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Apixaban for Prevention of Thromboembolism in Pediatric Heart Disease

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Apixaban in Pediatric Heart Disease for the Prevention of Thromboembolism: The SAXOPHONE Study

Running title: Apixaban in pediatric heart disease

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Tweet: Apixaban is a safe and well-tolerated alternative to vitamin K antagonists or low-molecular-weight heparin for thromboprophylaxis in pediatric heart disease.

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ABSTRACT (248 words – 250 max)

Background
Children with heart disease frequently require anticoagulation for thromboprophylaxis. The current standard of care (SOC), vitamin K antagonists (VKA) or low-molecular-weight heparin (LMWH), has significant disadvantages.

Objective
To describe safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of apixaban, a novel, oral, direct factor Xa (FXa) inhibitor, for prevention of thromboembolism in children with congenital or acquired heart disease.

Methods
Phase 2, open label trial in children (28 days to <18 years) with heart disease requiring thromboprophylaxis, with 2:1 randomization to apixaban or SOC for 1 year with intention-to-treat analysis. Primary endpoint: a composite of adjudicated major or clinically relevant non-major (CRNM) bleeding. Secondary endpoints: PK, PD, quality of life, and exploration of efficacy.

Results
From 2017 to 2021, 192 participants were randomized, 129 to apixaban and 63 to SOC. Diagnoses included single ventricle (74%), Kawasaki disease (14%), and other congenital/acquired heart disease (12%). One participant on apixaban (0.8%) and 3 on SOC (4.8%) had major or CRNM bleeding (% difference -4.0 [-12.8, 0.8]). Rates of all bleeding events were not different between arms (relative risk 1.0 [0.7, 1.5]). There were no thromboembolic events or deaths in either arm. Apixaban pediatric PK steady-state exposures were consistent with adult levels.

Conclusions
In this pediatric, multi-national, randomized trial, bleeding and thromboembolism were rare on apixaban and SOC. Apixaban PK data correlated well with data from large trials that demonstrated efficacy in adults. These results support the use of apixaban as an alternative to SOC for thromboprophylaxis in pediatric heart disease.

CONDENSED ABSTRACT: (98 words – 100 max)

The standard of care for anticoagulation in children with heart disease has significant disadvantages. This phase 2, open label, pediatric, multi-national randomized trial characterized the safety, pharmacokinetics, pharmacodynamics, and efficacy of apixaban, an oral, direct factor Xa inhibitor, for prevention of thromboembolism in 192 children with congenital or acquired heart disease. Bleeding and thromboembolism were rare on both apixaban and standard of care. Apixaban pharmacokinetic data correlated well with data from large trials that demonstrated efficacy in adults. These results support the use of apixaban as an alternative to standard of care for thromboprophylaxis in pediatric heart disease.

KEYWORDS (6): apixaban, pediatric, anticoagulation, thromboembolism, congenital, heart

Abbreviations: (Max 10)
CRNM = clinically relevant non-major
DOAC = direct oral anticoagulant
FXa = factor Xa
LMWH = low-molecular-weight heparin
PD = pharmacodynamics
PK = pharmacokinetics
SOC = standard of care
SV = single ventricle
TE = thromboembolism
VKA = vitamin K antagonist

(5,080 words - 5000 words max)

INTRODUCTION

Children with congenital or acquired heart disease are frequently at risk for clinically significant thrombosis including intracardiac, intravascular, and coronary thromboses. Thrombotic complications are increasingly recognized as important factors contributing to morbidity and mortality in pediatric heart disease.(1-3) Hemodynamic factors related to abnormal ventricular function, arrhythmias, catheterization, and complex cardiac anatomy are important contributors to the risk of thrombosis in children with cardiac disease. The highest risk groups include children with single ventricle (SV) congenital heart disease in whom all these factors may co-exist.(1,4) Acquired heart disease in children, such as in dilated cardiomyopathy or Kawasaki disease with giant coronary aneurysms, can also carry significant risk for thrombosis. Both the American Heart Association (3) and the American College of Chest Physicians (5) have provided clinical practice guidelines for prophylaxis to reduce pediatric thrombosis; however, most of the recommendations are based upon consensus opinion in the absence of randomized clinical trials (i.e., Level 2C evidence).

The current standard of care, vitamin K antagonists (VKA) or low-molecular-weight heparin (LMWH), has significant disadvantages in children. VKAs (e.g., warfarin) have a narrow therapeutic window requiring frequent therapeutic monitoring, interactions with medications and some foods, and a lack of liquid formulations. Long term bone density is also potentially adversely affected.(6,7)

LMWH requires subcutaneous administration and is associated with adverse effects such as heparin-induced thrombocytopenia and a potential decrease in bone mineral density. Therapeutic monitoring is also usually performed. Heparin's mechanism of action requires the co-factor antithrombin, which is frequently at physiologically low and variable levels in neonates and in children at other ages with cardiac-related complications (e.g., chylothorax).(8)

Direct oral anticoagulants (DOACs), such as the direct factor Xa (FXa) inhibitors, do not require antithrombin. Recent studies suggest that DOACs may be an important therapeutic alternative for anticoagulation of children(9,10), including those with heart disease.(11,12) However, there remains a pressing need for improved understanding of the pharmacokinetics (PK) and pharmacodynamics (PD) of DOACs with age-appropriate pediatric formulations. Trials of DOACs in children have been identified as a high research priority.(2)

Apixaban is a novel, orally active, direct inhibitor of FXa that has been studied in over 60,000 adults for various indications and demonstrated a favorable benefit-risk profile.(13-16) Apixaban does not require therapeutic monitoring and does not have significant interactions with food, drugs, or herbal products. Thus, apixaban could be an attractive option for prevention of thromboembolism (TE) in children with heart disease.

We undertook the SAXOPHONE (**S**afety of **A**pi**X**aban **O**n **P**ediatric **H**eart disease **O**n the preventio**N** of **E**mbolism) study, a prospective, randomized, open label, parallel-arm, phase 2 trial using the SOC (VKA or LMWH) as a comparator to assess the safety, PK, PD, and efficacy

of apixaban for the prevention of TE in children with a broad range of congenital or acquired heart disease requiring chronic thromboprophylaxis.

METHODS

Study Design: The methodology of SAXOPHONE has been previously described.(17) The study was designed to generate safety, PK, and PD data on apixaban, as well as exploratory efficacy, biomarker, quality of life, and bone density data to inform clinicians regarding apixaban dosing and management of thromboprophylaxis in children with congenital or acquired heart disease. Written informed consent was obtained from the parent or guardian of all participants. Assent was also obtained in age-appropriate adolescent participants if required by local guidelines. A centralized institutional review board was utilized for 24 centers who provided reliance agreements. For the remainder of centers, the local ethics committee or institutional review board approved the study protocol.

Population: Children with congenital or acquired heart disease needing anticoagulation for TE prophylaxis were recruited. If the indication was for secondary prophylaxis, the TE must have occurred > 6 months prior to enrollment. Randomization was 2:1 (apixaban:SOC) and was stratified by three age groups: 28 days to < 2 years, 2 to < 12 years, or 12 to < 18 years. Randomization was also stratified by clinical diagnosis of SV physiology versus other types of congenital or acquired heart disease. Neonates (< 28 days of age) were excluded from the study because of the low prevalence of thromboprophylaxis use in that age group at the time this study

was designed. Children with artificial or mechanical heart valves and on mechanical circulatory support were also excluded. The rationale for including a broad range of congenital and acquired heart disease was the high unmet medical need in these populations.(2)

Dosing: Weight-adjusted pediatric dose regimens of apixaban corresponding to the adult dose of 5 mg twice daily were determined by a population PK model that was developed by pooling adult and pediatric data from earlier apixaban studies.(18,19) A weight-based tiered dosing scheme was employed **(Table 1)**. VKA or LMWH dosing followed local SOC guidelines. The dose of VKA was recommended to be titrated to achieve a target INR of 2.0 to 3.0, and the dose of LMWH was recommended to target an anti-Xa level between 0.5 and 1.0 unit/mL when sampled 4 hours post-administration. Participants were treated for approximately 12 months or until anticoagulation was no longer needed, whichever was shorter. The expected minimum duration of thromboprophylaxis was 6 months for participants $\geq$ 2 years of age and 1 month for those < 2 years of age. Concomitant therapy with acetylsalicylic acid (up to 5 mg/kg/day) was permitted per protocol. At each study visit, diaries and pill counts/study liquid volume checks were used to record frequency of study drug administration, and adherence was calculated as the percentage of days in which the participant took a dose of study medication during the total number of days in their treatment period.

Primary Safety Endpoint: The primary endpoint was a composite of independently adjudicated major or clinically relevant non-major (CRNM) bleeding events during the treatment period. Safety endpoints were analyzed for all participants who received at least one dose of study

medication based on events occurring from the period between the first administration of study drug and two days after the last administration of study drug (or 30 days for serious adverse events).

Secondary Endpoints:

Bleeding: The secondary bleeding endpoints included each element of the composite outcome considered separately (e.g., major bleeding and CRNM bleeding), as well as all bleeding events.

Efficacy: Efficacy endpoints were analyzed for all randomized participants based on events occurring during the intended treatment period. Data were independently adjudicated on TE-related deaths as well as TE events (e.g., intra-cardiac, shunt, single ventricle pathway, pulmonary embolism, stroke, other deep venous or arterial thromboembolic events) detected by imaging or clinical diagnosis.

Exploratory Outcomes: Bone density was evaluated using dual energy x-ray absorptiometry in participants ≥ 5 years of age at baseline and at study completion, unless it was contraindicated, the participant or family was unwilling, or there was another valid clinical reason not to perform it. Quality of life was assessed by English-speaking participants and their parents at baseline, 6, and 12 months. PedsQL™ questionnaires were administered to participants ≥ 5 years of age and parents of participants ≥ 2 years of age. For PedsQL™ scores, higher scores indicate better quality of life. KIDCLOT© questionnaires were administered to participants ≥ 8 years of age and parents of participants ≥ 34 weeks of age, but only those on apixaban and warfarin, as the questionnaire was not validated for LMWH. In contrast to PedsQL™ scores, a higher KIDCLOT© score indicates that anticoagulation has a more negative effect and therefore results in a lower quality of life.

PK and PD Analysis: PK and PD samples were collected from participants who were randomized to apixaban and analyzed at a central core laboratory. Apixaban concentrations were determined using liquid chromatography with tandem mass spectrometry with a lower limit of quantification of 1.0 ng/mL. A population PK model was generated from the data in this study for stochastic simulations and compared against adult data for apixaban from the adult venous TE treatment and the adult stroke prevention ARISTOTLE populations, who were dosed at 5 mg twice a day of apixaban.(18,19) The exposure-matching between children and adults entailed using simulated steady state area under curve exposure values for virtual pediatric participants for each fixed dose by weight tier. These virtual participants were created by randomly assigning age within an age group and sex to each participant with equal probability. Body weight was then generated by random sampling from the United States Centers for Disease Control and Prevention growth chart based on the assigned age and sex for the individual participant.(20) The PD samples were analyzed for anti-FXa activity with the Diagnostica Stago Anti-Xa apixaban assay using exogenous FXa and apixaban calibrators, with the lowest reportable range of 35 ng/mL. The chromogenic FX assay was used to measure endogenous FX levels at baseline and the inhibition of FX by apixaban, with the lowest reportable range of 11%.

Statistics: All analyses were performed in SAS using version 9.4. Primary and secondary safety endpoints were quantified using descriptive statistics including event rates, difference of event rates, and 95% confidence intervals. Relative risk and 95% confidence intervals for relative risk

were calculated based on the stratified Mantel-Haenszel's method if the total number of events was above 5. This study was not powered for efficacy.

RESULTS

Baseline Characteristics: From January 2017 to October 2021, 198 infants and children between the ages of 28 days and < 18 years were screened at 33 centers in 12 countries (**Figure 1**). A total of 192 were randomized to either apixaban (n = 129) or SOC (n = 63) and were included in the efficacy analyses. In the apixaban arm, 126 participants received ≥ 1 dose and were included in safety analyses. A total of 123 (95%) participants on apixaban completed the follow-up period and therefore completed the study. In the SOC arm, 62 participants received ≥ 1 dose and were included in the safety analyses, and 61 (97%) completed the study. Minor protocol deviations occurred during the COVID-19 pandemic but had no significant impact on data quality or interpretation, and no participants were lost to follow-up due to the pandemic.

Participant demographic, clinical, and anatomic characteristics at the time of enrollment are summarized in **Table 2**. Most participants were between 2 years to < 12 years (69.0% on apixaban and 71.4% on SOC). All key characteristics were well-balanced by randomization between the treatment arms except for sex; the SOC arm had a higher proportion of male participants than the apixaban arm. Cardiac diagnoses are presented in **Table 3**, and specific cardiac diagnoses are presented in **Supplementary Table S1**. Of 142 participants with any form of SV, 128 had undergone Fontan completion, most commonly with an extra-cardiac conduit (n=91), whereas 23 had received a lateral tunnel Fontan (**Supplementary Table S2**). Of the

participants with a Fontan, 36 were randomized within 3 months of their Fontan surgery. The most common indications for primary TE prevention were routine anticoagulation for Fontan physiology (51%), and Kawasaki disease with giant coronary aneurysms (13.5%) **(Table 3)**.

Prior anticoagulation use among treated participants is summarized in **Supplementary Table S3**. The vast majority had been on prior anticoagulation (80.3%), with VKA being the most common class of medication (66.5%). Only 1 participant (0.5%) had prior exposure to a DOAC. During the study, 43.6% of participants were maintained on concomitant acetylsalicylic acid, 38.9% in the apixaban arm and 53.2% in the SOC arm.

Exposure: The mean duration of exposure to study drug was 330.6 days (± 83.0) days in the apixaban arm and 344.4 days (± 56.4) days in the SOC arm (**Supplementary Table S4**). The intended duration of exposure to study drug (≥ 337 days) was achieved by 101 (80.2%) participants in the apixaban arm and 47 (75.8%) participants in the SOC arm. For the 11 participants between 28 days - < 2 years, the mean duration of exposure was 260.4 days (± 109.9) to apixaban, and 204.0 days (± 119.6) to SOC.

Adherence to treatment was high in both arms, with 99.2% of participants in the apixaban arm and 98.4% in the SOC arm receiving a dose on at least 80% of days during the treatment period (**Supplementary Table S5**).

Safety: One participant (0.8%) in the apixaban arm met the primary safety endpoint by having both a major and a CRNM bleeding event, whereas 3 participants (4.8%) in the SOC arm had either a major or CRNM bleeding event (**Table 4)**. The percentage of participants experiencing all bleeding events was similar between treatment arms at 37% (relative risk 1.0 [0.7, 1.5]). In the apixaban arm, 12 participants had ≥ 4 bleeding events, of which 47.1% were epistaxis and were adjudicated as minor (**Figure 2**).

Accounting for duration of exposure to study drug, the incidence rate for major and CRNM bleeding in addition to all bleeding per 100 person-years is shown in **Table 5**. The incidence rate per 100 person-years for all bleeding events on apixaban was approximately twice the rate than on SOC (100.0 vs. 58.2). The increase in all bleeding in the apixaban arm was largely driven by the 12 participants with ≥ 4 bleeding events each.

The median steady state exposures for apixaban-treated participants who had bleeding events are compared to those for participants without bleeding events in **Figure 3**. Similar exposures between the two groups suggest a lack of correlation between apixaban exposures and bleeding events. The one participant on apixaban with both a major and a CRNM bleeding event had a high median steady-state exposure value that was similar to a participant in the group without bleeding events, i.e., both had high exposure values, but only one had bleeding.

The frequency of serious adverse events, treatment-related serious adverse events, and adverse events are shown in **Table 6**. Discontinuation of drug due to treatment-related adverse events was rare. Two thromboses in the Fontan conduit in the apixaban arm were reported as serious adverse events by sites but were subsequently adjudicated as non-events because they were found to be present on pre-study imaging **(Table 7)**. Exposure adjusted adverse events occurring in >5% of participants in either treatment arm are summarized in **Supplementary Table S6.** The incident rate per 100 person-years for total exposure adjusted adverse events was 523.5 in the apixaban arm versus 434.5 in the SOC arm. One participant (0.8%) on apixaban experienced heavy menstrual bleeding, and one (0.8%) experienced a mild vaginal hemorrhage. Both were adjudicated as minor bleeding events. No menorrhagia was noted in the SOC arm.

Efficacy: There were no thromboembolism-related deaths or thromboembolic events detected by imaging or clinical diagnosis in either arm during the study.

Bone Density: Paired bone density scans were only available for 16 participants on apixaban and 11 on SOC (**Supplementary Table S7**). The mean change in lumbar spine L1-L4 z-score from baseline was 0.5 (±2.3) for apixaban and 0.0 (±0.5) for SOC. The change in total body less head z-score from baseline was 0.2 (±0.3) for apixaban and -0.2 (±0.3) for SOC, suggesting the possibility of less loss of bone density among those on apixaban, but the amount of available paired data was too small to draw meaningful conclusions.

Quality of Life: (**Supplementary Tables S8, S9, and S10**). For both PedsQL™ and KIDCLOT© questionnaires, the mean changes from baseline were small in both arms for most sub-scores. However, on the PedsQL™ Cardiac Module, child-reported treatment anxiety sub-scores were higher among children on apixaban than SOC at 6 and 12 months, suggesting lower anxiety about taking apixaban. Interpretation was limited by small sample sizes.

PK/PD: Apixaban steady state exposures are shown in **Figure 4** for the 6 upper weight groups. The 3 lowest weight groups (3 - < 6 kg) were not included because samples were not collected from infants. Median exposures across the weight tiers were similar to the median exposure (1,240 ng•h/mL) in the adult venous TE treatment population (dashed horizontal line), and the overall exposures were comparable between the adult and weight-adjusted dosing in the pediatric age groups.

Apixaban demonstrated the expected mechanism of action for a direct FXa inhibitor. Anti-FXa activity increased post-dose, and comparable trough anti-FXa activity was observed at the Week 2 and Month 6 pre-dose time points. As expected, the chromogenic FX assay showed a decrease in apparent FX levels after treatment and similar chromogenic FX trough levels at the Week 2 and Month 6 pre-dose time points. The magnitude of apparent FX decrease (percent change from baseline) appeared to be greater 2-4 hours post-dose (near apixaban peak plasma concentrations) relative to that at pre-dose (near apixaban trough plasma concentrations). Complete SAXOPHONE PK/PD data will be reported separately.

DISCUSSION

In the SAXOPHONE trial, assessing the safety and efficacy of apixaban versus SOC for thromboprophylaxis for up to 1 year in children with congenital or acquired heart disease, apixaban was found to be safe, with rare bleeding events and no thromboembolism-related deaths or thromboembolic events detected by clinically indicated imaging or clinical diagnosis. Adherence to treatment was high in both arms. The PK of apixaban across a breadth of ages, weights, and cardiac diagnoses in children correlated well with adult data from prior large trials in which efficacy has been demonstrated, and the data suggest that apixaban exposure levels were not associated with bleeding events. These important findings support the use of apixaban as another safe and potentially more convenient option for thromboprophylaxis in children with heart disease.

Children have very different types of heart diseases compared to adults, and their responses to drugs typically used in adult medicine are neither predictable nor easily managed.(21) Factors that may influence their response include the wide range in their age and size, the developmental status of organ systems that affect the metabolism and elimination of medications, diet, and their greater activity and unpredictability when compared with adults. Managing diets in children on anticoagulation with a VKA can be especially challenging and can affect compliance and risk of bleeding. Younger children, such as infants, may be more reliably treated with LMWH, but this requires frequent injections and monitoring, which again can impact compliance and is a source of daily distress for families.(22)

Repair of congenital heart disease in children frequently involves the extensive use of synthetic materials, which may serve as a nidus for thrombus. In addition, slow flow in certain venous circuits, such as the venous return to the lungs or the intra-atrial flow found in the Fontan repair of SV heart disease, presents a risk for thrombosis. A recent retrospective study of 549 infants from the Pediatric Heart Network Single Ventricle Reconstruction trial found the cumulative incidence of symptomatic thrombosis was 21% from Stage I (Norwood procedure) through Stage II (Glenn shunt or Hemi-Fontan) of SV palliation.(1) A recent meta-analysis including 3,438 participants with Fontan circulation explored the safety and efficacy of the various options for anticoagulation, including DOACs, VKA, and acetylsalicylic acid. Compared to no thromboprophylaxis, all three options resulted in significantly lower rates of TE, with DOACs having the highest P score to prevent TE, while also demonstrating no significant differences in the rates of major bleeding.(23) In the SAXOPHONE trial, the largest group of participants belonged to one of the highest risk categories for TE in children: 74% of treated participants had a diagnosis of SV heart disease, and 67% had been palliated by the Fontan operation. Thus, SAXOPHONE provides additional important safety data on the use of DOACs in a high-risk population.

Comparison with previous trials: Two recent prospective clinical trials evaluated DOACs in children with congenital heart disease. McCrindle et al., randomized 100 children with SV, ages 2 – 8 years, within 4 months of Fontan completion to rivaroxaban vs. acetylsalicylic acid for 12 months (the UNIVERSE study).(12) Weight-based treatment with rivaroxaban gave exposures

similar to adults and led to no statistically significant difference in TE events compared to acetylsalicylic acid. They noted 8% combined major and CRNM bleeding events on rivaroxaban, compared to 9% combined major and CRNM bleeding events on acetylsalicylic acid. The rates of trivial bleeding were similar on rivaroxaban (33%) and acetylsalicylic acid (35%). Portman et al., randomized 167 children < 18 years with heart disease for 3 months in a 2:1 ratio to edoxaban or SOC (the ENNOBLE-ATE trial).(11) The trial offered a 9-month extension, in which 147 participated. As in the UNIVERSE trial, they found similar or lower rates of bleeding and TE when compared with SOC. Like the SAXOPHONE trial, both of these trials focused on children with congenital heart disease but with important differences. The UNIVERSE trial enrolled a restricted age range of children with SV that were within 4 months of Fontan completion and compared a DOAC to acetylsalicylic acid in a smaller sample of participants. The ENNOBLE-ATE trial enrolled children <18 years with congenital or acquired heart disease and compared against SOC, but for only 3 months. SAXOPHONE included a broader population of children with heart disease, larger numbers of participants exposed to a DOAC, and longer duration of exposure. Reassuringly, all three trials found that DOACs were at least as safe as SOC in the pediatric congenital and acquired heart disease population.

Safety profile: The safety of apixaban in children with congenital or acquired heart disease was the primary focus of this study. Although experience with apixaban has established that it is safe and efficacious in the adult population, there have been no studies in children with heart disease. Clinicians have had neither dosing nor safety data to guide their use of apixaban in the pediatric cardiac population. In the current study, the frequency of serious adverse events was similar on

apixaban and SOC, and treatment-related serious adverse events were infrequent in both arms. Participants on apixaban had a greater number of minor bleeds, predominantly epistaxis, contusion, and hematoma, but otherwise, the number of participants with any bleeding was balanced between arms. The rate of menorrhagia was quite low in this study, but only about one third of participants were old enough to menstruate. Currently, few studies have examined use of DOACs in menstruating women and none have examined DOAC use in women with CHD of menstruating age.(24,25) Adherence to apixaban was high and frequency of discontinuation of apixaban due to adverse events was low. Drug exposure across a wide range of weights and ages in pediatric participants correlated well with adult exposure data, and PD measures showed that apixaban performed as expected for a direct inhibitor of FXa in terms of changes in anti-FXa and FX activity. Bleeding events in pediatric participants did not appear to correspond to apixaban drug levels.

Study strengths and limitations: Strengths of the present study include the randomized treatment assignment, comparison against current SOC, large sample size of children across a wide range of age, weight, geography, and heart disease, blinded and centrally adjudicated clinical outcomes, and longer duration of therapy. Additionally, although the trial was continued through the COVID-19 pandemic, there was no compromise of study measures or data. This study provided crucial safety and dosing data for apixaban in this population to guide clinicians for prevention of TE in children with congenital or acquired heart disease such as Kawasaki disease with giant coronary artery aneurysms. However, the study also has several limitations. Small sample sizes limited the ability to perform some sub-group analyses of interest, such as

analyzing differences by type of Fontan operation. It was also not possible to reach firm conclusions about quality of life or bone density based on data from this study, two topics that should be high priorities for future studies. Finally, SAXOPHONE, like UNIVERSE and ENNOBALE-ATE, was not powered to demonstrate differences in efficacy. This is not unexpected given the rarity of both pediatric heart disease and TE events. Nonetheless, a recent meta-analysis of thromboprophylaxis in patients with Fontan circulation concluded that DOACs were as safe and efficacious as SOC (acetylsalicylic acid and warfarin) in this population.(26) This conclusion is supported by other prospective pediatric studies of DOACs, including dabigatran in DIVERSITY and rivaroxaban in EINSTEIN-JR.(9,10) Finally, a multicenter retrospective cohort study of DOAC use in adults after Fontan found that DOACs had the lowest incidence of both thrombotic and major bleeding events when compared with antiplatelet, VKA, or combination therapy (VKA plus antiplatelet).(23)

CONCLUSIONS

The SAXOPHONE study showed that apixaban was safe and well-tolerated in children with congenital or acquired heart disease who require chronic thromboprophylaxis. Predictable therapeutic drug levels were achieved with weight-based dosing. Significant bleeding on apixaban was rare. These findings support the use of apixaban as an alternative to SOC for chronic thromboprophylaxis in children with congenital or acquired heart disease.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Children with congenital or acquired heart disease are at significant risk of thromboembolism. Chronic anticoagulation with apixaban, a factor Xa inhibitor, is a safe alternative to VKA and LMWH for these children, without drawbacks such as the need for monitoring, injections, or interactions with medications and diet.

TRANSLATIONAL OUTLOOK: Outcomes among apixaban or other DOACs appear to be similar to SOC but without the difficulty of managing anticoagulation levels. Future studies should explore longer-term outcomes of DOACs, the impact on quality of life and bone density in larger sample sizes, and the use of apixaban or other DOACs in other high-risk populations (e.g., early-stage palliation of SV heart disease, menstruating females with CHD) and in other thrombogenic cardiac conditions such as prosthetic valves and mechanical circulatory support.

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FIGURE LEGENDS

Figure 1: CONSORT diagram of the SAXOPHONE trial. VKA = vitamin K antagonists, LMWH = low-molecular-weight heparin

Figure 2: Bleeding Events. Frequency distribution of all bleeding events by treatment arm. Analysis is based on the number of events, and each event is counted separately. VKA = vitamin K antagonists, LMWH = low-molecular-weight heparin

Figure 3: Apixaban exposures based on bleeding events. Box-and-whisker plot of median steady-state exposure among participants in the apixaban arm, based on whether any bleeding event was observed during the treatment period. AUC = area under curve, CRNM = clinically relevant non-major

Figure 4: Apixaban steady state exposures. The box plot represents the distribution of exposures for the virtual patient population by weight group, and the open circles represent exposures from the study participants. The shaded area represents the 90% confidence interval for adult exposure, and the dashed line represents the reference median adult exposure based on the adult venous TE treatment trial. AUC = area under curve