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A regional anticoagulation program improves safety and outcomes for both children and adults

Vilmarie Rodriguez[1,2] · Joseph Stanek[1,3] · Clifford L Cua[2] · Amanda Sankar[1,2,4] · Jean Giver[1] · Kay Monda[1] · Joan Canini[1] · Amy L. Dunn[1,2] · Bryce A. Kerlin[1,2,5]

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Abstract

Background: Evidence-based anticoagulation programs usually serve a local, adult patient population. Here we report outcomes for a regional combined pediatric-adult program. **Aims:** The aims of this study were: (1) Compare the pre- vs. post-implementation quality of therapy (% time in therapeutic range (%TTR) and compliance). (2) Assess anticoagulant-relevant outcomes (bleeding and thrombotic complications). **Methods:** Data were collected for the years 2014–2019. Rosendaal linear interpolation was used to calculate %TTR. Bleeding complications were categorized using ISTH-SSC standard nomenclature and new thrombotic events were reviewed. **Results:** The patients were divided into a long-term warfarin group (N = 308), 80.2% of whom had cardiac-related therapeutic indications (median age 24y), and a second group (N = 114) comprised of short-term and non-warfarin long-term anticoagulation (median age 16y). Median %TTR for those on long-term warfarin was 78.9%. The incidence of major and clinically relevant non-major bleeding events was 1.65 and 2.43 /100 person-years of warfarin use, respectively. Thromboembolism (TE) incidence was 0.78/100 patient-years of warfarin use. Neither bleeding nor thrombosis was associated with %TTR ($p = 0.48$). Anticoagulant indication was the only variable associated with bleeding risk ($p = 0.005$). The second group had no on-therapy TE events but 7.9% experienced bleeding. Complete data were available for a randomly sampled pre-program warfarin group (N = 26). Median %TTR improved from 17.5 to 87% pre- vs. post-implementation. Similarly, compliance (defined as ≥ 1 INR/month) improved by 34.3%. **Conclusions:** In conclusion, this program significantly improved and sustained %TTR and compliance. The lack of association between bleeding and thrombosis events and %TTR may be related to the high median %TTR (> 70%) achieved by this approach.

Highlights

- Our combined pediatric and pediatric comprehensive anticoagulation program achieved excellent anticoagulation quality as measured by %TTR.
- Median %TTR was 78.9% (recommended minimum 60%).
- This high %TTR was achievable in both children and adults.
- Bleeding and thrombotic events were not associated with %TTR.
- Quality of anticoagulation with non-warfarin therapy should be examined in larger cohorts.

Keywords Anticoagulation · Outcomes · Time in therapeutic range · Bleeding · Thrombosis

Introduction

The goals of anticoagulation are to treat and/or prevent thromboembolic (TE) events while minimizing bleeding risk [1]. Comprehensive warfarin management programs incorporate patient education, care coordination, self- or laboratory-testing, and real-time dose adjustments to optimize time spent in the therapeutic range (TTR) and

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Extended author information available on the last page of the article

decrease adverse events [2–23]. Therapy-related adverse events include bleeding and TE. Most evidence supporting this approach has been developed in programs serving adult patients living within the clinic's local catchment area. A few pediatric-only and combined pediatric-adult programs have reported improved care using this and other approaches [1–9, 11–14]. Because of its narrow therapeutic index, warfarin efficacy and safety are dependent upon maintaining the international normalized ratio (INR) within the therapeutic range defined by underlying indication. TTR < 60% is associated with suboptimal outcomes across the spectrum of warfarin indications [16, 20, 22, 24–33].

We established a combined pediatric-adult anticoagulation program in 2014 at a tertiary care children's hospital that serves 225 adult congenital heart disease survivors on long-term anticoagulation in addition to children and adolescents with cardiac and non-cardiac anticoagulant indications. In contrast to previously reported models that predominantly serve adult patients living in proximity to the host hospital, our program serves patients across a large and diverse (metropolitan and rural) geographic area encompassing central, southeastern, and northwestern Ohio. This is accomplished through a network of ambulatory laboratories strategically located within our 34-county catchment area. This program provides care to both adults and children on long-term warfarin therapy; a smaller group of patients on short-term warfarin therapy or other anticoagulants are also managed. The aims of this study were to compare the impact of our program on anticoagulation quality pre- vs. post-implementation. Quality metrics included %TTR, compliance, and adverse events (bleeding and TE) [34]. Potential variables associated with suboptimal anticoagulation management and adverse events were also examined.

Materials and methods

Medical records of patients receiving anticoagulant care at Nationwide Children's Hospital (a large tertiary care children's hospital that provides care for children and adult survivors of complex pediatric conditions) during 2014–2019 were reviewed. The study was approved by the Nationwide Children's Institutional Review Board. The requirement for informed consent was waived according to 45 CFR 46.116(d) of the US Code of Federal Regulations.

The cohort was divided into two groups: (1) Long-term warfarin therapy and (2) Short-term warfarin (6 weeks to 6 months) and/or non-warfarin anticoagulation. A sub-sample of patients who were followed from 2014 to 2019 and had adequate data to calculate pre-program implementation %TTR and compliance were used to evaluate the impact of the program on quality of care. Patient demographics, anticoagulant indication, anticoagulant agent, target INR range (if applicable), comorbidities (e.g., obesity, hypertension, liver, renal disease, diabetes mellitus, smoking), %TTR, compliance, bleeding, and thrombotic event data were collected.

Rosendaal linear interpolation was used to calculate %TTR [26]. %TTR was calculated for each patient annually and for the entire study period. Compliance was defined as ≥ 1 INR per month and was reported # of months with at least one INR / # of months followed per patient and calendar year [34]. INRs could be obtained from the hospital laboratory using a venipuncture sample or from a fingerstick point-of-care device. Our program utilizes the CoaguChek®XS system (Roche Diagnostics, Indianapolis, IN) for point-of-care testing in our ambulatory lab network. Results from both the hospital laboratory and point-of-care devices are routed to the clinical team via the electronic medical record for same-day clinical decision making. Clinical outcomes such as bleeding and TE were calculated as event rates per 100 person-years of warfarin use. Qlikview software was used to obtain anticoagulation quality data (https://www.qlik.com/us/info/software-ula). This software is linked to the EMR and captures data points of interest for TTR, compliance and duration of anticoagulation. Data for the 26 pre-implementation patients was manually abstracted and analyzed using *INR*Pro© Reporting Systems which utilizes the Rosendaal method for TTR calculation.

Bleeding complications were categorized according to the ISTH-SSC standards for non-surgical anticoagulated patients [35]. Briefly, Major Bleeding was defined as (a) Fatal hemorrhage, and/or (b) Symptomatic bleeding in a critical organ or area, and/or (c) Bleeding causing a ≥ 20 g/L drop in hemoglobin level or leading to transfusion of ≥ 2 units of blood [35]. Clinically relevant non-major bleeding (CRNMB) was defined as any sign or symptom of hemorrhage that did not meet the major bleeding criteria but did meet ≥ 1of the following criteria: (a) Requiring medical intervention by a healthcare professional, (b) Leading to hospitalization or increased level of care, or (c) Prompting a face-to-face evaluation [36]. All bleeds not meeting the Major Bleeding or CRNMB criteria were classified as Minor Bleeding. New or recurrent TE events while receiving anticoagulation were adjudicated by chart and imaging review by one of the authors (VR).

All data were summarized using descriptive statistics. Comparisons of %TTR and compliance between groups were made using Wilcoxon rank sum or Kruskal Wallis test. When comparing more than two groups, p-values were adjusted as appropriate using Dunn's method. Wilcoxon signed rank tests were used to compare pre- and post-implementation %TTR and compliance on the subset of patients who had pre-implementation data. Chi-square or Fisher's

exact tests were used to compare characteristics of those with or without bleeding and thrombotic events. P-values less than 0.05 were considered statistically significant. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary NC).

Results

Demographics

Our anticoagulation program served 422 patients from 2014 to 2019. 73% (N = 308) received long-term warfarin while the remainder (N = 114) were on short-term warfarin or other anticoagulants (Table 1). At its inception in 2014, the program served nearly 150 patients and saw steady growth thereafter (Figure S1). The median age of the long-term warfarin patients was 24 years (range: 2–69), 70.5% of these patients were ≥ 18 years old and 80.2% had cardiac-related warfarin indications. This group accumulated 1,028.2 patient-years of warfarin treatment. The short-term group median age was 16 years (range: 0–45) and was predominantly comprised of children (86%) with TE.

Anticoagulation quality

Following program implementation, %TTR was 78.9% (range 80–100%; Figure S2) in the long-term warfarin group. Mean compliance was 79.5% (range 14.8–100%). %TTR was not different between adult (80.3%) and pediatric patients (77.6%; p = 0.90). However, pediatric compliance was higher (87.6% vs. 77.2%; p = 0.0005). There was no difference in %TTR between females and males (77.4% vs. 79.4%; p = 0.84) but compliance was significantly higher in females (84.8% vs. 76.9%; p = 0.0352). Indication and target INR range were both associated with %TTR (p = 0.0055 and p < 0.0001, respectively; Fig. 1). Patients with mechanical valves had a lower %TTR compared to those with TE (adjusted p = 0.0343) but no other significant differences were noted by indication. Patients with target INR 1.5–2.5 had a significantly higher %TTR than those with a goal of 2.0–3.0 (adjusted p = 0.0164) or 2.5–3.5 (adjusted p < 0.0001). Compliance did not differ by indication or INR goal (data not shown).

Twenty-six (8.4%) of the long-term therapy patients who were followed at our institution and had complete data for both the pre- and post-program implementation periods were subjected to pre-implementation data collection and analysis [median follow up 4.1 years (range: 0.1–12.5 years)] (Table S1). Median pre-implementation %TTR for these 26 patients improved from 17.5 to 87% post-implementation (p < 0.0001; Fig. 2), resulting in a 62.7% overall improvement with 25 (96%) of the patients experiencing %TTR improvement. Compliance also significantly improved in this sub-cohort after program implementation (50% vs. 84.3%, pre- vs. post-, respectively; p < 0.0001; Fig. 2).

Bleeding and thrombosis outcomes

Following program implementation, the incidence of major bleeding events was 1.65/100 person-years of warfarin use whereas the incidence of CRNMB/minor bleeding events was 2.43/100 person-years of warfarin use. The incidence of TE was 0.78/100 person-years warfarin use for the long-term warfarin group. Neither bleeding nor TE complications were associated with %TTR when compared to those without an event (p = 0.48; Fig. 3). The underlying diagnosis or indication for anticoagulation was the only identifiable factor associated with bleeding risk (p = 0.0048; Table 2). Five patients died during the study period due complications related to their underlying condition (no deaths were attributable to bleeding or TE). In the pre- vs. post-implementation analysis, there was a trend toward fewer TE post-implementation (p = 0.15; Table S1). Bleeding complications were also insignificantly reduced.

Discussion

Anticoagulation programs were established with the goal to centralize, standardize, and improve the care of patients on warfarin therapy. Originally, they were implemented for adults with atrial fibrillation, but their scope soon expanded to other anticoagulant indications [37–42]. Several studies have documented the ability of these programs to reduce adverse events [2, 3, 5, 7–9, 13, 15, 19, 21, 23, 37–41, 43, 44]. Warfarin remains a commonly prescribed anticoagulant that is challenging to manage due to its long-onset and -offset of action, food-drug and drug-drug interactions, and narrow therapeutic index [44]. Moreover, the underlying indication and comorbidities may additionally complicate achievement of high-quality warfarin management. Whereas anticoagulation programs have traditionally served adult patients living near the host facility, pediatric patients and adult survivors of complex pediatric conditions often live over a geographically dispersed area served by a tertiary care children's hospital which adds logistical complexity to the provision of high-quality anticoagulant management.

Our program provides comprehensive care to both pediatric and adult patients using the previously established model of care but modified to efficiently serve a wider geographic area through a statewide network of ambulatory laboratories

Table 1 Demographics of Children and Adult Survivors of Complex Pediatric Conditions (N = 422) Enrolled in Comprehensive Anticoagulation Management Program

Long-Term Warfarin Cohort	N = 308
Male Sex, N (%)	180 (58.4)
Age in Years[#], Median (Range)	24 (2–69)
Age Group, N (%)	
Pediatric (< 18 y)	91 (29.5)
Adult	217 (70.5)
Warfarin Indication, N (%)	
Mechanical Valve	161 (52.3)
Fontan	55 (17.9)
TE	45 (14.6)
Atrial Fibrillation/Flutter	31 (10.1)
Other*	16 (5.2)
Duration on Anticoagulation (Years), Median (Range)	3.6 (0.1–9.5)
INR Point-of-Care Device in Home, N (%)	44 (14.3)
Aspirin Therapy Prescribed, N (%)	155 (50.3)
Bleeding Events, N (%)	
Major^	17 (5.5)
CRNMB/Minor[#]	25 (8.1)
Thromboembolic Events[+], N (%)	8 (2.6)
Short-Term Warfarin and Other Anticoagulant Cohort	**N = 114**
Male Sex, N (%)	54 (47.4)
Age in Years, Median (Range)	16 (0–45)
Age Group, N (%)	
Pediatric (< 18y)	98 (86.0)
Adult	16 (14.0)
Duration on Anticoagulation, Median (Range)	3 months (1 week-3 years)
On Ongoing/Lifelong Anticoagulation (DOAC/LMWH), N (%)	46 (40.4)
Bleeding Events[§], N (%)	9 (7.9)
Thromboembolic Events, N (%)	0 (0)

[#]Age at clinic enrollment. TE: Thromboembolic Event; INR: International Normalized Ratio; CRNMB: Clinically-Relevant Non-Major Bleeding; DVT: deep vein thrombosis; GI: gastrointestinal; CNS: central nervous system

*Other: Heart Failure (n = 1), pulmonary HTN (n = 3), complete atrioventricular canal (n = 1), coronary aneurysm/Kawasaki (n = 5), coronary fistula post coil occlusion (n = 1), right pulmonary artery hypoplasia (n = 1), Heart failure and transposition of great arteries (n = 2) coronary artery fistula (n = 1)

^Major Bleeds in Long-term Cohort: Hemorrhage Following Abortion (N = 1), Subarachnoid Bleed (N = 1), Pericardial Hematoma (N = 2), Subdural Hematoma (N = 2), Hemarthrosis (N = 1), Surgical (N = 3), GI Bleed (N = 4), Menorrhagia (N = 1), Subdural Hematoma (N = 1), Hemoptysis (N = 1); [#]CRNMB/ Minor in Long-Term Cohort: Muscle Hematoma (N = 1), Epistaxis (N = 15), Menorrhagia (N = 5), Oral Mucosa (N = 1), Perirectal (N = 3); [+]TE in Long-Term Cohort: Recurrent DVT (N = 1), Mechanical Valve (N = 2), Left Atrial Thrombus (N = 1), Stroke (N = 2), Pacemaker Lead-Associated DVT (N = 1), Stent Thrombosis (N = 1); [§]Bleeding Events in Short-Term and Other Anticoagulant Cohort: Perineal Hematoma after Childbirth (n = 1), CNS Bleed (n = 2), Epistaxis (n = 2), Rectal Bleeding (n = 1), Muscle Hematoma (n = 1), Menorrhagia (n = 1), Hemarthrosis (n = 1)

[+]TE: recurrent DVT (N = 1), mechanical Valve (N = 2), Left Atrial Thrombus (N = 1), Stroke (N = 2), Pacemaker Lead-Associated DVT (N = 1), Stent Thrombosis (N = 1)

[§]Major bleeding: perineal hematoma after childbirth (n = 1), CNS bleed (N = 2), hemarthrosis (N = 1), muscle hematoma (N = 1). CRNMB/minor: epistaxis (N = 2), rectal bleeding (N = 1), menorrhagia (N = 1)

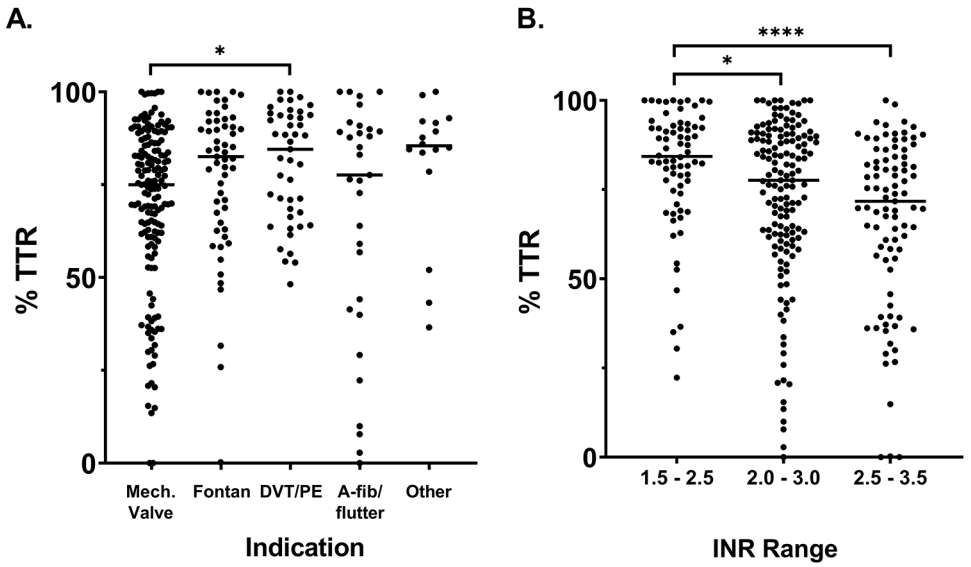

Fig. 1 Time in Therapeutic Range was Influenced by Diagnostic Indication and Goal INR Range. (**A**) Patients on long-term anticoagulation due to mechanical valve (Mech. Valve) placement spent less time in their goal therapeutic range than did patients being treated to prevent venous thromboembolism (TE) recurrence. No other between indication group differences were significant. (**B**) Patients on prophylactic warfarin with goal INR 1.5–2.5 achieved a significantly higher percentage time in therapeutic range (%TTR) than did patients whose therapeutic goal was to achieve a higher therapeutic range (2.0–3.0 or 2.5–3.5). A-fib/flutter: atrial fibrillation/flutter. P-values are adjusted using Dunn's method and denoted as: * < 0.05, ** < 0.01, *** <0.001, **** <0.0001. Median %TTR in each group is displayed with the horizontal bar

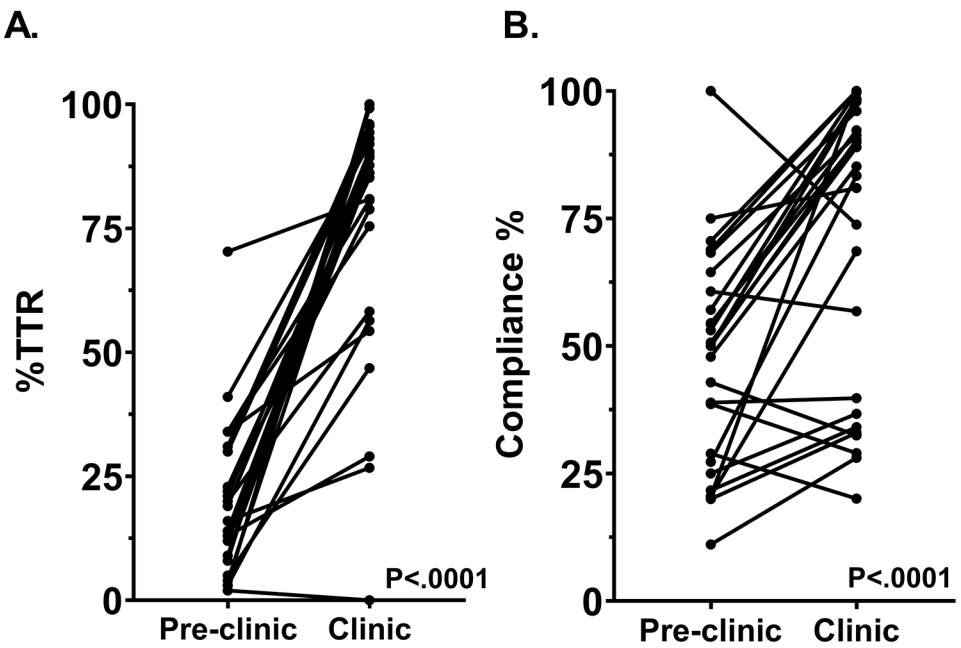

Fig. 2 Both Time in Therapeutic Range (%TTR) and Compliance Improved after Implementation of the Comprehensive Anticoagulation Management Program. (**A**) Twenty-five (96.2%) of the 26 patients included in the pre- vs. post-implementation analysis achieved an improved percentage of Time in Therapeutic Range (%TTR). (**B**) Similarly, 80.8% (21 of 26) patients were more compliant with INR therapeutic monitoring

[5]. The team is comprised of three physicians (VR, CC, BAK), a nurse practitioner (JG), and two registered nurse clinicians (KM, JC) who provide multidisciplinary care through collaborations between hematology, laboratory medicine, pharmacy, cardiology, and other referring subspecialties (see Figure S4). The excellent anticoagulation management parameters reported here are made possible through integrated practices. Prescribing practice variation is reduced through implementation of guidelines for each anticoagulant medication. The team provides consulting services to discuss indications, medication choice, therapeutic duration, patient/family education, counseling, care coordination, monitoring, and follow-up. The nurse clinicians are primarily involved in care coordination, laboratory

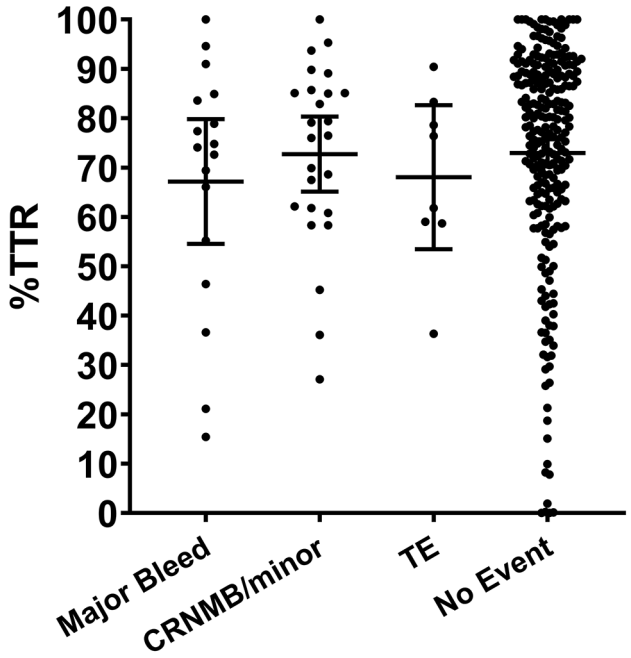

Fig. 3 There was No Difference in Median Time in Therapeutic Range for Patients with versus without Bleeding or Thromboembolic Events. Median (IQR) %TTR was similar in patients with vs. without an anticoagulant complication (bleeding or thromboembolic event), likely because the comprehensive anticoagulation management program was able to achieve the published goal %TTR (> 60%) beyond which no additional safety benefit is expected

results follow-up, and dose adjustment communicating to the patient/family. Testing compliance is enhanced through collaboration with laboratory medicine to make point-of-care INR monitors available in our ambulatory laboratories ("Close to Home [SM] Centers"). Patients on long-term warfarin who meet third-party payor pre-authorization criteria are prescribed in-home point-of-care INR monitors to further facilitate compliance. This integrated approach significantly improved %TTR and compliance as demonstrated by our pre- vs. post-implementation data. The median %TTR achieved by this approach (78.9%) exceeded the > 60% target previously proposed as the ideal adult patient goal [17, 20]. Compliance plateaued at 75–80%, further supporting the benefits of this integrated, multidisciplinary approach.

Pediatric warfarin therapy has similar or even greater challenges than encountered in adult populations. Factors affecting warfarin therapy in pediatrics are age-related dose-response rates, concurrent medications, dietary differences, and frequent concurrent illnesses [12, 14, 45–48]. Nonetheless, high-quality therapy is possible in this age group. An Australian program reported 63.4% TTR in 94 children with 1 major bleeding episode and 2 TE for a combined complication rate of 1.86 events/year [3]. All-cause mortality was 6.9% with 1 event related to thrombosis. A systematic review of 36 pediatric anticoagulation management studies, reported > 60% TTR with 0.5–1.7% bleeding and 1.3-7% TE per year for an overall adverse event rate of 0.5–3.2% per patient/year [1]. In the present study, our pediatric patient

Table 2 Patients with Mechanical Valves were Most Likely to Experience Bleeding Complications

	Bleeding Events			Thromboembolic Events		
Characteristic	Yes	No	p-value	Yes	No	p-value
N	42	266		8	300	
Male Sex, N (%)	27 (64.3)	153 (57.7)	0.42	4 (50.0)	176 (58.9)	0.72
Age^, Median (Range)	23.5 (2–48)	24 (2–69)	0.88	23 (16–42)	24 (2–69)	0.64
Age Group, N (%)						
Pediatric (< 18y)	15 (35.7)	76 (28.6)	0.35	3 (37.5)	88 (29.3)	0.70
Adult	27 (64.3)	190 (71.4)		5 (62.5)	212 (70.7)	
Diagnosis Group, N (%)						
Mechanical Valve	23 (54.8)	138 (51.9)	0.0048	3 (37.5)	158 (52.7)	0.40
Fontan	5 (11.9)	50 (18.8)		3 (37.5)	52 (17.3)	
Thromboembolism	5 (11.9)	40 (15.0)		2 (25.0)	43 (14.3)	
Atrial Fibrillation/Flutter	2 (4.8)	29 (10.9)		0 (0.0)	31 (10.3)	
Other*	7 (16.7)	9 (3.4)		0 (0.0)	16 (5.3)	
INR Group, N (%)						
1.5–2.5	11 (26.2)	59 (22.2)	0.54	1 (12.2)	69 (23.0)	0.14
2.0–3.0	17 (40.5)	132 (49.6)		2 (25.0)	147 (49.0)	
2.5–3.5	14 (33.3)	75 (28.2)		5 (62.5)	84 (28.0)	
Comorbidity Present[&]	17 (40.5)	72 (27.1)	0.07	1 (12.5)	88 (29.3)	0.45

^Age in Years; *Other: Heart Heart Failure (n = 1), pulmonary HTN (n = 3), complete atrioventricular canal (n = 1), coronary aneurysm/Kawasaki (n = 5), coronary fistula post coil occlusion (n = 1), right pulmonary artery hypoplasia (n = 1), Heart failure and transposition of great arteries (n = 2) coronary artery fistula (n = 1)

[&]Comorbidities: obesity, hypertension, renal disease, diabetes mellitus, liver disease, lung disease, smoking

bleeding, TE, and %TTR (77.2%) were not significantly different from those of our adult patients.

Warfarin efficacy and safety is related to its pharmacodynamics as measured by INR and proportion of time spent within the prescribed therapeutic INR range [37, 49]. Low INR values increase TE risk and high INR values increase bleeding risk. It is challenging to maintain a high %TTR due to wide inter- and intra-individual warfarin effects that lead to sub- or supra-therapeutic INRs 25–40% of the time [26, 49–53]. %TTR is inversely correlated with bleeding complications, thus the benefits of anticoagulation diminish with poor-quality warfarin therapy [24, 27, 28]. However, the correlation between %TTR and bleeding disappears when TTR is > 70% [55]. Several studies have demonstrated that bleeding and TE primarily occur with lower %TTR and the association between %TTR and complications is nonlinear [16, 28, 29, 56]. These data suggest that adverse events are much less likely when %TTR is > 70%. Thus, the lack of %TTR correlation with bleeding and TE in our long-term warfarin patients is likely explained by our program's achievement of %TTR > 70%.

The bleeding and TE rates in this study are similar to those reported in other studies [1, 3, 18, 20, 57]. Comorbidities did not significantly influence adverse outcomes in this study (Table 2). However, warfarin indication was significantly associated with bleeding, with the mechanical valve group appearing to drive this association, perhaps because these patients were more likely to be prescribed a higher target INR goal (50% of the patients with mechanical valves were in the highest INR range; Figure S3). Other factors such as age, gender, dual therapy with aspirin, and comorbidities were not associated with bleeding risk (Table 2). The 26-patient comparator cohort demonstrated that bleeding and TE complications were insignificantly reduced after program implementation. However, this analysis may have been underpowered due to the low number of patients with complete data available for inclusion. The second group of patients on short-term warfarin or other anticoagulants experienced no TE during the study period but did have 9 bleeding events (Table 1). Low molecular weight heparin and direct oral anticoagulant care quality should be explored in future studies, particularly in pediatrics.

Limitations

We were unable to obtain pre-implementation %TTR, compliance, bleeding, and thrombosis data on the entire cohort due to the lack of an electronic medical record (EMR) system that consistently captured these data. Our program was implemented concurrently with our hospital's adoption of Epic Healthcare Systems (Verona, WI) EMR which enabled the capture of these data post-implementation. Fortunately, we were able to manually abstract these data on 26 patients who were followed both pre- and post-implementation. These records enabled an evaluation of pre- versus post-implementation warfarin quality. Nonetheless, this small sample limited our ability to comprehensively compare outcomes for the entire cohort. An important strength, however, is that each of these 26 patients served as his/her own pre-implementation control. Although our program is moderate-to-large in comparison to patient volumes reported elsewhere, we were inadequately powered to perform comprehensive analyses adjusting for age, comorbidities, INR range, or underlying diagnoses. Compliance was measured in this study as ≥ 1 INR per month, a more comprehensive compliance definition might include patient/family understanding of medication adherence and cognizance of potential dietary and drug interactions, as reported elsewhere [58, 59]. Sociodemographic determinants impacting healthcare access and therapeutic compliance should be further explored in different models of anticoagulant care.

Another limitation to our study was the wide variability of surgical procedures and interventions in the CHD cohort, which limited our ability to compare groups of patients who underwent similar procedures and interventions. However, thrombotic events were reviewed for each patient through their EMR. These events relied on clinical documentation in the EMR. Additionally, Fontan patients are heterogenous in terms of their management (e.g., aspirin use, surgical interventions, type of anticoagulant used) limiting our ability to utilize this subgroup as a comparator. Only those patients managed with warfarin were used for comparative analysis. In addition, similar to other anticoagulation quality data it is not possible to causally link TTR and clinical endpoints (e.g. thrombosis, bleeding).

Conclusion

Our multidisciplinary comprehensive anticoagulation program consistently demonstrated > 70% TTR for both children and adults on warfarin therapy. This optimal %TTR and compliance was sustained during the study period, resulting in relatively low bleeding and TE rates. Further analysis suggested that underlying diagnosis is significantly associated with bleeding events, perhaps driven by patients with mechanical heart valves who often require a higher target INR range. %TTR did not differ between patients with vs. without a bleeding or TE event, likely because the program achieved a high median %TTR (> 70%) that has been reported to stabilize these event rates. This study demonstrates that both pediatric and adult patients can achieve high-quality anticoagulant therapy when managed

by a multidisciplinary team using an integrated approach to serve a wide geographic area.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11239-023-02806-w.

Author contributions VR designed study design, performed retrospective data acquisition and drafted the manuscript. JS performed statistical analysis and review manuscript. AD, CC, AS, KM, JG, JC reviewed the manuscript. BK contributed to study design and writing of the manuscript.

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Declarations

Conflict of interest The authors have no conflict of interest to declare that are relevant to the content of this article.

Ethical approval This study was approved by the Nationwide Children's Institutional Review Board. The requirement for informed consent was waived according to 45 CFR 46.116(d) of the US Code of Federal Regulations.

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Authors and Affiliations

Vilmarie Rodriguez[1,2] · Joseph Stanek[1,3] · Clifford L Cua[2] · Amanda Sankar[1,2,4] · Jean Giver[1] · Kay Monda[1] · Joan Canini[1] · Amy L. Dunn[1,2] · Bryce A. Kerlin[1,2,5]

✉ Vilmarie Rodriguez
vilmarie.rodriguez@nationwidechildrens.org

[1] Division of Hematology/Oncology/BMT, Nationwide Children's Hospital, The Ohio State University, 700 Children's Drive, Columbus, OH 43205, USA

[2] Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH, USA

[3] Biostatistics Resource at Nationwide Children's Hospital, Columbus, OH, USA

[4] Division of Cardiology, Nationwide Children's Hospital, Columbus, OH, USA

[5] Center for Clinical and Translational Research, Abigail Wexner Research Institute, Nationwide Children's Hospital, Columbus, OH, USA