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Full Length Article

Primary thromboprophylaxis in hospitalized children: A multi-center retrospective analysis

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ABSTRACT

Background/objectives: Hospital acquired venous thromboembolism in children is associated with significant morbidity/mortality. Prevention strategies include sequential compression devices and prophylactic anticoagulation but these interventions carry risk and are poorly studied in children.

Objectives were to evaluate primary thromboprophylaxis use in hospitalized children over time and the associated bleeding risk.

Materials and methods: Retrospective study of hospitalized patients aged 10–18 years within the Pediatric Health Information System administrative database from January 2008–September 2015. Factors associated with thromboprophylaxis receipt and bleeding were identified using generalized linear mixed effects models.

Results: Of 1,075,383 hospitalizations, 10,544 (1%) received prophylactic enoxaparin and 58,768 (5%) received mechanical compression. Mechanical thromboprophylaxis increased slightly over time (4.3% in 2008, 6.2% in 2015), enoxaparin use did not (0.8% in 2008, 1.2% in 2015). Patients aged 16–18 were more likely than younger children (10 − 12) to receive pharmacologic (adjusted odds ratio [aOR] 3.1, 95% confidence interval [CI] 2.9–3.3) or mechanical thromboprophylaxis (aOR 2.9, 95% CI 2.9–3). Patients on rehabilitation medical service were more likely to receive prophylactic enoxaparin (aOR 53, 95% CI 44.1–64.5). 5.6% (589/10,544) of patients receiving enoxaparin prophylaxis had bleeding. Thromboprophylaxis use by hospital varied with a range of 0.25–3.3% for enoxaparin and 2–26.2% for mechanical compression.

Conclusion: Thromboprophylaxis is infrequently utilized in hospitalized children. Pharmacologic prophylaxis with enoxaparin remains low and has not substantially increased over time. Significant variability exists across hospitals and services in the administration of both mechanical and pharmacologic thromboprophylaxis highlighting the need for further evidence to standardize practice.

1. Introduction

From 2001 to 2007, venous thromboembolism (VTE) incidence in hospitalized pediatric patients increased by 70% [1]. Hospital-associated VTE is associated with increased morbidity, cost, length of hospitalization, and mortality. [2] Risk factors for pediatric VTE include admission to an intensive care unit (ICU), respiratory failure, presence of a central venous access device (CVAD), trauma, surgery, use of oral contraceptives, and malignancy [3]. Evidence is lacking in how to prevent VTE in pediatric patients [4]. Individual hospital VTE prevention quality improvement projects have reported successful increases in use of thromboprophylaxis but these can be difficult to sustain or reproduce [5].

In 2012, the Children's Hospitals' Solutions for Patient Safety (SPS) formed a team to develop strategies to reduce harm caused by VTEs as this complication represents the 2nd largest contributor to harm across the SPS network (https://www.solutionsforpatientsafety.org). Current recommendations include VTE risk stratification for inpatients > 12 years of age and targeted thromboprophylaxis with mechanical compression. Risk stratification includes assessing the patient's mobility status and the presence of VTE risk factors. [6] Due to lack of data regarding efficacy and associated harm, prophylactic anticoagulation was not included in the SPS standard recommendations. Other guidelines consider immobility plus one or two additional risk factors as high

Abbreviations: VTE, venous thromboembolism; SCDs, sequential compression devices; PICU, pediatric intensive care unit; CVAD, central venous access device; SPS, Solutions for Patient Safety; PHIS, Pediatric Health Information System

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risk criteria and indication for mechanical prophylaxis and consideration of pharmacologic prophylaxis [7,8]. The American College of Chest Physicians evidence-based guidelines do not address primary thromboprophylaxis in hospitalized pediatric patients [9].

In the hospitalized adult population, pharmacologic thromboprophylaxis has been shown to be effective and safe and is considered standard of care [10–12]. However, prophylactic anticoagulation has not been well studied in pediatric inpatients [13]. In a survey of pediatric hematologists aimed at understanding current use of pharmacologic thromboprophylaxis, a wide variation in clinical practice was reported and universal adoption for high-risk patients was not identified [14]. Hesitancy to use pharmacologic prophylaxis likely stems from a lack of data on efficacy and concern regarding bleeding risk. One single center pediatric study demonstrated that in pediatric patients on prophylactic anticoagulation who are not post-surgical the risk of major bleeding is low (0%) [15]. Mechanical thromboprophylaxis with SCDs has been more widely accepted for high-risk pediatric patients given minimal risk but remains underutilized. In a multinational prospective study of critically ill children hospitalized in the PICU in 2012, 86.9% were identified to have one or more risk factor for VTE. Of these children, only 12.4% received pharmacologic thromboprophylaxis and only 23.8% of patients who met the minimum age requirement for mechanical thromboprophylaxis received it [16]. The objective of our study was to evaluate the use of primary thromboprophylaxis in hospitalized children over time and the associated harms.

2. Patients and methods

2.1. Study design

This was a retrospective multicenter cohort study of patients within the Pediatric Health Information System (PHIS; Children's Hospital Association, Lenexa, KS) database. PHIS is an inpatient/observation administrative and billing database of 50 tertiary children's hospitals. Participating hospitals are located in 27 states plus the District of Columbia. These hospitals provide inpatient and observation data, including patient demographics, up to 41 International Classification of Diseases, 9th and 10th revisions (ICD-9, ICD-10), diagnoses, and up to 41 ICD-9 and ICD-10 procedures as well as encrypted unique identifiers to track individual patients across admissions. Children's Hospital Association and participating hospitals jointly assure data quality. The Children's Mercy Hospital Institutional Review Board granted exempt status for this study.

2.2. Subjects

Our study included patients aged 10–18 years admitted from January 1, 2008 - September 30, 2015. Hospitals that did not provide data for all years in the study (N = 3), and hospitals that did not provide billing data for SCDs (i.e. ≤1% of hospitalizations, N = 14) were excluded, resulting in the inclusion of 33 hospitals. Patients with a diagnosis of venous or arterial thrombosis (Appendix A) within the last 6 months prior to the index hospitalization and during the index hospitalization were excluded as these patients could be on enoxaparin for treatment and not prevention of VTE. To validate that this would identify patients on enoxaparin for prophylaxis and not treatment, we conducted a retrospective chart review at one institution from January 1, 2015–December 31, 2015. Nineteen patients on prophylactic enoxaparin were identified by consult to the Hematology Coagulation Service. Seventeen (89.5%) of these patients were without thrombus prior to or during the current hospitalization. Patients with a diagnosis of a congenital bleeding disorder (Appendix B) were also excluded.

2.3. Study definitions

Receipt of prophylactic anticoagulation was determined using billing data for enoxaparin sodium. Receipt of mechanical compression was determined using a billed charge for compression stockings, sequential compression device, and/or compression sleeves for sequential compression device. Receipt of ICU care and/or intubation was determined using a billed charge for high frequency ventilation, mechanical ventilation, or an ICU room charge. Bleeding events were captured using ICD-9 codes validated in a prior study that used PHIS to evaluate antithrombin concentrate use and bleeding events in pediatric extracorporeal membrane oxygenation patients (Appendix B) [17]. Patients were classified using the pediatric complex chronic conditions (CCC) classification system created by Feudtner and colleagues which uses ICD-9 codes to group patients into 9 categories (cardiovascular, respiratory, neuromuscular, renal, gastrointestinal, hematologic or immunologic, metabolic, other congenital or genetic, and malignancy) [18].

2.4. Statistical analysis

All categorical variables were summarized with frequencies and percentages. Clinical and demographic characteristics of patients receiving thromboprophylaxis were compared to those not receiving thromboprophylaxis using chi-square tests. For continuous variables, we used medians with inter-quartile rages and Wilcoxon Rank-Sum tests for comparisons. In unadjusted analyses, we assessed hospital variation in the use of thromboprophylaxis with a chi-square test. This was performed in aggregate and by service lines. Additionally, we constructed generalized linear mixed effects models for receipt of thromboprophylaxis using a random intercept for each hospital (to account for patient clustering within hospital) and important clinical and demographic characteristics. For patients that received thromboprophylaxis, we determined the rates of major and minor bleeding events in aggregate and by hospital. We used bi-variate analyses, to compare clinical and demographic characteristics of children with bleeding events to those who did not experience bleeding events. We also constructed generalized linear mixed effects models to determine the characteristics of children most likely to experience bleeding events. All statistics were performed using SAS v.9.4 (SAS Institute, Cary, NC) and p-values < 0.05 were considered statistically significant.

3. Results

3.1. Subject demographics and characteristics

We identified 1,075,383 patients during the study time period; Table 1 provides summary demographics. There was an equal distribution of patients by age, group, and sex. The majority of the patients were non-Hispanic white and were discharged home.

3.2. Receipt of thromboprophylaxis

In the cohort, 10,544 (1%) received prophylactic enoxaparin, 58,768 (5%) received mechanical compression, and 3785 (0.4%) received both prophylactic enoxaparin and mechanical compression.

Over the course of the study period (2008–2015), the use of mechanical compression (4.3% in 2008 to 6.2% in 2015; $p < 0.0001$), enoxaparin prophylaxis (0.8% in 2008 to 1.2% in 2015; $p < 0.0001$), or either method (4.9% in 2008 to 7% in 2015; $p < 0.0001$) increased (Fig. 1).

As age increased, the percentage of patients who received thromboprophylaxis with mechanical compression (7.2% of patients aged 16–18 vs. 3.2% of patients aged 10–12; $p < 0.001$) or enoxaparin (1.6% of patients aged 16–18 vs. 0.5% of patients aged 10–12; $p < 0.001$) increased. There was no statistical difference in enoxaparin prophylaxis by gender ($p = 0.218$). There was a statistically significant difference in mechanical compression by gender (5.2% of male patients vs. 5.8% of female patients, $p < 0.001$). Patients discharged with home

Table 1
Baseline demographic information.

Characteristics	n (%)
Total patients	1,075,383
Age	
10–12	344,746 (32.1)
13–15	409,846 (38.1)
16–18	320,791 (29.8)
Gender	
Male	534,937 (49.7)
Female	540,247 (50.2)
Race	
Non-Hispanic White	561,951 (52.3)
Non-Hispanic Black	220,416 (20.5)
Hispanic	197,809 (18.4)
Asian	19,033 (1.8)
Other	76,174 (7.1)
Season	
Spring	278,608 (25.9)
Summer	281,312 (26.2)
Fall	259,607 (24.1)
Winter	255,856 (23.8)
Payor	
Government	523,626 (48.7)
Private	489,859 (45.6)
Other	61,898 (5.8)
Discharge disposition	
Home health services	16,820 (1.6)
Home	1,003,011 (93.3)
Other	48,431 (4.5)
Skilled facility	7121 (0.7)

health services had higher use of mechanical compression (10%) and enoxaparin (3.2%) prophylaxis during their hospitalization compared to patients discharged home or to other locations without services (Table 2). Surgical services had the highest percentage of patients using SCDs. The solid organ transplant service used SCDs for 45% of their patients over the study period, followed by reproductive surgery (28.5%) and plastic surgery (18.1%). Services with lower mechanical compression use despite likely higher risk patients included cancer care hematology (3.1%), cancer care oncology (4.2%), medical cardiac (3.1%), and medical digestive disease (3.3%). Rehabilitation services had the highest enoxaparin prophylaxis use (18.5%), followed by trauma surgery (7.5%). Services with lower rates of enoxaparin prophylaxis included cancer care hematology (0.4%), cancer care oncology (1.1%), and digestive disease medical (0.3%). 3.1% of intubated or ICU patients received enoxaparin prophylactically and 18.4% received mechanical compression.

Of the participating PHIS hospitals included in the study, the highest adjusted rate for enoxaparin prophylaxis use by institution was 3.3% and the highest adjusted rate for mechanical compression use by institution was 26.2%. This can be contrasted to other hospitals with an adjusted rate as low as 0.25% for anticoagulation prophylaxis and 2% for mechanical compression (Fig. 2). The hospitals with the highest use of thromboprophylaxis were medium to large, free-standing children's hospitals.

3.3. Factors associated with receipt of thromboprophylaxis

For anticoagulation prophylaxis, factors associated with receiving thromboprophylaxis in multivariable analysis included older age (16–18 years vs. 10–12 years, adjusted odds ratio [aOR] 2.9, 95% confidence interval [CI] 2.9–3.0, $p < 0.001$), ICU stay or intubation (aOR 2.4, 95% CI 2.2–2.5, $p < 0.001$), having a cardiovascular complex chronic condition (CCC) (aOR 1.9, 95% CI 1.8–2.0, $p < 0.001$), renal disease (aOR 1.9, 95% CI 1.8–2.0, $p < 0.001$), and medical service such as the rehabilitation service (aOR 53, 95% CI 44.1–64.5, $p < 0.001$), and the trauma care surgical service (aOR 12.6, 95% CI 10.4–15.2, $p < 0.001$). For mechanical compression, older age also increased the likelihood of receipt (age 16–18 vs. 10–12 aOR 3.1, 95% CI 2.9–3.3, $p < 0.001$). Other factors associated with receiving mechanical compression were being technology dependent (aOR 1.9, CI 1.8–1.9, $p < 0.001$), ICU stay or intubation (OR 5.1, CI 5.0–5.2, $p < 0.001$), and medical service such as reproductive surgical (aOR 16.8, 95% CI 15.0–18.7, $p < 0.001$), surgical digestive disease (aOR 5.9, 95% CI 5.5–6.4, $p < 0.001$), and rehabilitation (aOR 5.5, 95% CI 4.9–6.2, $p < 0.001$) (Table 3).

3.4. Bleeding events

Bleeding occurred in 5.6% (95% CI 5.1%–6.0%) of the patients with anticoagulation prophylaxis versus 4.7% (95% CI 4.6%–4.9%) with mechanical compression. Critically ill patients on enoxaparin prophylaxis experienced a bleeding rate of 10.4% as compared to critically ill patients who only received mechanical compression with a bleeding rate of 8.6%.

In unadjusted analyses, younger patients experienced more bleeding (6.6% of patients aged 10–12 versus 5% of patients aged 16–18, $p = 0.017$) (Table 4). In multivariable analysis, patients who were more likely to experience a bleeding event with anticoagulation prophylaxis had hematology and immunodeficiency CCC (aOR 1.9, 95% CI 1.5–2.4, $p < 0.001$), CVD CCC (aOR 1.7, 95% CI 1.4–2.1, $p < 0.001$) or were intubated or in the ICU (aOR 2.9, 95% CI 2.3–3.6, $p < 0.001$). ICU or intubated patients were most likely to bleed with mechanical compression alone (aOR 3.2, CI 2.8–3.5, $p < 0.001$) (Table 5).

4. Discussion

To our knowledge, this is the first multi-institutional study to evaluate the use of thromboprophylaxis with mechanical compression and/or anticoagulation in hospitalized children. Despite awareness that VTE in hospitalized pediatric patients continues to increase, we found that overall only 1% of patients studied received pharmacologic prophylaxis with enoxaparin and 5% received mechanical prophylaxis. Though statistically significant, the increase in pharmacologic

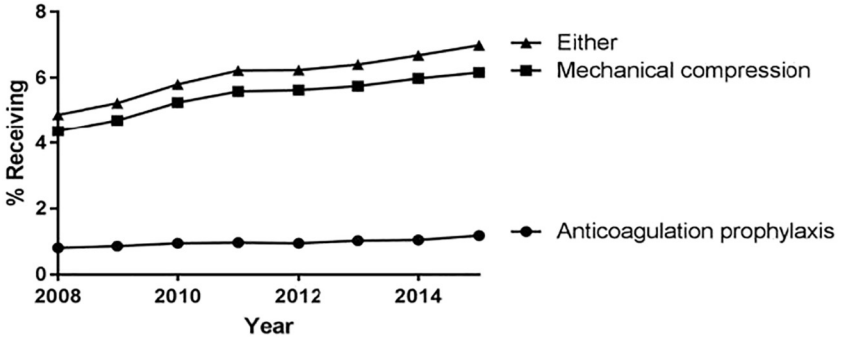

Fig. 1. Receipt of thromboprophylaxis over time.

Table 2
Bivariate multivariable analysis of demographic factors associated with receiving thromboprophylaxis.

Characteristics	Anticoagulation prophylaxis, n (%)		aOR anticoagulation prophylaxis[a]		Mechanical compression n (%)			aOR mechanical compression[a]	
	No	Yes	Estimate (95% CI)	*p*	No	Yes	*p*	Estimate (95% CI)	*p*
N	1,064,839	10,544			1,016,615	58,768			
Age									
10–12	343,110 (99.5)	1636 (0.5)	Reference	–	333,617 (96.8)	11,129 (3.2)	< 0.001	–	–
13–15	405,985 (99.1)	3861 (0.9)	1.88 (1.77, 2)	< 0.001	385,189 (94)	24,657 (6)		2.16 (2.1,2.21)	< 0.001
16–18	315,744 (98.4)	5047 (1.6)	3.07(2.89,3.25)	< 0.001	297,809 (92.8)	22,982 (7.2)		2.92 (2.85, 3)	< 0.001
Gender									
Male	529,773 (99)	5164 (1)			507,344 (94.8)	27,593 (5.2)	< 0.001		
Female	534,870 (99)	5377 (1)			509,088 (94.2)	31,159 (5.8)			
Discharge disposition									
Home health services	16,275 (96.8)	545 (3.2)	Reference	–	15,145 (90)	1675 (10)	< 0.001	–	–
Home	994,231 (99.1)	8780 (0.9)	0.57 (0.52, 0.63)	< 0.001	950,023 (94.7)	52,988 (5.3)		1.03 (0.97, 1.1)	0.317
Other	47,465 (98)	966 (2)	0.83 (0.73, 0.94)	0.003	44,919 (92.7)	3512 (7.3)		1.23 (1.14, 1.33)	< 0.001
Skilled facility	6868 (96.4)	253 (3.6)	1.23 (1.03, 1.46)	0.022	6528 (91.7)	593 (8.3)		1.57 (1.39, 1.77)	< 0.001

[a] aOR = adjusted odds ratio.

prophylaxis over the study period (0.8 to 1.2%) may not be clinically significant given the relatively small change in percentage. SCD use has increased (4.9 to 7%), highlighting that while providers may not be willing to prescribe anticoagulation secondary to the perceived risk of hemorrhage and lack of efficacy data they are willing to use SCDs. However, SCD use also remains disproportionally low despite the minimal risk of implementation. Additional barriers to SCD use include hospital cost and process implementation [19]. In addition, the most effective way to prevent hospital-acquired VTE in children remains unknown and this likely contributes to decreased use of thromboprophylaxis [20,21].

This study identified characteristics of patients receiving thromboprophylaxis. Older age has been documented as a VTE risk factor with one study calculating relative risks of 7.7, 4.3, and 1.5 for patients aged 18–21, 14–17, and 10–13 respectively as compared to 2–9 year olds [22]. With increasing age, our patients were more likely to receive mechanical and/or pharmacologic prophylaxis indicating that providers are aware of the increased VTE risk as patients age. Female patients are known to be at increased risk for VTE likely due to oral contraceptive use and pregnancy [23,24]. More female patients received mechanical prophylaxis and this was statistically significant. However, we found no clinical difference in receipt of prophylactic enoxaparin by gender. Patients discharged with home health services had higher rates of thromboprophylaxis likely due to being more medically complex. It has been shown that medically complex patients such as those with multiple CCCs are up to 4 times more likely to experience VTE [1,22].

There was significant variability in thromboprophylaxis use by medical service and across hospitals. Some medical services with patients at high risk for VTE, like rehabilitation services which have a large proportion of immobile patients, appear to have routinely implemented thromboprophylaxis with approximately one-third of their patients receiving it. Rehabilitation medicine has clinical practice guidelines which recommend anticoagulation prophylaxis for adolescents with spinal cord injury and this may account for their increased use. [25] Other services, such as solid organ transplant services have implemented mechanical compression in almost half of their patients. This may be due to concern for bleeding in post-operative transplant patients. Surgical services, especially trauma, infectious disease, and cardiac, contain patients at high risk for VTE, and our study shows these services are using some form of thromboprophylaxis more frequently [26].

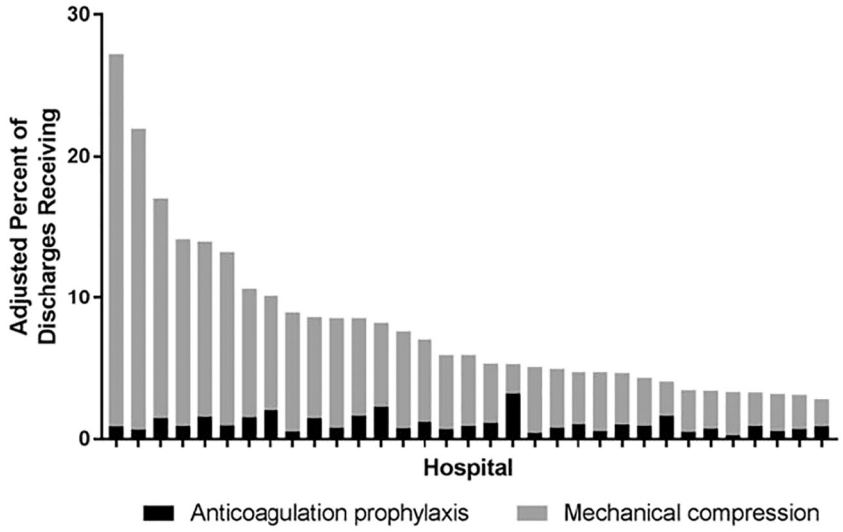

Fig. 2. Adjusted percent of discharges receiving thromboprophylaxis by hospital.

Table 3
Bivariate multivariable analysis of service lines associated with receiving thromboprophylaxis.

Service	Anticoagulation prophylaxis, n (%)	aOR anticoagulation prophylaxis*	Mechanical compression, n (%)	aOR mechanical compression*
Cancer hematology	197 (0.4)	Reference	1476 (3.1)	Reference
Cancer oncology	618 (1.1)	2.14 (1.79, 2.57)	2328 (4.2)	1.52 (1.4, 1.65)
Cardiac med	612 (2.4)	4.9 (4.11, 5.83)	766 (3.1)	0.61 (0.56, 0.68) $p = 0.935$
Cardiac surg	593 (3.6)	3.2 (2.66, 3.86)	2594 (15.6)	1.75 (1.6, 1.91)
Respiratory med	734 (0.9)	2.06 (1.73, 2.44)	2206 (2.6)	0.64 (0.6, 0.7)
Respiratory surg	59 (1.6)	1.73 (1.27, 2.35)	731 (19.7)	5.38 (4.81, 6.02)
Orthopedics med	210 (0.9)	3.49 (2.84, 4.28)	753 (3.4)	1.34 (1.22, 1.48)
Orthopedics surg	1536 (1.8)	5.1 (4.33, 6.02)	12,859 (14.7)	4.05 (3.78, 4.34)
Rheumatology	177 (1.9)	4.7 (3.81, 5.8)	238 (2.6)	0.93 (0.8, 1.07)
Bone marrow transplant	37 (1.9)	0.48 (0.31, 0.73)	192 (9.9)	0.17 (0.13, 0.21)
Solid organ transplant	114 (6.2)	0.76 (0.54, 1.07) $p = 0.113$	834 (45.1)	1.53 (1.3, 1.8)
Digestive disease med	380 (0.3)	1.02 (0.85, 1.22) $p = 0.860$	1702 (1.5)	0.54 (0.49, 0.58)
Digestive disease surg	1150 (1.5)	2.79 (2.35, 3.31)	9008 (11.8)	5.94 (5.54, 6.36)
Neuroscience med	391 (0.4)	1.35 (1.12, 1.62)	2087 (2.2)	0.71 (0.66, 0.77)
Neuroscience surg	305 (1.1)	1.27 (1.04, 1.55)	4701 (16.9)	2.83 (2.62, 3.06)
ID med	625 (1.1)	2.5 (2.1, 2.97)	1892 (3.3)	0.98 (0.91, 1.06)
ID surg	100 (4.6)	4.65 (3.55, 6.08)	380 (17.3)	3.31 (2.86, 3.83)
Dermatology med	30 (0.5)	1.69 (1.15, 2.5)	88 (1.4)	0.54 (0.43, 0.67)
Endocrinology med	156 (0.3)	0.77 (0.62, 0.96)	586 (1.1)	0.28 (0.25, 0.31)
Mental health med	47 (0)	0.15 (0.11, 0.21)	179 (0.2)	0.06 (0.05, 0.07)
Nephrology/urology med	159 (0.6)	1.43 (1.14, 1.78)	574 (2.2)	0.64 (0.57, 0.71)
Ophthalmology med	7 (0.2)	0.8 (0.37, 1.7) $p = 0.557$	24 (0.6)	0.26 (0.17, 0.4)
Otolaryngology med	52 (0.3)	0.95 (0.7, 1.3) $p = 0.763$	206 (1.1)	0.34 (0.3, 0.4)
Rehabilitation med	532 (18.5)	53.33 (44.11, 64.47)	617 (21.4)	5.5 (4.88, 6.19)
Trauma care med	225 (0.7)	1.18 (0.96, 1.46) $p = 0.112$	1405 (4.2)	0.71 (0.65, 0.77)
Nephrology/urology surg	99 (1)	1.57 (1.21, 2.04)	1283 (13.4)	4.11 (3.74, 4.52)
Ophthalmology surg	3 (0.2)	0.67 (0.21, 2.1) $p = 0.490$	75 (5.2)	1.82 (1.41, 2.35)
Otolaryngology surg	118 (0.5)	1.11 (0.87, 1.41) $p = 0.404$	1701 (6.9)	2.29 (2.1, 2.49)
Plastic surgery surg	94 (1.3)	2.65 (2.04, 3.43)	1276 (18.1)	5.71 (5.19, 6.28)
Reproductive surg	41 (1.4)	2.16 (1.53, 3.07)	821 (28.5)	16.75 (15.01, 18.69)
Trauma surg	428 (7.5)	12.58 (10.39, 15.22)	920 (16.2)	3.82 (3.44, 4.25)

* $p < 0.05$ unless listed, 95% CI; excluded services that did not have significant aOR for either anticoagulation prophylaxis or mechanical compression; med = medical, surg = surgical, ID = infectious disease.

Other medical services with patients at higher risk have not as readily adopted thromboprophylaxis. Malignancy is a significant risk factor for VTE development and recurrence, however the rate of use of thromboprophylaxis in cancer care oncology and hematology patients was relatively low [1]. While these patients may be at higher bleeding risk, only 3–4% of these patients even received mechanical compression as prophylaxis. Digestive disease patients include patients with inflammatory bowel disease and short bowel syndrome. These patients frequently have CVADs and are receiving TPN putting them at significantly increased VTE risk [27,28]. Only 0.3% of medical digestive

Table 4
Bivariate analysis for factors associated with bleeding while receiving thromboprophylaxis.

	Anticoagulation prophylaxis bleeding event*		Mechanical compression bleeding event*	
	No	Yes	No	Yes
N (%)	9955 (94.4)	589 (5.6)	55,985 (95.3)	2783 (4.7)
Age				
10–12	1528 (93.4)	108 (6.6)	10,556 (94.9)	573 (5.1)
13–15	3630 (94)	231 (6)	23,516 (95.4)	1141 (4.6)
16–18	4797 (95)	250 (5)	21,913 (95.3)	1069 (4.7)
Discharge disposition				
Home health services	517 (94.9)	28 (5.1)	1566 (93.5)	109 (6.5)
Home	8338 (95)	442 (5)	50,867 (96)	2121 (4)
Other	868 (89.9)	98 (10.1)	3032 (86.3)	480 (13.7)
Skilled facility	232 (91.7)	21 (8.3)	520 (87.7)	73 (12.3)
ICU/intubation	3901 (89.6)	454 (10.4)	23,350 (91.4)	2184 (8.6)
CCC				
Neuromuscular	1537 (92)	133 (8)	8956 (92.1)	767 (7.9)
CVD	1881 (88.3)	249 (11.7)	6383 (87.9)	878 (12.1)
Respiratory	737 (91.1)	72 (8.9)	1954 (89.5)	230 (10.5)
Renal	1181 (91.5)	110 (8.5)	4395 (90.5)	461 (9.5)
GI	1690 (92.8)	131 (7.2)	6595 (92)	572 (8)
Hematology immunodeficiency	931 (90.1)	102 (9.9)	3250 (86.8)	494 (13.2)
Metabolic	1146 (91.1)	112 (8.9)	4139 (89.6)	480 (10.4)
Congenital or genetic defect	892 (92.8)	69 (7.2)	10,685 (96)	444 (4)
Malignancy	1396 (94.3)	84 (5.7)	5072 (90.1)	558 (9.9)
Tech dependent	2631 (90.8)	265 (9.2)	16,588 (93.3)	1196 (6.7)
Transplant	371 (83.6)	73 (16.4)	1740 (84.5)	320 (15.5)

* All p values < 0.05.

Table 5
Multivariable analysis for factors associated with bleeding while receiving thromboprophylaxis.

	aOR (95% CI)[a] Anticoagulation prophylaxis	*p*	aOR (95% CI)[a] Mechanical compression	*p*
Illness severity	1.04 (1.03, 1.04)	< 0.001	1.04 (1.04, 1.04)	< 0.001
Age				
10–12	Reference			
13–15	0.99 (0.77, 1.28)	0.965	1.06 (0.95, 1.18)	0.309
16–18	0.96 (0.75, 1.23)	0.749	1.08 (0.96, 1.2)	0.187
Discharge disposition				
HHS	Reference			
Home	1.23 (0.81, 1.87)	0.334	0.99 (0.8, 1.24)	0.964
Skilled facility	1.59 (1, 2.53)	0.051	1.77 (1.4, 2.25)	< 0.001
Other	1.26 (0.67, 2.36)	0.472	1.62 (1.15, 2.27)	0.005
CCC				
Neuromuscular	0.9 (0.71, 1.14)	0.386	1.16 (1.05, 1.29)	0.005
CVD	1.7 (1.4, 2.07)	< 0.001	1.72 (1.56, 1.89)	< 0.001
Respiratory	0.75 (0.55, 1.03)	0.078	0.83 (0.7, 0.99)	0.036
Renal	1.05 (0.81, 1.35)	0.716	1.32 (1.16, 1.5)	< 0.001
GI	1.14 (0.88, 1.47)	0.331	1.41 (1.25, 1.58)	< 0.001
Hematology and immunodeficiency	1.88 (1.46, 2.41)	< 0.001	2.42 (2.14, 2.73)	< 0.001
Metabolic	1.12 (0.88, 1.42)	0.363	1.14 (1.01, 1.28)	0.030
Congenital or genetic defect	0.96 (0.72, 1.27)	0.781	0.67 (0.59, 0.75)	< 0.001
Tech dependent	1.23 (0.98, 1.55)	0.077	0.98 (0.88, 1.09)	0.715
Transplant	0.84 (0.57, 1.23)	0.367	0.65 (0.53, 0.78)	< 0.001
ICU/intubation	2.9 (2.32, 3.64)	< 0.001	3.16 (2.84, 3.51)	< 0.001

[a] aOR = adjusted odds ratio, HHS = home health services, CVD = cardiovascular disease, GI = gastroenterology, tech = technology, ICU = intensive care unit.

disease patients received prophylactic enoxaparin. ICU or intubated patients are also recognized to be at high risk for VTE due to immobility, CVAD, and mechanical ventilation [3,28]. However, these patients also had a relatively low use given their cumulative risk factors and were only 2.6 times more likely to receive pharmacologic prophylaxis and 6 times more likely to receive mechanical compression. These findings are consistent with published studies including a survey of PICU intensivists which documented heterogeneity in thromboprophylaxis practice and underutilization of thromboprophylaxis in patients with clearly defined risk factors [29].

In addition, we found significant discrepancy in hospital use of thromboprophylaxis. Adjusted rates for mechanical compression by hospital ranged from 2% to 26.2% of patients and for pharmacologic prophylaxis from 0.3% to 3.3% of patients. This variability clearly indicates that VTE prevention with thromboprophylaxis is not standardized across individual hospitals. This is despite national SPS efforts to provide standardization. As VTE remains a significant patient safety issue, VTE risk assessment and thromboprophylaxis strategies must be systemically evaluated and implemented to reduce harm in hospitalized children. [5].

One of the largest barriers to pharmacologic prophylaxis with enoxaparin is the perceived bleeding risk [14]. Our study demonstrates that the overall bleeding risk with enoxaparin prophylaxis (5.6%) is not different from the mechanical prophylaxis group (4.7%) and consistent with prior published rates which range from 4 to 5% [15,30]. This study shows bleeding risk did not significantly increase with prophylactic enoxaparin as compared to mechanical compression.

The major limitation of this study is that it is retrospective using a database that is ICD-9 code based. The validity of our results is dependent on the accuracy of the billing data. We may not have captured all patients receiving mechanical compression or prophylactic enoxaparin due to billing practices. Chart review was not possible in all patients to verify that enoxaparin was being used prophylactically and some of the patients could have been on it for treatment of a thrombus. Medication dosages are not available in PHIS so we were unable to verify enoxaparin was being used at prophylactic dosing. This would have overestimated the rate of prophylactic enoxaparin. In addition, we could not evaluate unfractionated heparin or aspirin as pharmacologic prophylaxis due to lack of dosage information. The rate of pharmacologic prophylaxis in hospitalized pediatric patients is likely slightly higher with the addition of heparin and aspirin prophylaxis. We could not examine thromboprophylaxis efficacy since PHIS does not provide coding data sequentially or by date so we could not see which patients were on enoxaparin prior to developing a thrombus and for this reason excluded patients with a thrombus. This also impacts bleeding events as we do not have the timing of the event and bleeding could have occurred prior to anticoagulation prophylaxis. We also did not assess for complications of SCDs such as skin breakdown or ulceration which may contribute to decreased use in some populations.

5. Conclusion

Currently, older pediatric patients and those on certain medical services, such as rehabilitation and solid organ transplant, are more likely to receive thromboprophylaxis. Although we demonstrated that thromboprophylaxis has slightly increased over time, both methods remain underutilized with significant variation across hospitals and site of service. This may reflect ongoing provider concerns regarding limited efficacy data and bleeding risk with enoxaparin prophylaxis. However, bleeding from pharmacologic prophylaxis appears to be an overall rare event. This high degree of variability by hospital and service highlights the need for further evidence to standardize practice, specifically determining which patients are at highest VTE risk and the most efficacious thromboprophylaxis strategy.

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Appendix A. International classification of diseases, ninth edition codes used for thrombosis

Venous thrombosis	451.0, 451.1, 451.11, 451.19, 451.2, 451.8, 451.81, 451.82, 451.83, 451.84, 451.89, 451.9, 452, 453.0, 453.1, 453.2, 453.3, 453.40, 453.41, 453.42, 453.5, 453.51, 453.52, 453.6, 453.7, 453.71, 453.72, 453.73, 453.74, 453.75, 453.76, 453.77, 453.79, 453.8, 453.81, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9, 572.1, 325, 362.35, 415.1, 415.11, 415.12, 415.13, 415.19, 362.3, 362.30, 362.31, 362.32, 362.33
Arterial thrombosis	433.0, 433.01, 433.1, 433.10, 433.11, 433.2, 433.20, 433.21, 433.3, 433.30, 433.31, 433.8, 433.80, 433.81, 433.9, 434.00, 434.01, 434.1, 434.10, 434.11, 434.9, 434.90, 434.91, 435.9, 410.0, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.2, 410.20, 410.21, 410.22, 410.3, 410.30, 410.31, 410.32, 410.4, 410.40, 410.41, 410.42, 410.5, 410.50, 410.51, 410.52, 410.6, 410.60, 410.61, 410.62, 410.7, 410.70, 410.71, 410.72, 410.8, 410.80, 410.81, 410.82, 410.9, 410.90, 410.91, 410.92, 444.0, 444.01, 444.09, 444.1, 444.2, 444.21, 444.22, 444.8, 444.81, 444.89, 444.9, 449, 593.81

Appendix B. International classification of diseases, ninth edition codes used for bleeding and congenital bleeding disorders

Central nervous system bleeds	430, 431, 432, 432.0, 432.1, 432.9, 772.10, 772.11, 772.12, 772.13, 772.14, 772.2
Gastrointestinal bleeds	770.3, 786.3, 786.30, 786.30, 786.31
Pulmonary bleeds	770.3, 786.3, 786.30, 786.30, 786.31
Bleeds associated with a procedure	998.11
Other bleeds	432.0, 423.3, 459.0, 511.89, 530.82, 568.81, 599.71, 772.0, 772.8, 772.9, 782.7, 784.8, 786.39
Congenital bleeding disorders	286.0, 286.1, 286.2, 286.4, 287.1, 287.33, 286.3

References

[1] L. Raffini, Y.-S. Huang, C. Witmer, C. Feudtner, Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007, Pediatrics 124 (4) (2009) 1001–1008.

[2] A. Goudie, L. Dynan, P.W. Brady, E. Fieldston, R.J. Brilli, K.E. Walsh, Costs of venous thromboembolism, catheter-associated urinary tract infection, and pressure ulcer, Pediatrics 136 (3) (2015) 432–439.

[3] A. Mahajerin, B.R. Brachford, E.K. Amankwah, L. Raffini, E. Chalmers, C.H. van Ommen, N.A. Goldenberg, Hospital-associated thromboembolism in pediatrics: a systematic review and meta-analysis of risk factors and risk-assessment models, Haematologica 100 (2) (2015) 1045–1050.

[4] A.A. Sharathkumar, A. Mahajerin, L. Heidt, et al., Risk-prediction tool for identifying hospitalized children with a predisposition for development of venous thromboembolism: Peds-Clot clinical Decision Rule, J. Thromb. Haemost. 10 (2) (2012) 1326–1334.

[5] L. Raffini, T. Trimarchi, J. Beliveau, D. Davis, Thromboprophylaxis in a pediatric hospital: a patient-safety and quality improvement initiative, Pediatrics 127 (5) (2011) 1326–1332.

[6] Children's Hospitals Solutions for Patient Safety, Solutions for patient safety prevention bundles, Available at www.solutionsforpatientsafety.org/for-hospitals/hospital-resources/ (Accessed February 8, 2017).

[7] A.J. Braga, A.E.R. Young, Preventing venous thrombosis in critically ill children: what is the right approach? Paediatr. Anaesth. 21 (4) (2011) 435–440.

[8] K.A. Meier, E. Clark, C. Tarango, R.S. Chima, E. Shaughnessy, Venous thromboembolism in hospitalized adolescents: an approach to risk assessment and prophylaxis, Hosp. Pediatr. 5 (1) (2015) 44–51.

[9] P. Monagle, A. Chan, N.A. Goldenberg, R.N. Ichord, J.M. Journeycake, U. Nowak-Gottl, S.K. Vesely, Antithrombotic therapy in neonates and children. American College of Chest Physicians evidence-based clinical practice guidelines (9th edition), Chest 141 (Suppl. 2) (2012) e737S–e801S.

[10] S. Laporte, J. Liotier, L. Bertoletti, F.X. Kleber, G.F. Pineo, C. Chapelle, N. Moulin, P. Mismetti, Individual patient data meta-analysis of enoxaparin vs. unfractionated heparin for venous thromboembolism prevention in medical patients, J. Thromb. Haemost. 9 (3) (2011) 464–472.

[11] E.V. Faustino, L.J. Raffini, Prevention of hospital-acquired venous thromboembolism in children: a review of published guidelines, Front. Pediatr. 5 (2017) 9.

[12] E. Montero Ruiz, G. Baldominos Utrilla, J. López Álvarez, R. Santolaya Perrin, Effectiveness and safety of thromboprophylaxis with enoxaparin in medical inpatients, Thromb. Res. 128 (5) (2011) 440–445.

[13] L.R. Brandão, N. Shah, P.S. Shah, Low molecular weight heparin for prevention of central venous catheterization-related thrombosis in children, Cochrane Database Syst. Rev. 3 (2014) CD005982, https://doi.org/10.1002/14651858.CD005982.pub2.

[14] S.M. Badawy, K. Rychlik, A.A. Sharathkumar, Current practice of pharmacological thromboprophylaxis for prevention of venous thromboembolism in hospitalized children: a survey of pediatric hemostasis and thrombosis experts in North America, J. Pediatr. Hematol. Oncol. 38 (2016) 301–307.

[15] J. Stem, A. Christensen, D. Davis, L. Raffini, Safety of prophylactic anticoagulation at a pediatric hospital, J. Pediatr. Hematol. Oncol. 35 (7) (2013) e287–e291.

[16] E.V. Faustino, S. Hanson, P.C. Spinella, M. Tucci, S.H. O'Brien, A. Rodriguez Nunez, M. Yung, E. Truemper, L. Qin, S. Li, K. Marohn, A.G. Randolph, A multinational study of thromboprophylaxis practice in critically ill children, Crit. Care Med. 42 (5) (2014) 1232–1240.

[17] T.E. Wong, T. Nguyen, S.S. Shah, T.V. Brogan, C.M. Witmer, Antithrombin concentrate in pediatric extracorporeal membrane oxygenation: a multicenter cohort study, Pediatr. Crit. Care Med. 17 (12) (2016) 1170–1178.

[18] Feudtner Chris, J.A. Feinstein, W. Zhong, M. Hall, D. Dai, Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation, BMC Pediatr. 14 (2014) 199.

[19] M. Sharma, S.L. Carpenter, Thromboprophylaxis in a pediatric hospital, Curr. Probl. Pediatr. Adolesc. Health Care 43 (7) (2013) 178–183.

[20] A.J. Thompson, S.D. McSwain, S.A. Webb, M.A. Stroud, C.J. Streck, Venous thromboembolism prophylaxis in the pediatric trauma population, J. Pediatr. Surg. 48 (6) (2013) 1413–1421.

[21] M. Cavo, W. Wang, S.H. O'Brien, Use of low molecular weight heparin for thromboprophylaxis in a pediatric inpatient population: reasons for use and incidence of bleeding complications, Thromb. Res. 125 (4) (2010) 370–372.

[22] C.M. Takemoto, S. Sohi, K. Desai, R. Bharaj, A. Khanna, S. McFarland, S. Klaus, A. Irshad, N.A. Goldenberg, J.J. Strouse, M.B. Streiff, Hospital-associated venous thromboembolism in children: incidence and clinical characteristics, J. Pediatr. 164 (2) (2014) 332–338.

[23] C.A. Sabapathy, T.N. Djouonang, S.R. Kahn, R.W. Platt, V. Tagalakis, Incidence trends and mortality from childhood venous thromboembolism: a population-based cohort, J. Pediatr. 172 (5) (2016) 175–180.

[24] A. Mahajerin, S. Croteau, Epidemiology and risk assessment of pediatric venous thromboembolism, Front. Pediatr. 10 (5) (2017) 68.

[25] D. Chen, W.H. Geerts, M.Y. Lee, J.R. Strayer, L.C. Vogel, Prevention of venous thromboembolism in individuals with spinal cord injury. Clinical practice guideline for health care providers (3rd edition), Paralyzed Veterans Am. (2016) 1–37.

[26] S.H. O'Brien, J. Klima, B.A. Gaines, S. Betz, M.S. Zenati, Utilization of low-molecular weight heparin prophylaxis in pediatric and adolescent trauma patients, J. Trauma Nurs. 19 (2) (2012) 117–121.

[27] C.M. Nylund, A. Goudie, J.M. Garza, G. Crouch, L.A. Denson, Venous thrombotic events in hospitalized children and adolescents with inflammatory bowel disease, JPGN 56 (5) (2013) 485–491.

[28] S. Wisecup, S. Eades, Y. Turiy, Characterizing the risk factors associated with venous thromboembolism in pediatric patients after central venous line placement, J. Pediatr. Pharmacol. Ther. 20 (5) (2015) 358–366.

[29] E.V. Faustino, S. Patel, R.R. Thiagarajan, D.J. Cook, V. Northrup, A.G. Randolph, Survey of pharmacologic thromboprophylaxis in critically ill children, Crit. Care Med. 39 (7) (2011) 1773–1778.

[30] D. Dix, M. Andrew, V. Marzinotto, K. Charpentier, S. Bridge, P. Monagle, G. deVeber, M. Leaker, A.K.C. Chan, M.P. Massicotte, The use of low molecular weight heparin in pediatric patients: a prospective cohort study, J. Pediatr. 136 (4) (2000) 439–445.