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

David N. Rosenthal, MD,[a,b,1] Chacy A. Lancaster,[a,b,1] Doff B. McElhinney, MD,[a,b,c] Sharon Chen, MD,[a,b] MaryLyn Stein, MD,[b,d] Aileen Lin, NP,[a,b] Lan Doan, MPH,[a,b] Jenna M. Murray, NP,[a,b] Mary Alice Gowan, RN,[a,b] Katsuhide Maeda, MD,[b,c] Olaf Reinhartz, MD,[b,c] and Christopher S. Almond, MD, MPH[a,b]

From the [a]Department of Pediatrics, Stanford University, Palo Alto, California, USA; [b]The Heart Center Clinical and Translational Research Program, The Lucile Packard Children's Hospital, Palo Alto, California, USA; [c]Cardiothoracic Surgery, Stanford University, Palo Alto, California, USA; and the [d]Department of Anesthesia, Stanford University, Palo Alto, California, USA.

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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

[1]The first 2 authors (D.N.R. and C.N.L.) contributed equally to this study.

Reprint requests: David Rosenthal, MD, Department of Pediatrics, Stanford University, 750 Welch Road, Suite 325, Palo Alto, CA 94304. Telephone: +650-723-7913. Fax: +650-725-8343.

E-mail address: davidnr@stanford.edu

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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

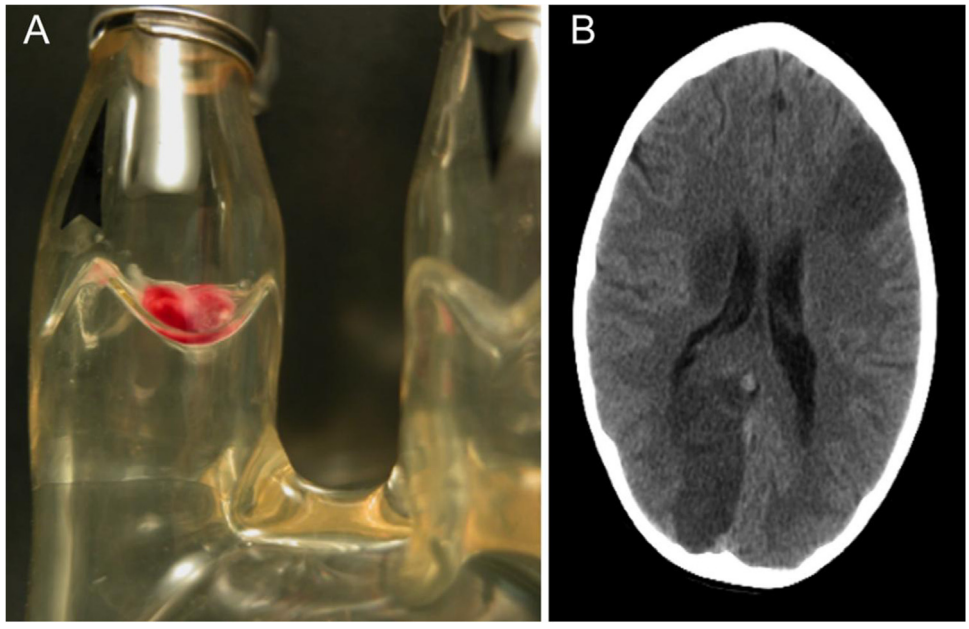

Figure 1 (A) Thrombus located on the outflow valve of a Berlin Heart EXCOR pediatric LVAD. (B) Computed tomography image of a child with embolic stroke on EXCOR support.