REGULAR ARTICLE

blood advances

Dabigatran in the treatment and secondary prophylaxis of venous thromboembolism in children with thrombophilia

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Key Points

- The efficacy and safety of dabigatran for acute VTE demonstrated noninferiority to standard of care in children with thrombophilia.
- Dabigatran demonstrated a favorable safety profile in secondary prevention of VTE in children with thrombophilia.

In the phase 2b/3 DIVERSITY trial, 3 months treatment with dabigatran was noninferior to standard of care (SOC) for acute venous thromboembolism (VTE) in children. In a single-arm, phase 3, secondary VTE prevention study, up to 12 months dabigatran use was associated with favorable safety. Dabigatran is approved by the European Medicines Agency and US Food and Drug Administration for pediatric indications. We assessed primary composite efficacy (complete thrombus resolution and freedom from VTE recurrence/VTE-related death) in subgroups with thrombophilia vs those with negative/unknown thrombophilia status in the DIVERSITY trial and safety in both studies. Thrombophilia types were similar between the DIVERSITY trial (total population) and secondary prevention studies: factor V Leiden, 42% vs 33%; prothrombin mutation (G20210A), 19% vs 17%; antithrombin deficiency, 15% vs 20%; protein C/S deficiency, 23% vs 25%; and antiphospholipid antibodies, 18% vs 20% of patients, respectively. In DIVERSITY, 36% and 22% of thrombophilia subgroup patients treated with dabigatran and SOC, respectively, met the primary end point (Mantel-Haenszel–weighted rate difference, −0.135; 95% confidence interval, −0.36 to 0.08; noninferiority $P = .0014$); comparable to the total DIVERSITY trial population (46% vs 42%) showing dabigatran noninferiority to SOC. Within this subgroup, numerically fewer patients experienced VTE recurrence or progression of index thrombus in the dabigatran treatment group vs SOC. In the secondary prevention study, VTE recurrence at 12 months occurred in 2.8% of patients with thrombophilia vs 0% with negative/unknown thrombophilia. Safety profiles were consistent with those reported previously. Although they should be interpreted with caution, these exploratory findings

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Data are available on request from the corresponding author, Leonardo R. Brandão (leonardo.brandao@sickkids.ca).

The full-text version of this article contains a data supplement.

suggest dabigatran could be an appropriate long-term anticoagulant for children with thrombophilia. These trials were registered at www.clinicaltrials.gov as #NCT01895777 and #NCT02197416.

Introduction

In children, venous thromboembolism (VTE; including deep vein thrombosis [DVT] and pulmonary embolism [PE]) is a severe multifactorial disease. Common clinical risk factors include use of central venous catheters (CVCs), underlying disease, and thrombophilia.[1-5] For example, a significant association between inherited thrombophilic disorders and VTE onset, as well as recurrence, has been shown in a meta-analysis of observational studies in children[6]; therefore, screening for inherited thrombophilia defects, which typically include factor V Leiden (FVL), prothrombin (PT) mutations, and deficiencies of antithrombin, protein C, or protein S, could be of clinical value.[5,7]

Longer term complications of VTE include recurrence, post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension, and death.[4,8-10] The VTE recurrence rate has been reported to be ~3% in newborns and 8% in older children,[6,11] with risk increasing to as high as 29% in children with certain inherited thrombophilia traits.[12] VTE-related death in children has been reported to be 0% to 3.7% and PTS has been reported with a frequency of 9.5% to 70%.[13-15]

Anticoagulation is the standard treatment for VTE.[16] The exact duration for optimal anticoagulation therapy has yet to be established in children with acute VTE. Recent evidence-based recommendations suggest longer duration for unprovoked thromboembolic events (6-12 months), regardless of inherited thrombophilia markers, than provoked events (3 months).[16,17] Continuation of treatment is dependent on the benefits of maintaining a reduced risk of VTE recurrence vs the risk of bleeding.[18,19]

Standard of care (SOC) anticoagulation is typically low-molecular-weight heparin (LMWH) or vitamin K antagonists (VKAs) in pediatric patients with symptomatic VTE.[16] Direct oral anticoagulants (DOACs) have shown superiority or noninferiority to SOC in lowering the prospect of thromboembolic complications, with comparable or diminished bleeding risk, and, therefore, current adult-based recommendations favor their use in the treatment of patients with proximal DVT and nonmassive PE, except for patients with antiphospholipid syndrome.[20] Currently, there is no preferred anticoagulation agent recommended for long-term use, particularly in thrombophilia subgroups; however, use of DOACs might be advantageous because of the requirement for less clinical monitoring and follow-up than SOC treatments, and also, fewer food and drug interactions.[20] The potential benefits of DOAC use, including stability and lower residual thrombus burden, along with a lower bleeding risk, have yet to be fully investigated in children with unprovoked VTE.

Two large international, multicenter, pediatric phase 2b/3 studies have examined the efficacy and safety of the DOAC dabigatran etexilate in the treatment of acute VTE and in long-term secondary VTE prevention in children.[21,22] The acute VTE treatment (DIVERSITY, #NCT01895777) open-label, randomized, phase 2b/3 study demonstrated the noninferiority of dabigatran compared with SOC in children from birth to the age of <18 years.[21] The secondary VTE prevention (#NCT02197416) phase 3, single-arm, cohort study showed a favorable safety profile for dabigatran in secondary VTE prevention in children with persistent VTE risk factor(s) from birth to the age of <18 years.[22] Based on the results of these 2 pivotal, global studies, dabigatran etexilate was approved by the European Medicines Agency and US Food and Drug Administration for pediatric indications in January and June 2021, respectively.[23,24] We present herein, a subgroup analysis from these studies of the efficacy and safety of dabigatran in children with thrombophilia vs those with negative/unknown thrombophilia status.

Methods

Trial designs

The findings presented here are from subgroup analyses of children with thrombophilia vs those with negative/unknown thrombophilia status from the acute VTE treatment (DIVERSITY) and secondary VTE prevention studies. Both study designs have been described previously and key exclusion criteria were: "conditions associated with increased bleeding risk, renal dysfunction, hepatic disease, active infective endocarditis, heart valve prosthesis requiring anticoagulation, and children aged 0 to <2 years with gestational age at birth <37 weeks or with bodyweight lower than the third percentile (according to World Health Organization standards)."[21,22,25,26] The studies were conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and were approved by all investigational site ethics committees. Written informed consent was obtained before participation, according to the International Conference on Harmonisation Good Clinical Practice, and the regulatory and legal requirements of each participating country. Both studies were sponsored by Boehringer Ingelheim. As listed, both studies were registered at www.clinicaltrials.gov.

Trial populations

For the acute VTE treatment study (DIVERSITY), patients from birth to the age of <18 years with a diagnosis of VTE (ie, DVT, PE, or cerebral venous sinus thrombosis) objectively confirmed by compression ultrasound, computed tomography, or magnetic resonance imaging, and who were initially treated for 5 to 21 days with SOC (eg, unfractionated heparin or LMWH), with parenteral anticoagulation therapy expected to last for ≥3 months, were eligible for inclusion.[21,25]

For the secondary VTE prevention study, patients aged 3 months to <18 years with an objectively confirmed diagnosis of VTE, who had been treated for acute VTE with SOC for ≥3 months, or who had completed dabigatran or SOC treatment in the acute VTE treatment study and had an unresolved clinical thrombosis risk factor requiring further anticoagulation for secondary prevention of VTE, were eligible for inclusion.[22,26]

In the current analysis, patients were assessed for thrombophilia status and were classified as "thrombophilia positive" or "thrombophilia status negative/unknown."

Randomization and treatments

In the acute VTE treatment study (DIVERSITY), patients were randomized (2:1) to receive open-label dabigatran or SOC, treated for 3 months from randomization, and followed up for an additional month.[21,25] In the secondary VTE prevention study, patients were treated with dabigatran for up to 12 months.[22,26] Dabigatran was dosed according to an age- and weight-adjusted nomogram derived from estimated renal function to achieve exposure comparable to that of adult populations treated with dabigatran.[25-27]

Outcomes

Primary and secondary end points differed according to the individual study. In the acute VTE treatment study, the primary efficacy end point was a composite (centrally adjudicated by an independent, blinded committee) of the proportion of children with complete thrombus resolution, freedom from recurrent VTE (including symptomatic and asymptomatic, contiguous progression or noncontiguous new thrombus, DVT, PE, paradoxical embolism, and thrombus progression), and freedom from VTE-related death.[21,25] Secondary/other end points included residual thrombotic burden by the end of study treatment (defined as complete or partial thrombus resolution, stabilization of thrombus, or thrombus progression); incidence of bleeding events; major bleeding events (MBEs; defined as fatal bleeding, clinically overt bleeding [≥20 g/L decrease in hemoglobin over 24 hours], retroperitoneal, pulmonary, intracranial, central nervous system bleeding; bleeding requiring surgical intervention) clinically relevant nonmajor (CRNM) bleeding events (defined as overt bleeding for which a blood product was administered and that was not directly attributable to the patient's underlying medical condition, or bleeding that required medical or surgical intervention to restore hemostasis, other than in an operating suite);[28] and other safety/tolerability/adherence outcomes.[21,25]

In the secondary VTE prevention study, all outcomes were considered safety related.[22] Primary end points included recurrence of VTE, mortality, MBEs, CRNM bleeding events, and minor bleeding events; assessed at 3, 6, and 12 months after enrollment.[22] Secondary end points included the occurrence of newly diagnosed or worsening of baseline PTS (per the modified Villalta scale)[29,30] at 3, 6, and 12 months after enrollment. PTS was assessed at 3 months to capture any patients enrolled with a history of VTE who might subsequently present with PTS.

At each on-treatment study visit in both studies, adherence was calculated as adherence (%) = (actual number of dabigatran doses taken since last count ÷ planned number of dabigatran doses that should have been taken in the same period) × 100. The overall average adherence was calculated as the average of adherence at each visit.

Patients with thrombophilia subgroup

Thrombophilia screening was not a requirement of the clinical trials, therefore, patients' requirement for thrombophilia screening was determined by the attending physician at each site. The study databases were reviewed, and patient thrombophilia status was determined and classified as "thrombophilia positive" or "thrombophilia status negative/unknown"; a further subset of patients with confirmed inherited thrombophilia[32] (those with only FVL and/or PT [G20210A] mutation) was also established. For the thrombophilia-positive subgroup, thrombophilia was additionally categorized as "major" or "minor" based on predefined criteria. Major thrombophilia included patients with homozygous FVL, homozygous PT mutation, compound heterozygous FVL and PT mutations, antithrombin deficiency, protein C deficiency, protein S deficiency, or those who were antiphospholipid antibody (APLA)– and/or lupus anticoagulant (LA)–positive, as well as specified combinations of these or other thrombophilic conditions or mutations (listed in Table 3 footnotes).[31] Minor thrombophilia included coagulation disorders not defined as major thrombophilia: heterozygous FVL, heterozygous PT gene mutation (including those whose zygosity was recorded as unknown), specified combinations of thrombophilic conditions, and specified other mutations and conditions with uncertain thrombophilic significance (Table 3 footnotes).[31]

Statistical analysis

For both studies, patient demographics, medical history, and baseline clinical characteristics were analyzed descriptively. Time-to-event analyses were summarized as Kaplan-Meier estimates; other end points, including safety and adverse events (AEs) were analyzed descriptively. In the acute VTE treatment study, noninferiority testing for the composite primary end point was performed on Mantel-Haenszel–weighted rate difference with a margin of 20% used for a 2-sided test at significance level of .05.[33]

Results

Study populations

The acute VTE treatment study (DIVERSITY) took place across 65 centers in 26 countries. The analysis population comprised 267 patients; 62 patients with documented thrombophilia (32 with confirmed inherited thrombophilia [FVL and/or PT mutations]) and 205 patients with thrombophilia-negative/unknown status (Figure 1). Within the thrombophilia subgroup, 37 patients were categorized as having major thrombophilia and 25 with minor thrombophilia. A sensitivity analysis of the thrombophilia-negative (n = 145) and thrombophilia-unknown (ie, not tested; n = 60) subgroups found both groups to be largely similar in terms of safety and efficacy outcomes (supplemental Table 1). Therefore, these subgroups were merged into 1 "thrombophilia-negative/unknown" group.

The secondary VTE prevention study took place across 60 sites in 22 countries. The analysis population included 213 patients; 106 with documented thrombophilia (44 with confirmed inherited thrombophilia [FVL and/or PT mutations]) and 107 with thrombophilia-negative/unknown status (Figure 1). Within the thrombophilia subgroup, 73 patients were categorized as having major thrombophilia and 33 with minor thrombophilia. The electronic case report form captured data on thrombophilia and thrombophilia types, therefore, all patients for whom thrombophilia status was not captured were automatically considered "thrombophilia negative/unknown." Of the patients included in the analyses, 91 were previously enrolled in the acute VTE treatment study (47 with thrombophilia and 44 as thrombophilia negative/unknown); supplemental Tables 2 and 3 detail the 35 patients with thrombophilia who rolled over from the DIVERSITY study to the secondary VTE prevention study.

Table 1. Baseline patient demographics and clinical characteristics by study, treatment, and thrombophilia status

	Acute VTE treatment study (DIVERSITY)						Secondary VTE prevention study	
	Thrombophilia negative/unknown			Thrombophilia documented			Thrombophilia negative/ unknown	Thrombophilia documented
	Dabigatran (N = 138)	SOC (N = 67)	Total (N = 205)	Dabigatran (N = 39)	SOC (N = 23)	Total (N = 62)	Total (N = 107)	Total (N = 106)
Age, mean (SD), y	10.5 (6.1)	10.4 (6.6)	10.5 (6.3)	13.4 (5.3)	12.9 (4.3)	13.2 (4.9)	11.5 (5.2)	14.1 (3.6)
Male, n (%)	62 (44.9)	39 (58.2)	101 (49.3)	19 (48.7)	13 (56.5)	32 (51.6)	59 (55.1)	58 (54.7)
Race, n (%)								
White	124 (89.9)	62 (92.5)	186 (90.7)	39 (100.0)	20 (87.0)	59 (95.2)	93 (86.9)	101 (95.3)
Black or African American	1 (0.7)	1 (1.5)	2 (1.0)	0	2 (8.7)	2 (3.2)	5 (4.7)	3 (2.8)
Asian	10 (7.2)	2 (3.0)	12 (5.9)	0	1 (4.3)	1 (1.6)	5 (4.7)	2 (1.9)
Multiple	2 (1.4)	0	2 (1.0)	0	0	0	3 (2.8)	0
Missing	1 (0.7)	2 (3.0)	3 (1.5)	0	0	0	1 (0.9)	0
Body mass index, mean (SD), kg/m^2	20.3 (5.6) [n = 137]	19.0 (4.6)	19.9 (5.3) [n = 204]	21.4 (5.8)	23.5 (5.8)	22.2 (5.8)	21.8 (5.8)	24.0 (5.4)
Estimated glomerular filtration rate, mean (SD),* mL/min per 1.73 m^2	118.1 (34.8) [n = 137]	121.5 (35.2)	119.2 (34.8) [n = 204]	107.4 (18.8)	105.6 (28.6)	106.7 (22.7)	113.8 (32.2)	101.4 (22.1)
SOC treatment, n (%)								
VKA	NA	37 (55.2)	37 (18.0)	NA	12 (52.2)	12 (19.4)	NA	NA
LMWH	NA	30 (44.8)	30 (14.6)	NA	10 (43.5)	10 (16.1)	NA	NA
Fondaparinux	NA	0	0	NA	1 (4.3)	1 (1.6)	NA	NA
Index/most recent VTE event, n (%)†								
DVT	79 (57.2)	38 (56.7)	117 (57.1)	31 (79.5)	22 (95.7)	53 (85.5)	82 (76.6)	82 (77.4)
PE	16 (11.6)	3 (4.5)	19 (9.3)	4 (10.3)	1 (4.3)	5 (8.1)	6 (5.6)	14 (13.2)
Central line thrombosis	26 (18.8)	20 (29.9)	46 (22.4)	1 (2.6)	0	1 (1.6)	5 (4.7)	2 (1.9)
CVT and/or sinus thrombosis	17 (12.3)	6 (9.0)	23 (11.2)	3 (7.7)	0	3 (4.8)	15 (14.0)	9 (8.5)
Days since index VTE until randomization, mean (SD), d	16.4 (6.9)	17.4 (5.6)	16.7 (6.5)	14.8 (4.9)	13.5 (5.4)	14.4 (5.1)	199.6 (413.3)	313.3 (444.2)
Interventions for index/most recent VTE, n (%)								
Unfractionated heparin	20 (14.5)	11 (16.4)	31 (15.1)	12 (30.8)	5 (21.7)	17 (27.4)	25 (23.4)	34 (32.1)
LMWH	130 (94.2)	63 (94.0)	193 (94.1)	35 (89.7)	20 (87.0)	55 (88.7)	81 (75.7)	82 (77.4)
Fondaparinux	0	0	0	0	1 (4.3)	1 (1.6)	0	1 (0.9)
VKA	0	0	0	0	0	0	38 (35.5)	42 (39.6)
Non-VKA oral anticoagulant	0	0	0	0	0	0	32 (29.9)	33 (31.1)
Other parenteral anticoagulation	3 (2.2)	1 (1.5)	4 (2.0)	4 (10.3)	1 (4.3)	5 (8.1)	2 (1.9)	12 (11.3)
Nonanticoagulation therapy	0	1 (1.5)	1 (0.5)	0	0	0	6 (5.6)	3 (2.8)

NA, not applicable; SD, standard deviation.
*Estimated glomerular filtration rate for children using Schwartz formula.
†Index event for the acute VTE treatment study and most recent event for the secondary VTE prevention study. Patients could be assessed with more than 1 type of most recent VTE.

Table 2. Medical history by study, treatment, and thrombophilia status

	Acute VTE treatment study (DIVERSITY)						Secondary VTE prevention study	
	Thrombophilia negative/unknown			Thrombophilia documented			Thrombophilia negative/unknown	Thrombophilia documented
	Dabigatran (N = 138)	SOC (N = 67)	Total (N = 205)	Dabigatran (N = 39)	SOC (N = 23)	Total (N = 62)	Total (N = 107)	Total (N = 106)
Patients with medical history collected, n (%)	137 (100)	67 (100)	204 (100)	39 (100)	23 (100)	62 (100)	106 (100)	104 (100)
History of previous VTE other than index VTE, n (%)	9 (6.6)	7 (10.4)	16 (7.8)	5 (12.8)	7 (30.4)	12 (19.4)	21 (19.8)	18 (17.3)
1 confirmed previous VTE	8 (5.8)	6 (9.0)	14 (6.9)	5 (12.8)	6 (26.1)	11 (17.7)	6 (5.7)	5 (4.8)
2 confirmed previous VTEs	1 (0.7)	1 (1.5)	2 (1.0)	0	1 (4.3)	1 (1.6)	10 (9.4)	10 (9.6)
≥3 confirmed previous VTEs	0	0	0	0	0	0	5 (4.7)	3 (2.9)
Previous VTE unprovoked*	7 (5.1)	2 (3.0)	9 (4.4)	3 (7.7)	3 (13.0)	6 (9.7)	14 (13.2)	13 (12.5)
Previous VTE provoked*	2 (1.5)	5 (7.5)	7 (3.4)	2 (5.1)	4 (17.4)	6 (9.7)	9 (8.5)	5 (4.8)
PTS, n (%)	NA	NA	NA	NA	NA	NA	12 (11.3)†	24 (23.1)
Other medical history, n (%)								
Solid organ cancer	8 (5.8)	0	8 (3.9)	0	0	0	4 (3.8)	0
Hematologic cancer	10 (7.3)	2 (3.0)	12 (5.9)	0	0	0	11 (10.4)	1 (1.0)
Congenital heart disease	20 (14.6)	26 (38.8)	46 (22.5)	1 (2.6)	1 (4.3)	2 (3.2)	14 (13.2)	3 (2.9)
Hypertension	1 (0.7)	1 (1.5)	2 (1.0)	0	0	0	2 (1.9)	1 (1.0)
Diabetes mellitus	3 (2.2)	1 (1.5)	4 (2.0)	1 (2.6)	0	1 (1.6)	0	0
Heart failure	6 (4.4)	16 (23.9)	22 (10.8)	0	0	0	5 (4.7)	0
Stroke or transient ischemic attack	0	0	0	0	0	0	0	1 (1.0)
Liver disease (currently not active)	0	0	0	0	0	0	1 (0.9)	0
Major or clinically relevant bleeding event	1 (0.7)	0	1 (0.5)	0	0	0	0	1 (1.0)
Medical circumstances that increase risk of thrombosis, n (%)								
Recent immobilization‡	16 (11.7)	6 (9.0)	22 (10.8)	6 (15.4)	3 (13.0)	9 (14.5)	7 (6.6)	1 (1.0)
Presence of central venous line/catheter	37 (27.0)	23 (34.3)	60 (29.4)	3 (7.7)	1 (4.3)	4 (6.5)	11 (10.4)	0
Presence of other venous/arterial catheter	9 (6.6)	2 (3.0)	11 (5.4)	1 (2.6)	0	1 (1.6)	3 (2.8)	1 (1.0)
Total parenteral nutrition dependency	1 (0.7)	0	1 (0.5)	0	0	0	1 (0.9)	0
Other medical circumstances that increase risk of thrombosis§	25 (18.2)	22 (32.8)	47 (23.0)	14 (35.9)	2 (8.7)	16 (25.8)	NA	NA
Other conditions requiring secondary VTE prophylaxis								
Recurrent unprovoked VTE	NA	NA	NA	NA	NA	NA	24 (22.4)	6 (5.7)
Structural venous abnormality‖	12 (8.8)	7 (10.4)	19 (9.3)	2 (5.1)	2 (8.7)	4 (6.5)	19 (17.8)	10 (9.4)
Other¶	NA	NA	NA	NA	NA	NA	71 (66.4)	32 (30.2)

*Patients may be counted in >1 category.

†One missing value.

‡Illness requiring bed rest, or paralysis.

§Other medical circumstances that increase risk of thrombosis include congenital heart disease (both operated and not operated), cancer, and systemic inflammatory conditions (eg, systemic lupus erythematosus, inflammatory bowel disease).

‖Structural venous abnormalities may have been thoracic outlet syndrome, inferior vena cava atresia, May-Thurner syndrome; Klippel-Trenaunay syndrome; or CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevis, spinal/skeletal anomalies/scoliosis) syndrome or arteriovenous/venous malformation.

¶"Other conditions requiring secondary VTE prophylaxis" includes a variety of medical conditions with unclear thrombophilic significance considered to be conditions requiring secondary VTE prophylaxis in accordance with local VTE treatment/prophylactic protocols and comprise residual/unresolved DVT or sinus vein thrombosis, recurrent provoked VTE, strong family history of PE, and implantable medical devices other than central venous or arterial catheters (eg, ports, esndocardial electrodes). Most of these are conditions requiring secondary VTE prophylaxis only in combination with categories or VTE risk factors listed in other rubrics of the table, that is, medical circumstances that increase risk of thrombosis or thrombophilic conditions.

Table 3. Details of thrombophilia conditions by study, treatment, and thrombophilia status

	Acute VTE treatment study (DIVERSITY)						Secondary VTE prevention study	
	Thrombophilia negative/unknown			Thrombophilia documented			Thrombophilia negative/unknown	Thrombophilia documented
	Dabigatran (N = 138)	SOC (N = 67)	Total (N = 205)	Dabigatran (N = 39)	SOC (N = 23)	Total (N = 62)	Total (N = 107)	Total (N = 106)
Thrombophilia conditions, n (%)*								
FVL	0	0	0	18 (46.2)	8 (34.8)	26 (41.9)	0	35 (33.0)
PT mutation	0	0	0	9 (23.1)	3 (13.0)	12 (19.4)	0	18 (17.0)
Antithrombin deficiency	0	0	0	6 (15.4)	3 (13.0)	9 (14.5)	0	21 (19.8)
Protein C/S deficiency	0	0	0	7 (17.9)	7 (30.4)	14 (22.6)	0	26 (24.5)
APLA/LA	0	0	0	4 (10.3)	7 (30.4)	11 (17.7)	0	21 (19.8)
Thrombophilia conditions in detail, n (%)								
Major thrombophilia*	0	0	0	20 (51.3)	17 (73.9)	37 (59.7)	0	73 (68.9)
FVL (homozygous)	0	0	0	1 (5.0)	0	1 (2.7)	0	5 (6.8)
PT mutation (homozygous)	0	0	0	1 (5.0)	0	1 (2.7)	0	4 (5.5)
FVL (heterozygous) + PT mutations (heterozygous)	0	0	0	3 (15.0)	2 (11.8)	5 (13.5)	0	6 (8.2)
Protein C/S deficiency	0	0	0	7 (35.0)	7 (41.2)	14 (37.8)	0	26 (35.6)
Antithrombin deficiency	0	0	0	6 (30.0)	3 (17.6)	99 (24.3)	0	21 (28.8)
APLA and/or LA	0	0	0	4 (20.0)	7 (41.2)	11 (29.7)	0	21 (28.8)
Combined† (including other mutations and conditions‡)	0	0	0	4 (20.0)	2 (11.8)	6 (16.2)	0	11 (15.1)
Minor thrombophilia*	0	0	0	19 (48.7)	6 (4.3)	25 (40.3)	0	33 (31.1)
FVL (heterozygous)	0	0	0	11 (57.9)	5 (83.3)	16 (64.0)	0	15 (45.5)
PT mutation (heterozygous or unknown)	0	0	0	3 (15.8)	1 (16.7)	4 (16.0)	0	5 (15.2)
Other mutations and conditions‡ with unclear thrombophilic significance	0	0	0	5 (26.3)	1 (16.7)	6 (24.0)	0	13 (39.4)
MTHFR mutation	0	0	0	4 (21.1)	1 (16.7)	5 (20.0)	0	11 (33.3)
PAI-1 mutation	0	0	0	2 (10.5)	0	2 (8.0)	0	3 (9.1)
FGB mutation	0	0	0	3 (15.8)	0	3 (12.0)	0	2 (6.1)
ACE mutation	0	0	0	1 (5.3)	0	1 (4.0)	0	0
MTR mutation	0	0	0	1 (5.3)	0	1 (4.0)	0	0
GPIA/GPIIIA	0	0	0	1 (5.3)	0	1 (4.0)	0	1 (3.0)
Dyslipidemia	0	0	0	1 (5.3)	0	1 (4.0)	0	0
Thrombocytopathy	0	0	0	0	0	0	0	1 (3.0)
Fibrinolysis enzyme activity abnormality	0	0	0	0	0	0	0	1 (3.0)
Combined‡	0	0	0	5 (26.3)	1 (16.7)	6 (24.0)	0	13 (39.4)

ACE, angiotensin I-converting enzyme; FGB, fibrinogen β chain; GPIA, glycoprotein Ia; GPIIIA, glycoprotein IIIa; MTHFR, methylenetetrahydrofolate reductase; MTR, methionine synthase reductase; PAI-1, plasminogen activator inhibitor 1.

*Patients may be counted in >1 category.

†For acute VTE treatment study, combined for "major thrombophilia": APLA/LA + other mutations and conditions, MTHFR (n = 1); APLA/LA + other mutations and conditions, PAI-1, MTHFR, MTR (n = 1); antithrombin deficiency + other mutations and conditions, MTHFR (n = 1); antithrombin deficiency + PT mutation (heterozygous) + other mutations and conditions, PAI-1, thrombospondins, ACE (n = 1); protein C/S deficiency + other mutations and condition, PAI-1 (n = 1); protein C/S deficiency + PT mutation (heterozygous) + other mutations and conditions, MTHFR, FGB, PAI-1 (n = 1). Combined "minor thrombophilia": FVL (heterozygous) + other mutations and conditions, MTHFR (n = 1); other mutations and conditions, dyslipidemia (n = 1); other mutations and conditions, FGB, MTHFR, PAI-1, GPIA, GPIIIA, ACE (n = 1); other mutations and conditions, FGB, PAI-1, MTHFR (n = 1); other mutations and conditions, FGB, MTHFR, MTR (n = 1); other mutations and conditions, MTHFR (n = 1). For secondary VTE prevention study, combined for "major thrombophilia": APLA/LA + other mutations and conditions, MTHFR (n = 1); APLA//LA + other mutations and conditions, MTHFR, integrin A2 pathology (n = 1); APLA/LA + other mutations and conditions, PAI-1, GPIA, GPIIIA (n = 1); antithrombin deficiency + other mutations and conditions, factor XII deficiency (n = 1); antithrombin deficiency + other mutations and conditions, MTHFR (n = 2); FVL (heterozygous) + PT mutation (heterozygous) + other mutations and conditions, MTHFR (n = 1); FVL (homozygous) + other mutations and conditions, MTHFR (n = 1); protein C/S deficiency + other mutations and conditions, MTHFR (n = 2); protein C/S deficiency + other mutations and conditions, sustained elevated factor VIII level (n = 1). Combined for "minor thrombophilia": FVL (heterozygous) + other mutations and conditions, MTHFR (n = 1); FVL (heterozygous) + other mutations and conditions, thrombocytopathy (n = 1); other mutations and conditions, FGB + GPIA (n = 1); other mutations and conditions, MTHFR (n = 7); other mutations and conditions, MTHFR + PAI 4G polymorphism + FGB (n = 1); other mutations and conditions, MTHFR + PAI 4G/5G polymorphism (n = 1); other mutations and conditions, MTHFR + PAI-1 + fibrinolysis enzyme activity abnormality (n = 1).

‡Other mutations and conditions with indefinite thrombophilic significance: MTHFR, PAI-1, sustained elevated factor VIII level, factor XII deficiency, ACE mutation,[53] thrombospondin mutations, MTR mutation,[54] GPIA, GPIIIA, integrin A2 pathology, thrombocytopathy, FGB mutation, and fibrinolysis enzyme activity abnormality.

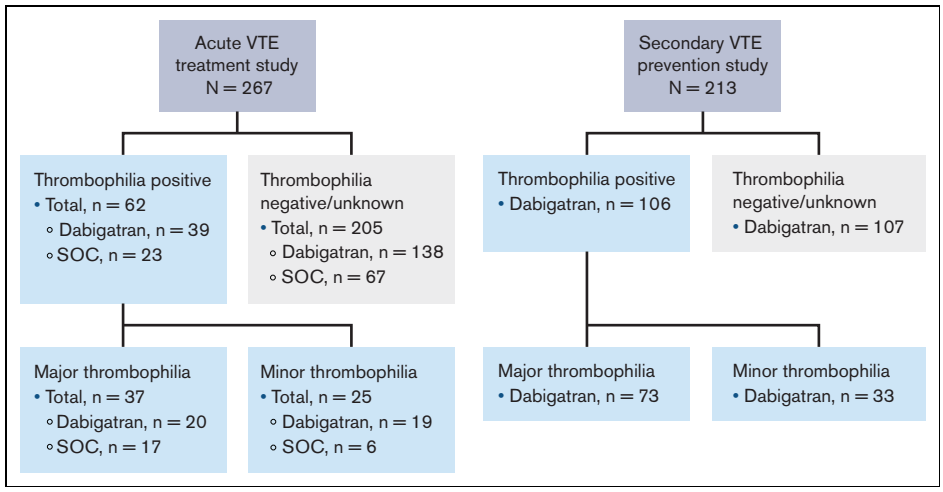

Figure 1. Disposition of patients in the acute VTE treatment study and secondary VTE prevention study by thrombophilia status. In the acute VTE treatment study, 267 patients were randomized and all but 1 patient randomized to dabigatran were treated; 176 patients received dabigatran and 90 received SOC. In the secondary VTE prevention study, 213 of 221 enrolled patients received dabigatran.

Baseline demographics, clinical characteristics, and medical history

Patient demographics and clinical characteristics at baseline in each study are described in Table 1 (by thrombophilia status) and supplemental Table 4 (by major or minor thrombophilia classification). In the acute VTE treatment and secondary VTE prevention studies, ~23% and ~50% of patients had thrombophilia diagnosed, respectively. In both studies, patients with documented thrombophilia were ~2.5 years older, on an average, than patients with negative/unknown thrombophilia status.

Patients with thrombophilia, and in particular, major thrombophilia, were predominantly male. In the secondary VTE prevention trial, patients with thrombophilia were more likely to have PE as their index VTE event than those with negative/unknown thrombophilia status. In the acute VTE treatment study, a higher proportion of patients had previous VTE in the thrombophilia group than in the thrombophilia-negative/unknown group but rates were similar between groups in the secondary prevention study (Table 2).

Medical history and details of thrombophilia conditions are shown in Tables 2 and 3, respectively (by thrombophilia status), and supplemental Table 5 (by major or minor thrombophilia classification). Presence of a CVC was recorded for a greater proportion of the thrombophilia-negative/unknown groups. In the secondary VTE prevention study, a greater proportion of patients with thrombophilia than those negative/unknown had other conditions requiring secondary VTE prophylaxis (including recurrent unprovoked VTE or structural venous abnormality).

In the secondary VTE prevention study, 24 patients (23.1%) with thrombophilia had a history of PTS compared with 12 (11.3%) in the thrombophilia-negative/unknown group. Of the 73 patients with major thrombophilia and 33 patients with minor thrombophilia, 12 (16.9%) and 12 (36.4%) patients, respectively, had a history of PTS.

Efficacy and safety

Acute VTE treatment study (DIVERSITY)

VTE OUTCOMES. By day 84 (or end of therapy [EOT]), few patients experienced progression of index thrombus. Thrombus progression was experienced by 8.1% of patients with documented thrombophilia (Table 4), mostly those with major thrombophilia (6.3% of patients with confirmed inherited thrombophilia [FVL and PT mutations]; Table 5; supplemental Table 6) and by 2.0% of patients with negative/unknown thrombophilia status (Table 4). The VTE recurrence rate was 12.9% among patients with thrombophilia (mostly those with major thrombophilia; supplemental Table 6) and 2.9% for those with negative/unknown thrombophilia status (Table 4; Figure 2A). For the thrombophilia group, 5.1% of patients treated with dabigatran and 13.0% treated with SOC experienced thrombus progression, and 7.7% and 21.7%, respectively, experienced VTE recurrence (Table 4). For these patients, partial thrombus resolution was achieved in 43.6% and 34.8% of patients treated with dabigatran and SOC, respectively, and complete thrombus resolution in 35.9% and 21.7% of patients, respectively. For the high-risk group of patients with major thrombophilia, the frequency of thrombus progression was 10.0% for those treated with dabigatran and 11.8% for those with SOC, and the VTE recurrence rate was 15.0% and 23.5%, respectively (supplemental Table 6). The proportion of patients with VTE outcomes was similar between treatment groups within the negative/unknown thrombophilia group.

Complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related death (composite primary end point) was achieved in 19 out of 62 patients (30.6%) in the thrombophilia group (9/32 patients [28.1%] with confirmed inherited thrombophilia) compared with 100 out of 205 (48.8%) in the thrombophilia-negative/unknown group (Tables 4 and 5). There was no notable difference between major (10/37, 27.0%) and minor (9/25, 36.0%) thrombophilia groups (supplemental Table 6). In the thrombophilia subgroup, the treatment comparison showed noninferiority of dabigatran to SOC for this end point, and it was achieved by numerically more patients treated with dabigatran than those

treated with SOC: 35.9% vs 21.7% (Mantel-Haenszel–weighted difference in rates for SOC minus dabigatran, −0.135; 95% confidence interval (CI), −0.36 to 0.08; *P* for noninferiority = .0014; Table 4; Figure 3). For patients with confirmed inherited thrombophilia (n = 32), 34.8% and 11.1% treated with dabigatran and SOC, respectively, met this end point (*P* for noninferiority = .0009; Table 5). For the subgroup of patients with major thrombophilia (n = 37), 25.0% treated with dabigatran and 29.4% treated with SOC met the primary end point (*P* for noninferiority = .1806; supplemental Table 6). In patients with minor thrombophilia (n = 25), 47.4% treated with dabigatran achieved the composite primary end point vs 0% treated with SOC (noninferiority $P < .0001$). Dabigatran was also noninferior to SOC in patients with thrombophilia-negative/unknown status: 48.6% vs 49.3% (Mantel-Haenszel–weighted difference, 0.002; 95% CI, −0.14 to 0.15; noninferiority *P* = .0033; Table 4; Figure 4).

PTS. In the acute VTE treatment study, within the treated set, PTS (newly identified or worsening from baseline) was reported as an AE in 2 out of 62 patients (3.2%) in the thrombophilia group (1 each with minor and major thrombophilia) and 5 out of 204 (2.4%) in the thrombophilia-negative/unknown group (Table 4).

BLEEDING. Bleeding events were observed in 23.0% of patients with documented thrombophilia (31.3% with confirmed inherited thrombophilia) and in 21.0% of patients with negative/unknown thrombophilia status (Tables 4 and 5), and in 18.9% and 24.0% with major and minor thrombophilia, respectively. Within the thrombophilia subgroup, 17.9% of patients treated with dabigatran compared with 26.1% treated with SOC had bleeding events (Table 4; Figure 4A; by thrombophilia status), although the difference was not statistically significant (*P* = .66). For patients with confirmed inherited thrombophilia, 26.1% treated with dabigatran and 44.4% treated with SOC experienced bleeding events (Table 5). No patients with thrombophilia had an MBE over the course of the study. Among patients with negative/unknown thrombophilia status, bleeding events were similar between the SOC and dabigatran treatment groups (Table 4; Figure 4A).

Secondary VTE prevention study

RECURRENCE. VTE recurrence at 12 months was reported for 3 out of 106 patients (2.8%) with thrombophilia (2.3%, 1/44 patients with confirmed inherited thrombophilia) compared with 0 out of 107 (0%) with negative/unknown thrombophilia status, with no discernible difference between major and minor thrombophilia subgroups (Tables 6 and 7; Figure 2B). VTE recurrence at 12 months was reported for 2 out of 73 patients (2.7%) with major thrombophilia (Table 6).

PTS. In the secondary VTE prevention study, newly identified or worsening of baseline PTS was reported as a study outcome at 12 months by 3 out of 106 patients (2.8%) with thrombophilia and 0 out of 107 patients without thrombophilia (Table 5).

Table 4. Acute VTE treatment study: composite primary end point, thrombus assessment at EOT, and on-treatment bleeding events by treatment and thrombophilia status

	Acute VTE treatment study (DIVERSITY)					
	Thrombophilia documented			Thrombophilia negative/unknown		
	Dabigatran	SOC	Total	Dabigatran	SOC	Total
Efficacy end points (randomized set, intention-to-treat period), N	39	23	62	138	67	205
Composite primary end point,* n (%)	14 (35.9)	5 (21.7)	19 (30.6)	67 (48.6)	33 (49.3)	100 (48.8)
Mantel-Haenszel–weighted difference in rates for SOC − dabigatran (95% CI)	−0.135 (−0.36 to 0.08)			0.002 (−0.14 to 0.15)		
Noninferiority *P*	.0014			.0033		
VTE recurrence rate at d 84 or EOT, n (%)	3 (7.7)	5 (21.7)	8 (12.9)	4 (2.9)	2 (3.0)	6 (2.9)
Residual thrombotic burden at d 84 or EOT, n (%)						
Thrombus progression†	2 (5.1)	3 (13.0)	5 (8.1)	3 (2.2)	1 (1.5)	4 (2.0)
Stabilization	4 (10.3)	5 (21.7)	9 (14.5)	7 (5.1)	5 (7.5)	12 (5.9)
Partial resolution	17 (43.6)	8 (34.8)	25 (40.3)	40 (29.0)	17 (25.4)	57 (27.8)
Complete resolution	14 (35.9)	5 (21.7)	19 (30.6)	67 (48.6)	33 (49.3)	100 (48.8)
Missing	2 (5.1)	2 (88.7)	4 (6.5)	21 (15.2)	11 (16.4)	32 (15.6)
VTE-related death	0	0	0	0	1 (1.5)	1 (0.5)
Partial or complete resolution and freedom from recurrent VTE or VTE-related death, n (%)	30 (76.9)	12 (52.2)	42 (67.8)	107 (77.5)	50 (74.6)	157 (76.6)
On-treatment bleeding and PTS (treated set, on-treatment period), N	39	23	62	137	67	204
Any bleeding event, n (%)	7 (17.9)	6 (26.1)	13 (21.0)	31 (22.6)	16 (23.9)	47 (23.0)
MBE, n (%)	0	0	0	4 (2.9)	2 (3.0)	6 (2.9)
PTS,‡ n (%)	1 (2.6)	1 (4.3)	2 (3.2)	5 (3.6)	0	5 (2.4)

*Complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related death.
†Defined as any symptomatic or asymptomatic contiguous progression of the index thrombus.
‡PTS (newly identified or worsening from baseline) was not specified as an outcome in the acute treatment study but was reported as an AE within the treated set.

Table 5. Acute VTE treatment study: composite primary end point, thrombus assessment at EOT, and on-treatment bleeding events by treatment for patients with confirmed inherited thrombophilia

	Confirmed inherited thrombophilia (only FVL and/or PT gene)		
	Dabigatran	SOC	Total
Efficacy end points (randomized set, intention-to-treat period), N	23	9	32
Composite primary end point,* n (%)	8 (34.8)	1 (11.1)	9 (28.1)
Mantel-Haenszel–weighted difference in rates for SOC − dabigatran (95% CI)	−0.246 (−0.482 to −0.010)		
Noninferiority *P*	0.0009		
VTE recurrence rate at d 84 or EOT, n (%)	1 (4.3)	1 (11.1)	2 (6.3)
Residual thrombotic burden at d 84 or EOT, n (%)			
Thrombus progression†	1 (4.3)	1 (11.1)	2 (6.3)
Stabilization	3 (13.0)	1 (11.1)	4 (12.5)
Partial resolution	9 (39.1)	4 (44.4)	13 (40.6)
Complete resolution	8 (34.8)	1 (11.1)	9 (28.1)
Missing	2 (8.7)	2 (22.2)	4 (12.5)
VTE-related death	0	0	0
On-treatment bleeding and PTS (treated set, on-treatment period), N	23	9	32
Any bleeding event, n (%)	6 (26.1)	4 (44.4)	10 (31.3)
MBE, n (%)	0	0	0
PTS,‡ n (%)	0	1 (11.1)	1 (3.0)

*Complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related death.
†Defined as any symptomatic or asymptomatic contiguous progression of the index thrombus.
‡PTS (newly identified or worsening from baseline) was not specified as an outcome in the acute treatment study but was reported as an AE within the treated set.

BLEEDING. The proportion of patients with any bleeding while on treatment was numerically higher for patients with thrombophilia (29/106, 27.4%; and 16/44, 36.4% with confirmed inherited thrombophilia) compared with those with negative/unknown thrombophilia status (19/107, 17.8%; Figure 4B; Tables 6 and 7). In the thrombophilia group, this included 2 patients (1.9%) with CRNM bleeding and 1 (0.9%) with major bleeding. In the thrombophilia-negative/unknown group, 1 patient (0.9%) had CRNM bleeding, and 2 (1.9%) had major bleeding. No patients died from bleeding during the study (supplemental Table 8). Bleeding incidence was similar between major and minor thrombophilia subgroups (19/73, 26.0%; and 10/33, 30.0% at 12 months, respectively; Table 6).

None of the patients with thrombophilia who rolled over from the acute VTE treatment study (22 treated with dabigatran and 13 with SOC) and continued anticoagulation by dabigatran in the long-term secondary VTE prevention study experienced MBEs (supplemental Table 3).

AEs

In the acute VTE treatment study, rates of AEs, serious AEs, and AEs leading to treatment discontinuation were similar across subgroups (supplemental Table 7). The most common AEs included headache, nasopharyngitis, alopecia, and epistaxis.

In the secondary VTE prevention study, rates of AEs, serious AEs, and AEs leading to treatment discontinuation were higher among patients with thrombophilia (supplemental Table 8). The most common AEs included headache, nasopharyngitis, dyspepsia, and upper respiratory tract infection.

Adherence

Adherence with study medication was routinely high in both studies. In the acute VTE treatment study, adherence exceeded 98% in all subgroups of thrombophilia status, and in the secondary VTE prevention study, adherence exceeded 96% in all subgroups.

Discussion

Two large studies, 1 phase 2b/3 and 1 phase 3, have demonstrated the effectiveness and safety of dabigatran for the treatment of acute VTE and for secondary prevention of VTE in children.[21,22] This analysis from the same studies examined patient characteristics and outcomes in the subgroup of children with thrombophilia. It should be noted that testing for thrombophilia was not a protocol-specified requirement for either study. However, for those children with known thrombophilia, and also for those newly tested for thrombophilia markers, the assignment for thrombophilia tests and the interpretation of results was the responsibility of the treating pediatrician, who, in most cases, specialized in pediatric hematology and, therefore, was privy to international definitions on inherited and acquired thrombophilia in children.[34-36] Furthermore, collected and interpreted thrombophilia test results were verified with patients' source data during regular monitoring procedures; 100% source data verification should be conducted according to the monitoring plan of both trials. Therefore, we have a reasonable degree of certainty that the subgroup classified as thrombophilia positive has been correctly identified.

Although the frequency of unfavorable VTE outcomes such as recurrence and progression of index thrombus were low in the acute VTE treatment study, the current analysis of data showed a

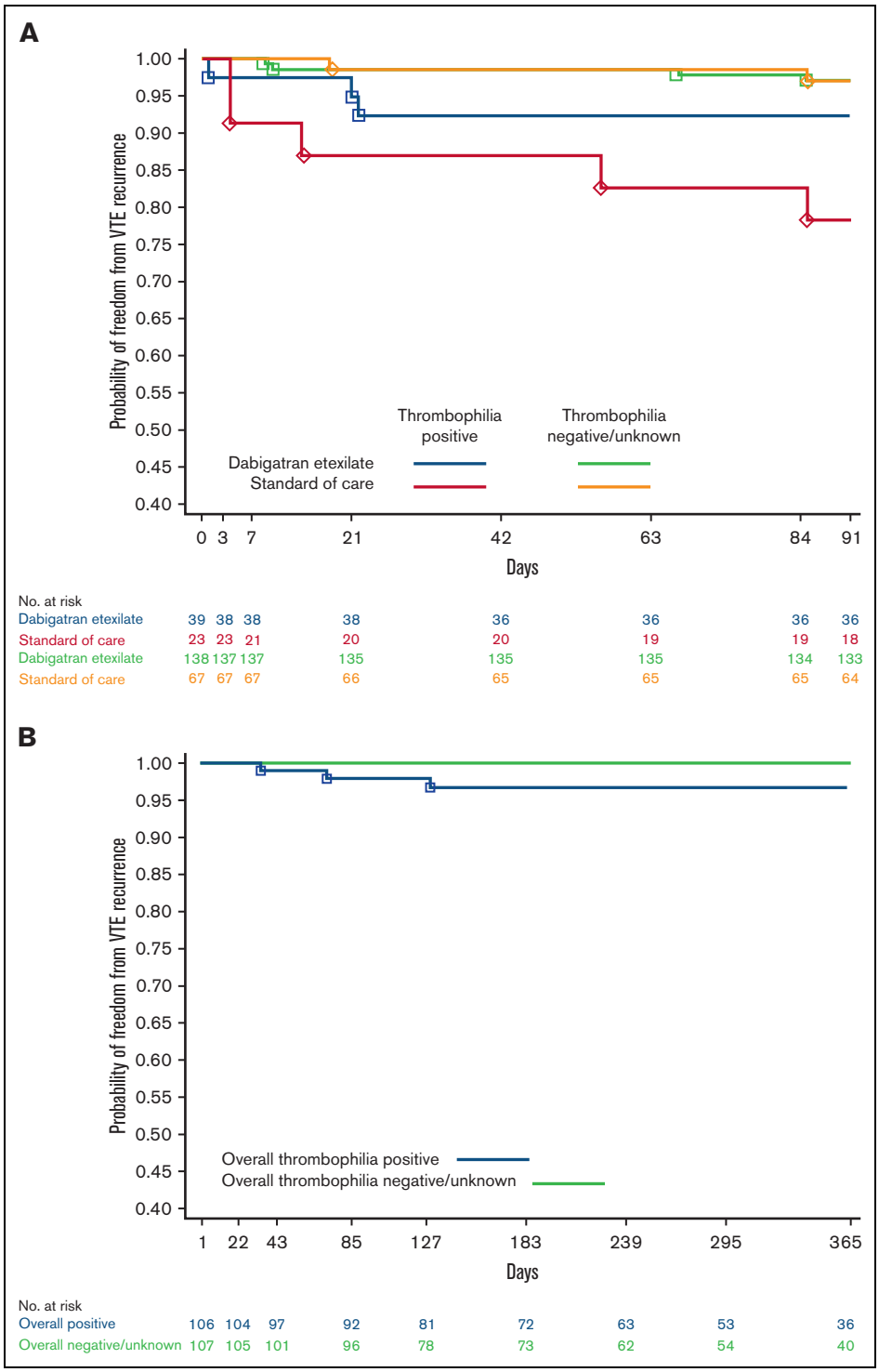

Figure 2. Kaplan-Meier curves of freedom from recurrent VTE by study, thrombophilia status, and treatment.

higher proportion of patients with thrombophilia compared with those with negative/unknown thrombophilia status experienced these outcomes. Consequently, complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related death (primary end point) was achieved by a lower proportion of patients in the thrombophilia group (but similarly for major and minor subgroups) than those in the thrombophilia-negative/unknown status group. For the thrombophilia-negative/unknown status group, there was no obvious difference in VTE outcomes between dabigatran and SOC treatment groups. Of note, we observed that a numerically higher proportion of patients who were thrombophilia positive, and particularly those with confirmed inherited

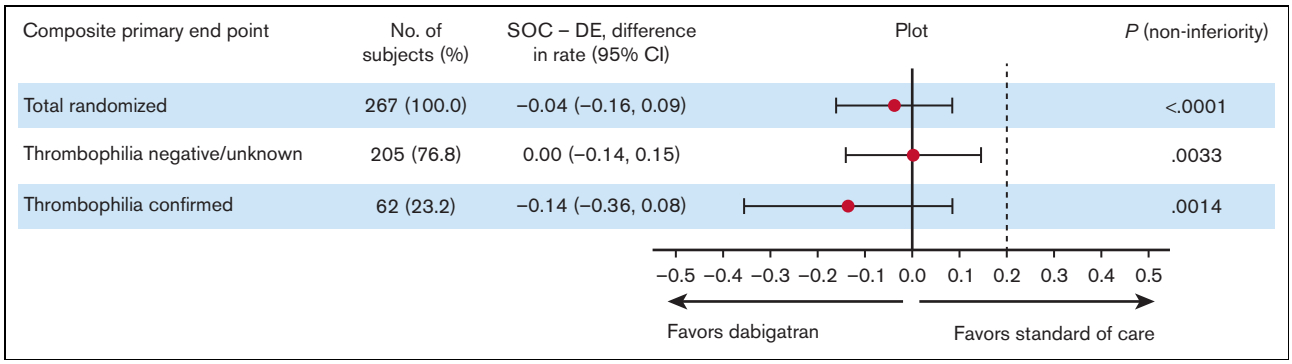

Figure 3. Forest plot for the acute VTE treatment study of the Mantel-Haenszel–weighted rate difference for composite primary efficacy end point (complete VTE resolution, freedom from recurrent VTE, and freedom from VTE-related death) by subgroup. DE, dabigatran etexilate.

thrombophilia with FVL and/or PT mutations, experienced complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related death with dabigatran vs SOC. Similarly, numerically lower rates of VTE recurrence and thrombus progression, and higher rates of partial thrombus resolution and complete thrombus resolution were observed in patients from the thrombophilia-positive group treated with dabigatran vs SOC. Although differences between treatment cohorts did not reach statistical significance, this is not unexpected because of the small sample sizes. Irrespective of thrombophilia status, consistency of effect with the overall study results,[21] in terms of noninferiority of dabigatran to SOC, was observed for the primary end point. Similar proportions of patients with and without thrombophilia experienced bleeding events. For the thrombophilia group, numerically fewer patients treated with dabigatran experienced bleeding events, including major and CRNM bleeding events, compared with those treated with SOC, although no statistical differences were observed between treatments. In the negative/unknown thrombophilia group, frequency of bleeding events was similar between treatment groups.

In the analysis of data from the secondary VTE prevention study, higher rates of VTE recurrence and any bleeding events were observed among children with thrombophilia compared with children in whom thrombophilia status was negative/unknown. However, rates of major or CRNM bleeding were low, with no clear difference in rates according to thrombophilia status.

The findings of greater VTE risk associated with presence of thrombophilia are broadly in line with previous observational studies of VTE recurrence in pediatric populations with so-called major thrombophilia, particularly in non–CVC-related events. Of note, only ~15% (dabigatran arm) and ~22% (SOC arm) of patients in the DIVERSITY study, and only ~3% of patients enrolled in the secondary prophylaxis study, had central line–related events.[21,22] For instance, in a previous German-wide national pediatric study, the presence of single vs combined prothrombotic defects was both associated with higher odds of VTE recurrence (single defect: odds ratio, −4.6; 95% CI, −2.3 to 9.0; $P < .0001$; combined defects: odds ratio, −24.0; 95% CI, −5.3 to 108.7; $P < .0001$).[5] In terms of adult data, a post hoc analysis of dabigatran studies in adults (ie, phase 3 studies comparing dabigatran and warfarin, RE-COVER [#NCT00291330][37] and RE-COVER II [#NCT00680186][38] for acute symptomatic VTE, and RE-MEDY [#NCT00329238][39] for secondary VTE prevention) revealed no difference in symptomatic VTE recurrence/VTE-related deaths between patients with thrombophilia treated with dabigatran or warfarin, with a similar safety profile.[40] More recent adult reports, including a systematic review, confirmed a similar efficacy of DOACs, including dabigatran, as an alternative anticoagulation strategy for patients with thrombophilia, except for cases of heparin-induced thrombocytopenia, APLA (eg, triple positive), and paroxysmal nocturnal hemoglobinuria, not included in our report because of their rarity in children.[41-43] To date, comparable evaluations of the performance of other DOACs in children with venous thrombotic events associated with thrombophilia are scant but are starting to emerge. A previous randomized trial on rivaroxaban in children, evaluating its efficacy and safety for acute VTE treatment, included 32 patients with inherited thrombophilia (intervention arm, 27 patients [8%]; SOC, 5 patients [3%]). However, no sensitivity analysis could be conducted because of its limited sample size.[44]

If the signal for a differential effect of dabigatran vs SOC on residual thrombus burden translates into meaningful differences in outcomes, this would be expected to confer benefits in reducing VTE recurrences and PTS. In adults, persistence of thrombosis despite a course of anticoagulation is a predictor of VTE recurrence and PTS;[45,46] for example, a lack of thrombus resolution was associated with a statistically significant fourfold increase in the odds for PTS in the original pediatric cohort reporting the modified Villalta scale, 1 of the 2 pediatric PTS scales accepted by the International Society on Thrombosis and Haemostasis.[30,47] Nonetheless, a recent cross-sectional follow-up study of adults diagnosed with VTE randomized to receive either dabigatran or warfarin did not identify a difference in prevalence of PTS in either treatment group.[48] The generalizability of this finding to the pediatric population remains to be proven. Consistent with our results, pediatric studies have shown patients with CVC-related DVT to be younger than those with non–CVC-related DVT.[49] PTS predictors included increased residual DVT burden, which is relevant for our study findings.[50] For non-catheter–related DVT, like our findings, patients had thrombophilia more often, along with DVT recurrences. Furthermore, studies in adults have shown an increased risk of persistence of residual thrombus in patients with thrombophilia, highlighting the need to further investigate the role of DOACs in children with thrombophilia to prevent unfavorable VTE-related outcomes.[51]

Considering the limited data available on the topic of DOACs in children with thrombophilia, we believe that the data summarized herein provides unique hypothesis-generating findings. We acknowledge that

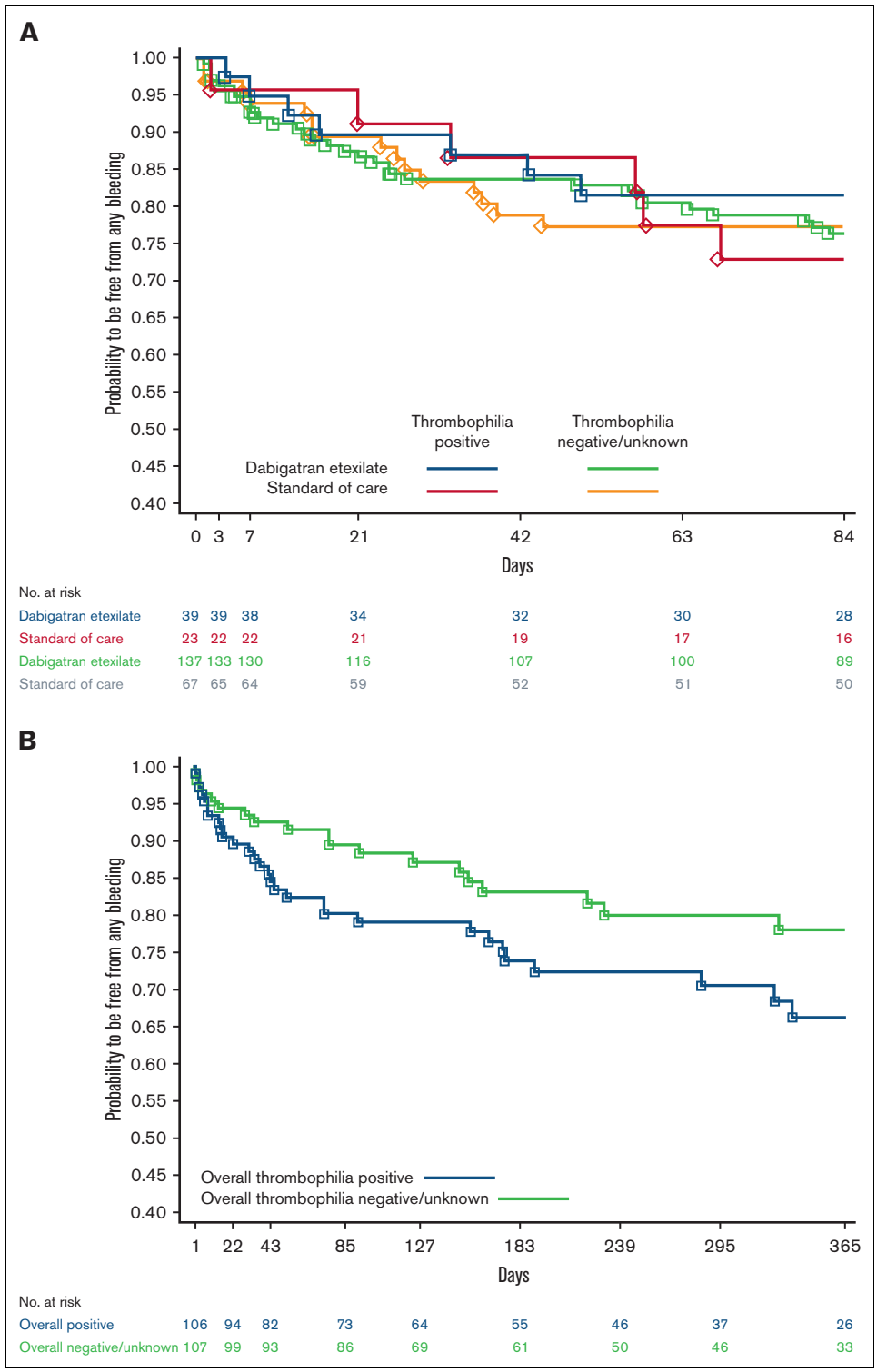

Figure 4. Kaplan-Meier curves of freedom from bleeding by study, thrombophilia status, and treatment.

this analysis has some limitations. There is no generally accepted classification for categorizing thrombophilia in major and minor subgroups, but similar approaches have been used previously.[11,31,52] Major thrombophilia includes inherited and acquired coagulopathies that increase coagulability and frequency of thrombotic events. Minor thrombophilia includes other mutations and conditions with less clear clinical consequences. We have provided a detailed listing of coagulopathies and categorization into major/minor in the manuscript, as well as of those patients with confirmed inherited thrombophilia with FVL and/or PT mutations. Thrombophilic coagulopathies were prespecified

Table 6. Secondary VTE prevention study: time to first recurrence of VTE, major or minor bleeding events, and PTS, on-treatment, by thrombophilia status

	Thrombophilia			Thrombophilia negative/unknown
	Overall (N = 106)	Major (N = 73)	Minor (N = 33)	(N = 107)
Recurrence of VTE, n (%)				
At 3 mo	2 (1.9)	1 (1.4)	1 (3.0)	0
At 6 mo	3 (2.8)	2 (2.7)	1 (3.0)	0
At 12 mo	3 (2.8)	2 (2.7)	1 (3.0)	0
Any bleeding event, n (%)				
At 3 mo	20 (18.9)	13 (17.8)	7 (21.2)	11 (10.3)
At 6 mo	25 (23.6)	16 (21.9)	9 (27.3)	16 (15.0)
At 12 mo	29 (27.4)	19 (26.0)	10 (30.3)	19 (17.8)
MBE, n (%)				
At 3 mo	0	0	0	1 (0.9)
At 6 mo	0	0	0	2 (1.9)
At 12 mo	1 (0.9)	1 (1.4)	0	2 (1.9)
CRNM, n (%)				
At 3 mo	0	0	0	0
At 6 mo	1 (0.9)	1 (1.4)	0	1 (0.9)
At 12 mo	2 (1.9)	2 (2.7)	0	1 (0.9)
PTS, n (%)				
At 3 mo	2 (1.9)	1 (1.4)	1 (3.0)	0
At 6 mo	3 (2.8)	2 (2.7)	1 (3.0)	0
At 12 mo	3 (2.8)	2 (2.7)	1 (3.0)	0

Table 7. Secondary VTE prevention study: time to first recurrence of VTE, major or minor bleeding events, and PTS, on-treatment, for confirmed inherited patients with thrombophilia

	Confirmed inherited thrombophilia (only FVL and/or PT gene) (N = 44)
Recurrence of VTE, n (%)	
At 3 mo	1 (2.3)
At 6 mo	1 (2.3)
At 12 mo	1 (2.3)
Any bleeding event, n (%)	
At 3 mo	12 (27.3)
At 6 mo	14 (31.8)
At 12 mo	16 (36.4)
MBE, n (%)	
At 3 mo	0
At 6 mo	0
At 12 mo	0
CRNM, n (%)	
At 3 mo	0
At 6 mo	0
At 12 mo	0
PTS, n (%)	
At 3 mo	2 (4.5)
At 6 mo	3 (6.8)
At 12 mo	3 (6.8)

and captured on the medical history page of the electronic case report forms, but there were no requirements to perform any tests concerning thrombophilia (including repeat, genetic, and/or family investigations) after a patient had been enrolled. However, FVL/PT mutations were confirmed by genetic tests (source-verified data were entered into the electronic case report forms) and, therefore, we were able to identify patients with confirmed inherited thrombophilia. Rare coagulopathies or mutations and conditions with indefinite thrombophilic significance were entered in the case report form as free text. Concentrations of antithrombin, protein C/S, and APLA/LA were not captured in a standardized manner, nor were types of APLA (immunoglobulin, subclasses G or M), or whether triple-positive status was present. As mentioned, we derive confidence in the thrombophilia diagnoses because these were based on the judgment of the pediatrician, who, in most cases, specialized in pediatric hematology and was familiar with the concept of developmental hemostasis and age-specific levels of thrombophilic markers. A sample selection bias might be present because testing for thrombophilia status was not protocol mandated. To mitigate this issue, a sensitivity analysis comparing patients with negative vs unknown thrombophilia status did not identify differences on the patient characteristics of both groups. Another limitation is the small number of patients in some of the subgroups analyzed herein; hence, our findings should be considered exploratory and be interpreted with caution.

Conclusion

Given that thrombophilia is associated with a higher risk of long-term complications of VTE, it is important to establish appropriate and stable treatments for prolonged duration in this patient group. The

exploratory findings of this study suggest that dabigatran could potentially have improved efficacy in these higher risk patients with thrombophilia compared with those without thrombophilia, who are at lower risk. Taken together, these data suggest that dabigatran could be appropriate for long-term anticoagulation in pediatric patients with thrombophilia. Future studies might add to the evidence on the treatment effects of DOACs, such as dabigatran vs SOC.

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Authorship

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Conflict-of-interest disclosure: L.R.B. is a member of a pediatric advisory board for Boehringer Ingelheim, and reports fees to his institution from Boehringer Ingelheim. I.T., M.S., and Z.S. are employees of Boehringer Ingelheim. M.A. is a member of a pediatric advisory board for Boehringer Ingelheim and has received advisory board fees from Daiichi Sankyo. J.H. is a member of a pediatric advisory board for Boehringer Ingelheim and has received honoraria from Boehringer Ingelheim for congress presentation. L.B. is a member of a pediatric advisory board for Boehringer Ingelheim and reports fees to her institution from Janssen Pharmaceuticals. E.C. is a member of a pediatric advisory board for Boehringer Ingelheim and reports personal fees from Roche, Sobi, Bristol Myers Squibb, CSL Behring, and Shire/Takeda. M.L. is a member of a pediatric advisory board for Boehringer Ingelheim. P.S. and J.F. significantly contributed to the enrollment of patients with thrombophilia in the program in their role as investigators (pediatric hematologists). O.L. significantly contributed to the enrollment of patients with thrombophilia in the program (investigator; pediatric hematologist) and has an Investigator Agreement with Bristol Myers Squibb, Novartis, and UCB. L.G.M. is a member of a pediatric advisory board for Boehringer Ingelheim and has received a research grant from Bristol Myers Squibb.

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