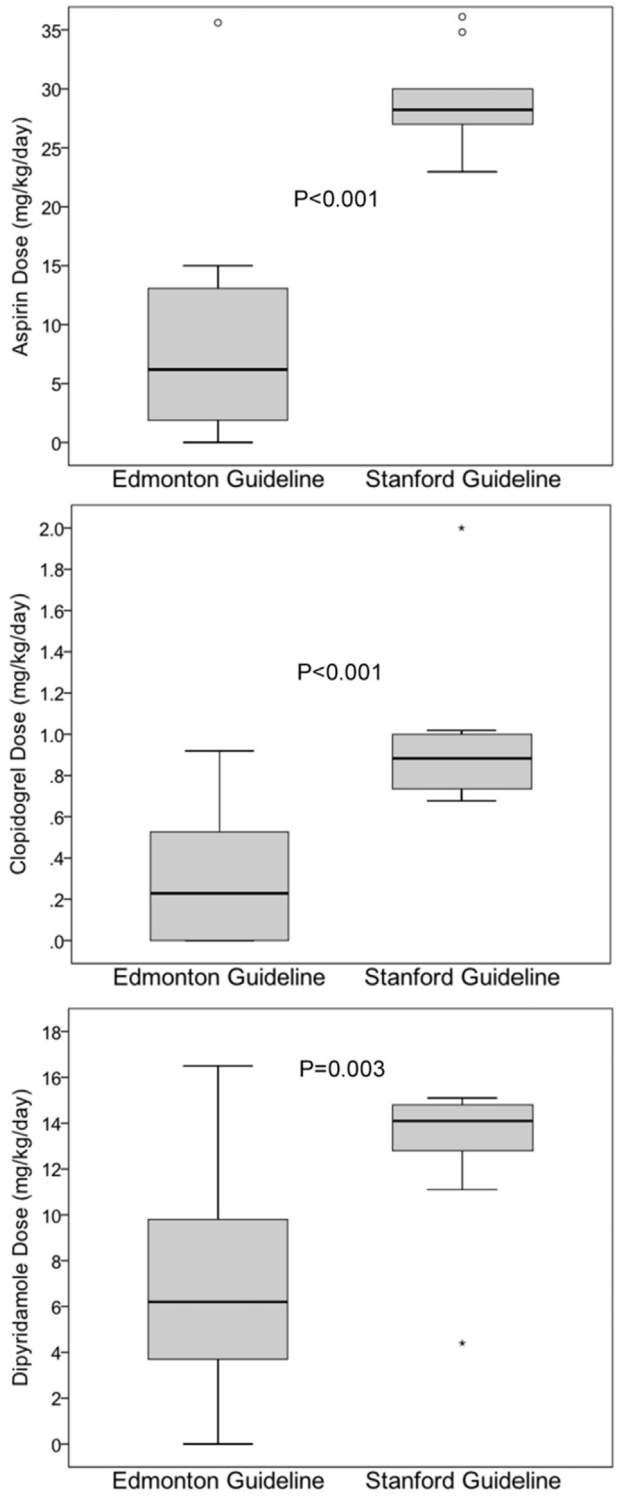

Figure 2 Boxplots depicting steady-state aspirin and clopidogrel doses in the Edmonton and Stanford Guideline cohorts. The box presents 25th to 75th percentiles, with the bold line in the middle of the box indicating the median. The error bars indicate minimum and maximum, other than outliers (indicated by a circle or asterisk).

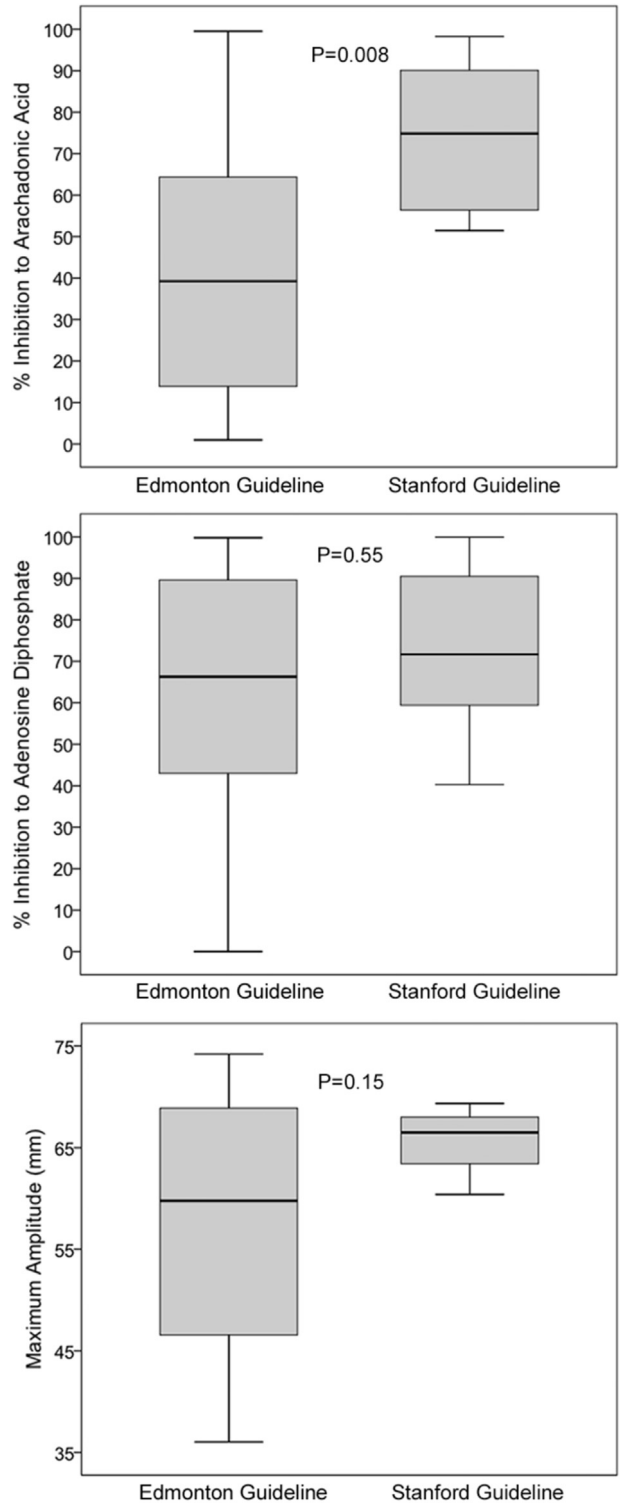

Figure 3 Boxplots depicting TEG/PM parameters in the Edmonton and Stanford Guideline cohorts. The box presents 25th to 75th percentiles, with the bold line in the middle of the box indicating the median. The error bars indicate the minimum and maximum values.

improvement was due to other, uncaptured management changes, such as: experience of the VAD team or surgical implantation; general improvements in care in the intensive care unit; or altered patient selection criteria. Although we have attempted to identify these factors in our analysis, such efforts cannot be regarded as definitive given the design of this report.

It is notable that the percentage of patients who were INTERMACS Level 1 at implantation was lower in the cohort treated with the modified anti-coagulation protocol

(SG cohort). This difference is a potential confounder of the association between anti-thrombotic group and outcome as studies have shown that higher patient acuity at implant is associated with poorer outcomes.[2] However, it is worth noting that, in the largest EXCOR study, although both INTERMACS profile and ECMO pre-implant were associated with outcome in the univariable analysis, they were not found to be independently associated with outcome after adjusting for renal function, hepatic function, size and use of biventricular VAD.[2] In the present analysis, these factors were relatively similar across both study groups. Had we included patients from the first 5 years of the EXCOR experience at Stanford (2004 to 2008) we strongly suspect we would have observed more significant differences in these 4 factors, which could have created a significant problem with confounding by era.

Earlier single-center studies have documented reductions in the incidence of stroke in children supported with the EXCOR device. In 2006, Hetzer and colleagues reported a decline in stroke risk, which they attributed primarily to a heparin coating on the blood-contacting surfaces of the EXCOR.[16] In 2005, Stiller and colleagues attributed higher survival and fewer thrombotic complications to a move from activated clotting time (ACT)-based heparin dosing to activated partial thromboplastin time (aPTT)-based dosing and the addition of platelet inhibitors (aspirin and dipyridamole) after the early post-operative period.[6] Then, in 2013 and 2015, Byrnes and colleagues reported a decline in stroke risk where the EG was used, which they attributed to several factors, including steroid use around inflammation, single-provider responsibility for anti-thrombotic therapy and global team experience with the device, as well as nurse education.[10,17] Although the era effect in outcome was striking, the change did include patients implanted during the well-described learning curve for each center, and did not include a control group. To our knowledge, the present study is the first to evaluate a major revision to the widely used EG since the Berlin Heart IDE study, which included a control group and excluded patients from the analysis who were implanted during the center's learning phase.

Our findings have several implications. First, the 29% risk of stroke frequently cited for the Berlin Heart EXCOR pediatric VAD should not be viewed as a fixed risk associated with EXCOR's use, but rather one that can be reduced significantly by refining the anti-thrombotic therapy with the device. This is important for patient selection practices because the stroke risk—widely believed to be a high and fixed risk—is a primary reason many centers choose not to implant the EXCOR until a patient deteriorates enough to justify such a risk. Although this tendency is understandable, it can become self-fulfilling because waiting for a patient to become sicker before implantation is known to drive up the probability of a negative outcome with the EXCOR.[2] If the device risks can be lowered significantly, then the threshold to implant the device may fall and the population of device-eligible children may increase.

Second, our findings indicate that higher doses of platelet inhibitors can be used safely in this population when they are uptitrated in a stepwise fashion to weight-based target doses. Titrating platelet inhibitors to higher, weight-based targets rather than sliding-scale PM values has 2 potential advantages: (1) it ensures that a robust dose known to inhibit platelets physiologically is administered to each patient; and (2) it reduces reliance on PM testing, which, although approved by the U.S. Food and Drug Administration, has never been adequately validated for graduated dosing algorithms against a "gold standard," such as optical platelet aggregometry. Also confounding PM interpretation is that the results may be affected by other common cardiac medications, such as milrinone.[18] By contrast, the M_A, a global measure of clot strength, which factors in platelet number, platelet function and fibrinogen levels, has a considerably longer history of use, and appears to correlate well empirically with the clinical risk of bleeding and thrombosis and, therefore, may be a more compelling laboratory target for dose titration. It is worth emphasizing that early surgical hemostasis is absolutely necessary to allow patients to tolerate doubling of platelet doses on consecutive days to reach the target dose as quickly as possible.

Last, our findings may carry implications for anti-coagulation of miniaturized extracorporeal circuits beyond the Berlin Heart EXCOR pediatric VAD. Indeed, preventing thrombosis in small, low-flow circuits for extended periods is a fundamental bioengineering challenge that is common to many existing and evolving medical device technologies undergoing progressive miniaturization; these include emerging VADs such as the Jarvik 2015[18] being evaluated through the National Heart, Lung and Blood Institute's PumpKIN program, smaller extracorporeal membrane oxygenation circuits and implantable renal replacement devices. Although it remains to be seen, it is conceivable that challenges in providing safe and effective anti-coagulation may prove to be the major constraint limiting medical device miniaturization for the foreseeable future.

Our study has several limitations related to the study design. First, our sample size was small and event rates were low, raising the possibility that the lower event rate with the SG could be explained by Type I statistical error. However, although the total number of patients was small, the cumulative VAD exposure was relatively large (2,499 days) and comparable to the IDE trial cohort (2,787 days), and the primary study finding significant, suggesting that the observed decrease is unlikely to be a function of chance alone. Second, although we sought to examine changes in anti-thrombotic therapy, it is possible that the other changes in care, such as improved thrombus detection at the bedside or implantation of less sick patients over time, may have accounted for the lower event rates in the SG cohort. However, the baseline characteristics of the study cohort were relatively similar across cohorts with the exception of INTERMACS profile, and we deliberately excluded from the analysis all EXCOR implants at Stanford during the first 5 years in an effort to limit the study period to an era in which we felt anti-thrombotic practices had matured to reach a steady state for drawing inferences. Also, the number of clinicians responsible for managing anti-coagulation at Stanford increased over the study period, if

anything, suggesting that restricting management to 1 or 2 individuals was not the primary mechanism behind the reduction in adverse events. Of note, the pump exchange rate was lower in the more recent era, suggesting a higher pump exchange rate was not responsible for the decline in events. Nevertheless, a randomized study would be the best way to ensure that our findings could not be explained by confounding. Last, an intervention to intensify platelet coverage may be expected to improve late but not early strokes, which is when most EXCOR strokes occur. However, we found that that early strokes were also less common in the SG cohort, which we speculate may be related to a steeper uptitration rate of platelet inhibitors (e.g., daily doubling of the clopidogrel without waiting for platelet mapping results) combined with aggressive management of M_A values exceeding 65 mm in the early post-operative period, thus accounting for improved stroke protection during the first 30 days.

In conclusion, we found that the incidence of stroke decreased significantly over the past few years in conjunction with a more intensive anti-thrombotic guideline in which platelet inhibitors were titrated to higher, weight-based target doses rather than values derived from platelet function tests, and steroids were used pre-emptively to mitigate rises in clot strength (M_A) in the setting of inflammation. The change in dosing strategy led to significantly higher doses of platelet inhibitors being used and much less variability in dosing across patients. Despite the higher intensity anti-thrombotic guideline, the frequency of bleeding adverse events, including intracranial hemorrhage, was similar. Although a higher dose of aspirin was associated with a more effective platelet inhibition to arachidonic acid by PM, the percent inhibition to ADP did not change significantly despite the addition of clopidogrel to the guideline. This raises questions about the validity of using percent ADP inhibition to measure the effect of ADP inhibitors. Most importantly, our findings suggest that the 29% stroke risk widely cited for the EXCOR VAD should no longer be viewed as a fixed risk, which may impact patient selection practices for the Berlin Heart EXCOR pediatric VAD, and this can be a lifesaving measure in the appropriate setting.

Disclosure statement

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