

# Effect of Anticoagulant Therapy for 6 Weeks vs 3 Months on Recurrence and Bleeding Events in Patients Younger Than 21 Years of Age With Provoked Venous Thromboembolism

## The Kids-DOTT Randomized Clinical Trial

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**IMPORTANCE** Among patients younger than 21 years of age, the optimal duration of anticoagulant therapy for venous thromboembolism is unknown.

**OBJECTIVE** To test the hypothesis that a 6-week duration of anticoagulant therapy for provoked venous thromboembolism is noninferior to a conventional 3-month therapy duration in patients younger than 21 years of age.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized clinical trial involving 417 patients younger than 21 years of age with acute, provoked venous thromboembolism enrolled at 42 centers in 5 countries from 2008-2021. The main exclusions were severe anticoagulant deficiencies or prior venous thromboembolism. Patients without persistent antiphospholipid antibodies and whose thrombi were resolved or not completely occlusive upon repeat imaging at 6 weeks after diagnosis underwent randomization. The final visit for the primary end points occurred in January 2021.

**INTERVENTIONS** Total duration for anticoagulant therapy of 6 weeks (n = 207) vs 3 months (n = 210) for provoked venous thromboembolism.

**MAIN OUTCOMES AND MEASURES** The primary efficacy and safety end points were centrally adjudicated symptomatic recurrent venous thromboembolism and clinically relevant bleeding events within 1 year blinded to treatment group. The primary analysis was noninferiority in the per-protocol population. The noninferiority boundary incorporated a bivariate trade-off that included an absolute increase of 0% in symptomatic recurrent venous thromboembolism with an absolute risk reduction of 4% in clinically relevant bleeding events (1 of 3 points on the bivariate noninferiority boundary curve).

**RESULTS** Among 417 randomized patients, 297 (median age, 8.3 [range, 0.04-20.9] years; 49% female) met criteria for the primary per-protocol population analysis. The Kaplan-Meier estimate for the 1-year cumulative incidence of the primary efficacy outcome was 0.66% (95% CI, 0%-1.95%) in the 6-week anticoagulant therapy group and 0.70% (95% CI, 0%-2.07%) in the 3-month anticoagulant therapy group, and for the primary safety outcome, the incidence was 0.65% (95% CI, 0%-1.91%) and 0.70% (95% CI, 0%-2.06%). Based on absolute risk differences in recurrent venous thromboembolism and clinically relevant bleeding events between groups, noninferiority was demonstrated. Adverse events occurred in 26% of patients in the 6-week anticoagulant therapy group and in 32% of patients in the 3-month anticoagulant therapy group; the most common adverse event was fever (1.9% and 3.4%, respectively).

**CONCLUSIONS AND RELEVANCE** Among patients younger than 21 years of age with provoked venous thromboembolism, anticoagulant therapy for 6 weeks compared with 3 months met noninferiority criteria based on the trade-off between recurrent venous thromboembolism risk and bleeding risk.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT00687882](https://clinicaltrials.gov/ct2/show/study/NCT00687882)

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The evidence underlying use of anticoagulant therapy for venous thromboembolism stems from a randomized clinical trial (RCT) in the 1960s<sup>1</sup> and subsequent uncontrolled studies demonstrating a reduction in the risk of recurrent venous thromboembolism. Recurrent venous thromboembolism encompasses deep vein thrombosis (DVT) and pulmonary embolism; recurrent DVT can increase the risk of chronic venous insufficiency (postthrombotic syndrome) and pulmonary embolism can be fatal.<sup>2,3</sup> Anticoagulant therapy for venous thromboembolism involves a trade-off between risks of recurrent venous thromboembolism and bleeding. As a statistical model for this trade-off, Kittelson et al<sup>4-7</sup> described a bivariate end point analytic approach, and applied this method to evaluate the net clinical benefit of antithrombotic therapies in RCTs.

Duration of anticoagulation in the treatment of first-episode venous thromboembolism in adults is mainly based on the findings of an RCT conducted in the 1990s.<sup>8</sup> Evidence in patients younger than 21 years of age is lacking; nevertheless, the standard of care for provoked venous thromboembolism (ie, venous thromboembolism temporally associated with a prothrombotic clinical risk factor) has been a 3-month course of anticoagulant therapy, as recommended for adults.<sup>9</sup> In children, more than 90% of venous thromboembolism events are provoked.<sup>10</sup> Since 2008, clinical practice guidelines for pediatric venous thromboembolism treatment have suggested a 6-week course of antithrombotic therapy as an alternative to 3 months, while emphasizing the need for definitive evidence.<sup>10-12</sup>

The primary aim of this multinational RCT was to compare the net clinical benefit (as measured by the 1-year risks of symptomatic recurrent venous thromboembolism and clinically relevant bleeding events) of a shortened duration of anticoagulant therapy (6 weeks) vs a conventional (3 months) duration for the treatment of first-episode acute provoked venous thromboembolism in patients younger than 21 years of age. It was hypothesized that a 6-week course of anticoagulant therapy would be noninferior to a 3-month course.

## Methods

### Study Design and Oversight

The Multicenter Evaluation of the Duration of Therapy for Thrombosis in Children (Kids-DOTT trial) was an investigator-initiated RCT conducted at 42 children's hospitals and academic medical centers in Australia, Austria, Canada, the Netherlands, and the US. Details of the trial design (a parallel-cohort RCT using the prospective, randomized, open-label, blinded end point [PROBE] methods) have been described<sup>13</sup> and the pilot/feasibility phase findings have been published.<sup>14</sup> The trial protocol (Supplement 1) was approved by the executive steering committee and the independent data and safety monitoring board, as well as by the institutional review board or research ethics committee at all participating sites. Signed informed consent (and assent from children as appropriate) was required for all participants.

## Key Points

**Question** Among patients younger than 21 years of age with acute provoked venous thromboembolism, is a 6-week duration of anticoagulant therapy noninferior to a conventional 3-month duration?

**Findings** In this randomized clinical trial that included 417 patients with provoked venous thromboembolism, anticoagulant therapy for 6 weeks vs 3 months resulted in symptomatic recurrent venous thromboembolism in 0.66% vs 0.70%, respectively, and clinically relevant bleeding events in 0.65% vs 0.70% within 1 year. The differences met the criteria for noninferiority.

**Meaning** Among patients younger than 21 years of age with provoked venous thromboembolism, anticoagulant therapy for 6 weeks compared with 3 months met noninferiority based on a combination of recurrent venous thromboembolism risk and bleeding risk.

The clinical coordinating center (Johns Hopkins All Children's Hospital) and the data coordinating center (CPC Clinical Research) collaborated in conducting trial monitoring. Details of the trial monitoring plan appear in Supplement 1. The trial was overseen by an executive steering committee and an independent data and safety monitoring board run by the National Heart, Lung, and Blood Institute of the US National Institutes of Health. Investigator-reported primary outcomes were adjudicated by an independent, blinded clinical end point adjudication committee.

### Participants

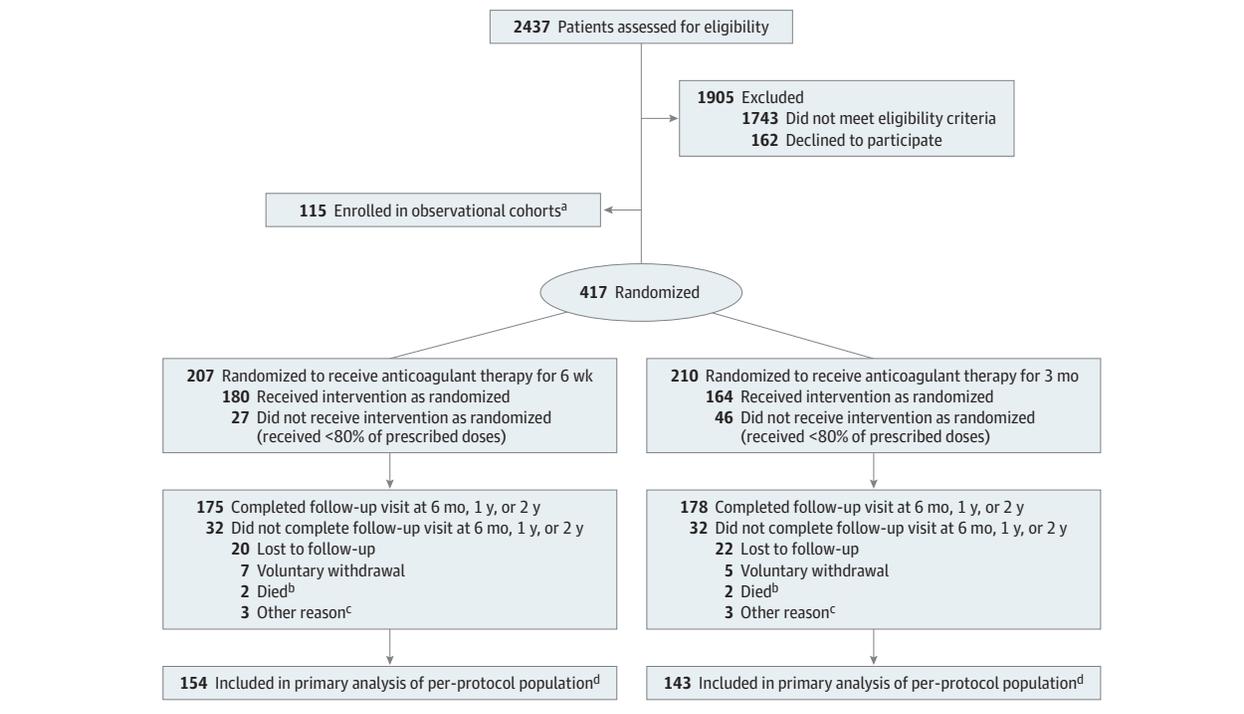
Complete inclusion and exclusion criteria are provided in eTable 1 in Supplement 2. In summary, patients eligible for enrollment were younger than 21 years of age with an acute venous thromboembolism confirmed radiologically via compression ultrasound with Doppler, computed tomography with venography, magnetic resonance venography, or conventional venography within the previous 30 days, with a provoking factor (eg, recent hospitalization, traumatic injury, central venous catheterization) identified by the investigators. The main exclusion criteria were prior venous thromboembolism, active malignancy, systemic lupus erythematosus, pulmonary embolism unaccompanied by DVT, thrombolytic therapy for the index venous thromboembolism, and clinically significant deficiencies of natural anticoagulants (ie, protein C, protein S, antithrombin). Given the challenges in the reliability of symptom reporting in children, both symptomatic and asymptomatic provoked venous thromboembolism were eligible for inclusion.

Race and ethnicity (as self-identified by participants using fixed categories) were recorded in accordance with National Institutes of Health requirements for tracking inclusion of racial and ethnic minority groups in clinical trials, and given the racial and ethnic disparities in venous thromboembolism incidence and outcomes.<sup>15,16</sup>

### Procedures Prior to Randomization

The schedule of participant assessments appears in eTable 2 in Supplement 2. All participants received treatment for venous

Figure 1. Screening, Randomization, and Follow-up of Patients in the Kids-DOTT Trial



Kids-DOTT indicates Multicenter Evaluation of the Duration of Therapy for Thrombosis in Children.

<sup>a</sup> The findings related to the observational cohort aims will be published separately.

<sup>b</sup> Two additional deaths occurred per group that were outside the per-protocol population.

<sup>c</sup> Included withdrawal by site principal investigator (n = 1 per group); informed

consent no longer in effect due to change in child custody (n = 1 per group); and eligibility criteria no longer met due to underlying disease diagnosis (n = 1 per group).

<sup>d</sup> Calculated as the number of patients randomized minus the number of patients not completing the follow-up visit at 6 months or later, minus the additional number of patients who received less than 80% of prescribed doses of anticoagulant therapy.

thromboembolism with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparins acutely, followed by low-molecular-weight heparins, fondaparinux, oral vitamin K antagonists, or direct oral anticoagulants. The choice of anticoagulant was at the discretion of the treating physician, but followed dosing and monitoring guidelines from the American College of Chest Physicians,<sup>10,11</sup> as referenced in the study protocol.

At the 6-week visit after diagnosis of index venous thromboembolism, the presence or absence of complete veno-occlusive disease was assessed via follow-up imaging, using the same imaging modality that had been used to confirm the index venous thromboembolism. When antiphospholipid antibodies were detected at the time of enrollment, persistence of these antibodies was assessed by follow-up testing. Patients with venous flow evident in the involved vessel segments, and without persistent antiphospholipid antibodies, underwent randomization.

### Randomization and Blinding

Randomization (allocation ratio of 1:1), with randomly permuted block sizes of 4 to 8 patients, was executed via a web-based electronic data capture system, with stratification by age group (<30 days, 30 days–<13 years, and 13 years–<21 years) and

anatomical site of thrombosis (lower-extremity DVT, upper-extremity DVT, cerebral sinovenous thrombosis, and other) (Figure 1). Randomization coding was developed and validated by the data coordinating center. In accordance with the PROBE design, treatment assignment was not blinded (open label), whereas outcome assessments were blinded (blinded end point assessment).

### Intervention

Randomized patients were assigned to discontinue anticoagulant therapy vs continue anticoagulant therapy for a total of 3 months after diagnosis of venous thromboembolism.

### Procedures After Randomization

Patients were followed up for the development of recurrent venous thromboembolism or clinically relevant bleeding events at 3 months, 6 months, 1 year, and 2 years. No routine surveillance imaging was performed. Adverse events were collected from randomization through day 94 after diagnosis of index venous thromboembolism.

### Outcomes

All outcomes were defined according to criteria established by the Scientific and Standardization Committee of the International

Society on Thrombosis and Hemostasis<sup>17-19</sup> (additional details appear in eTable 3 in Supplement 2). The primary efficacy end point was centrally adjudicated symptomatic recurrent venous thromboembolism and the primary safety end point was centrally adjudicated clinically relevant (ie, major plus clinically relevant nonmajor) bleeding events within 1 year after diagnosis of index venous thromboembolism. Symptomatic recurrent venous thromboembolism was defined by objective radiological evidence of new DVT or pulmonary embolism relative to the study-qualifying imaging study for index venous thromboembolism, accompanied by signs or symptoms corresponding to (and in temporal association with) the site of DVT or pulmonary embolism.

The clinically relevant bleeding event met 1 of the following criteria: (1) fatal; (2) clinically overt and associated with a decrease in hemoglobin level of at least 2 g/dL within a 24-hour period; (3) clinically overt and for which blood product was administered but not attributable to the patient's underlying condition; (4) retroperitoneal, pulmonary, or involving the central nervous system; (5) requiring surgical intervention in an operating suite; (6) requiring medical or surgical intervention outside an operating suite; or (7) for which the patient sought medical attention. All investigator-reported recurrent venous thromboembolism and clinically relevant bleeding events were centrally adjudicated by a clinical end point adjudication committee, with blinding to treatment group. Materials reviewed by the committee included deidentified records of clinical history, physical examination, and pertinent clinical laboratory details from hospitalizations or outpatient visits relating to investigator-reported events, along with pertinent radiological imaging studies.

The composite of centrally adjudicated symptomatic recurrent venous thromboembolism or the development of chronic venous insufficiency within 1 year among patients with index DVT of the limbs was a secondary efficacy end point. Chronic venous insufficiency was assessed by blinded, trained, local clinicians using a validated pediatric outcome instrument for postthrombotic syndrome.<sup>17,18</sup> Additional secondary end points included symptomatic recurrent venous thromboembolism within 2 years and chronic venous insufficiency (postthrombotic syndrome) within 1 year and 2 years among patients with index DVT of the limbs; data collection for 2-year outcomes is ongoing. Adverse events were coded using the Medical Dictionary for Regulatory Activities and reviewed by the data coordinating center for possible outcome events meeting primary end point criteria, for further assessment, and for end point reporting by the participating site investigator.

### Sample Size Calculation

Assuming that the risks of symptomatic recurrent venous thromboembolism and clinically relevant bleeding events are 3% and 1%, respectively, based on the findings of the pilot phase,<sup>14</sup> the trial design provided 81.3% power with a sample size of 312 patients in the per-protocol population (and greater power in the analysis of all randomized patients) under the hypothesis of no increased absolute risk of symptomatic recurrent venous thromboembolism and an absolute risk difference (6-week regimen minus 3-month regimen) in clinically

relevant bleeding events of -1.4% ( $1.64 \times$  the SE for bleeding events, 0.83%).

### Statistical Analyses

The statistical analysis plan was approved by the executive steering committee and independent data and safety monitoring board (Supplement 3). In testing the primary hypothesis, the principal analysis was noninferiority for the primary end points in the per-protocol population, with further assessment in all randomized patients. A "positive" trial was prespecified as one in which the primary hypothesis is true for both analyses. The per-protocol population consisted of all randomized patients who had no protocol violations for the eligibility criteria, received between 80% and 120% of the assigned anticoagulant therapy doses (protocol-defined adherence to anticoagulant regimen), and completed follow-up through the 6-month visit or later.

The statistical approach for testing the primary hypothesis used bivariate end point analysis as previously described.<sup>4,7</sup> The derivation of the noninferiority boundary, as well as the sample size estimation and power calculation for the trial, are described in detail in the statistical analysis plan (Supplement 3). The noninferiority boundary was constructed based on 3 scenarios of risk-benefit trade-off (ie, points on the noninferiority boundary described by the bivariate function) informed by consensus of the executive steering committee and approved by the data and safety monitoring board. Specifically, these points consisted of absolute risk differences (6-week regimen minus 3-month regimen) in symptomatic recurrent venous thromboembolism and clinically relevant bleeding events, respectively, as follows: 1% and -12%; 0% and -4%; and -5% and 4%. One-year risks and corresponding 95% CIs were calculated from the Kaplan-Meier curves. Absolute risk differences and 95% CIs were estimated using the exact methods of Fay et al<sup>20</sup> and the R package exact2x2.<sup>21</sup> A determination of noninferiority required that the 95% confidence rectangle formed from the absolute risk difference for the primary efficacy and safety end points excluded the noninferiority boundary.

The secondary analyses descriptively evaluated noninferiority in the secondary efficacy end points via calculation of the absolute risk difference and corresponding 95% CI using exact methods.<sup>20,21</sup> The upper limit of the 95% CI for the absolute risk difference was used to report and evaluate the magnitude of the absolute increase in risk of each secondary end point that could be excluded when comparing the 6-week and 3-month regimens.

Adverse events were descriptively analyzed within the safety population, which was defined as all randomized patients who had received at least 1 dose of anticoagulant therapy after enrollment.

No interim analyses were conducted. Given that the per-protocol population was prespecified as the primary analysis population, and included patients with primary end point data from the 6-month follow-up visit or later, no imputation of missing data was performed. Because of the potential for type I error due to multiple comparisons, the findings for the analyses of the secondary end points should be interpreted as

Table 1. Characteristics of Patients and Venous Thromboembolism at Enrollment in the Per-Protocol Population

|   | Per-protocol population                  |  |
|---|--|--|
|   | Anticoagulant therapy for 6 wk (n = 154) | Anticoagulant therapy for 3 mo (n = 143) |
| Age at time of consent, y   |  |  |
| Mean (SD)   | 8.5 (6.8)                                | 8.1 (6.6)                                |
| Median (range)  | 9.0 (0.04-20.9)                          | 7.6 (0.05-20.5)                          |
| Age stratum, No. (%)  |  |  |
| Neonate (<30 d)   | 6 (3.9)                                  | 6 (4.2)                                  |
| Child (30 d-<13 y)  | 95 (61.7)                                | 92 (64.3)                                |
| Teenager (13 y-<21 y)   | 53 (34.4)                                | 45 (31.5)                                |
| Sex, No. (%)  |  |  |
| Male  | 87 (56.5)                                | 67 (46.9)                                |
| Female  | 67 (43.5)                                | 76 (53.2)                                |
| Race, No./total (%)   |  |  |
| American Indian/Alaska Native   | 0  | 0  |
| Asian   | 6/142 (4.2)                              | 5/135 (3.7)                              |
| Black   | 20/142 (14.1)                            | 15/135 (11.1)                            |
| Multiple races  | 1/142 (0.7)                              | 1/135 (0.7)                              |
| White   | 112/142 (78.9)                           | 111/135 (82.2)                           |
| Other <sup>a</sup>  | 3/142 (2.1)                              | 3/135 (2.2)                              |
| Hispanic ethnicity, No./total (%)                                       | 19/142 (13.4)                            | 20/136 (14.7)                            |
| Index venous thromboembolism anatomical site, No. (%)                   |  |  |
| Lower-extremity DVT, pulmonary embolism, or both                        | 70 (45.5)                                | 66 (46.2)                                |
| Upper-extremity DVT, pulmonary embolism, or both                        | 50 (32.5)                                | 42 (29.4)                                |
| Cerebral sinovenous thrombosis  | 16 (10.4)                                | 22 (15.4)                                |
| Other venous thromboembolism site                                       | 14 (9.1)                                 | 9 (6.3)                                  |
| Splanchnic vein thrombosis  | 3 (1.9)                                  | 1 (0.7)                                  |
| Kidney vein thrombosis  | 1 (0.6)                                  | 1 (0.7)                                  |
| Right atrial thrombosis   | 0  | 2 (1.4)                                  |
| Provoking factor for index venous thromboembolism, No. (%) <sup>b</sup> |  |  |
| Central venous catheter   | 84 (43.5)                                | 72 (38.3)                                |
| Infection   | 49 (25.4)                                | 52 (27.7)                                |
| Trauma or surgery within previous 30 d                                  | 29 (15.0)                                | 30 (16.0)                                |
| Prothrombotic medication <sup>c</sup>                                   | 8 (4.2)                                  | 10 (5.3)                                 |
| Flare of autoimmune disease   | 2 (1.0)                                  | 6 (3.2)                                  |
| Hospitalization within previous 30 d <sup>d</sup>                       | 2 (1.0)                                  | 2 (1.1)                                  |
| Congenital or acquired cardiac disease                                  | 1 (0.5)                                  | 3 (1.6)                                  |
| Other <sup>e</sup>  | 5 (2.6)                                  | 4 (2.1)                                  |
| Not specified   | 13 (6.7)                                 | 9 (4.8)                                  |
| Interval from index venous thromboembolism to informed consent, d       |  |  |
| Mean (SD)   | 13.4 (9.0)                               | 12.7 (8.4)                               |
| Median (range)  | 12.5 (1-30)                              | 13.0 (0-30)                              |

Abbreviation: DVT, deep vein thrombosis.

<sup>a</sup> Self-described as none of the aforementioned categories.

<sup>b</sup> Due to patients with more than 1 provoking factor, the sum of individual frequencies exceeds 100%. The site principal investigator verified that the index venous thromboembolism was associated with at least 1 provoking factor per the study protocol's eligibility criteria. This assessment was the same for patients with index DVT of the limbs as for those with index venous thromboembolism at other anatomical sites.

<sup>c</sup> Included systemic estrogen, glucocorticoids, and L-asparaginase.

<sup>d</sup> Signs and symptoms of venous thromboembolism were absent at time of preceding hospitalization.

<sup>e</sup> Included dehydration, inborn error of metabolism, and genetic syndrome.

exploratory. All statistical tests were 2-sided. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.4.2 (R Foundation for Statistical Computing).

## Results

A total of 417 patients younger than 21 years of age underwent randomization at 42 participating centers in 5 countries

(Figure 1). The first patient was enrolled in the interventional trial in November 2008 during the pilot/feasibility phase. The last patient was enrolled in December 2019 and the final visit for the primary end points occurred in January 2021. There were 297 patients in the per-protocol population. Patient characteristics at enrollment appear in Table 1 and were similar in the 2 treatment groups. The data for all randomized patients appear in eTable 4 in Supplement 2. The median age of participants was 8.3 years (range, 0.04-20.9 years) and 49% were

Table 2. Adjudicated Primary Efficacy and Safety End Points

|   | Anticoagulant therapy for 6 wk |                                |                                   | Anticoagulant therapy for 3 mo |                                |                                   | Absolute risk difference, % (95% CI) <sup>c</sup> |
|---|--------------------------------|--------------------------------|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|---|
|   | No. of events                  | Patients, No. (%) <sup>a</sup> | 1-y risk, % (95% CI) <sup>b</sup> | No. of events                  | Patients, No. (%) <sup>a</sup> | 1-y risk, % (95% CI) <sup>b</sup> |   |
| <b>Per-protocol population</b>                          |                                |                                |                                   |                                |                                |                                   |   |
| No. of patients   |                                | 154                            |                                   |                                | 143                            |                                   |   |
| Symptomatic recurrent venous thromboembolism within 1 y | 1                              | 1 (0.65)                       | 0.66 (0 to 1.95)                  | 2                              | 2 (1.40)                       | 0.70 (0 to 2.07)                  | -0.04 (-3.81 to 3.56)                             |
| Clinically relevant bleeding events <sup>d</sup>        | 5                              | 1 (0.65)                       | 0.65 (0 to 1.91)                  | 1                              | 1 (0.70)                       | 0.70 (0 to 2.06)                  | -0.05 (-3.78 to 3.54)                             |
| <b>All randomized patients</b>                          |                                |                                |                                   |                                |                                |                                   |   |
| No. of patients   |                                | 207                            |                                   |                                | 210                            |                                   |   |
| Symptomatic recurrent venous thromboembolism within 1 y | 3                              | 2 (0.97)                       | 1.03 (0 to 2.43)                  | 4                              | 4 (1.91)                       | 1.60 (0 to 3.38)                  | -0.57 (-4.10 to 2.90)                             |
| Clinically relevant bleeding events <sup>d</sup>        | 6                              | 2 (0.97)                       | 1.06 (0 to 2.53)                  | 6                              | 5 (2.38)                       | 2.47 (0.31 to 4.59)               | -1.41 (-5.19 to 2.28)                             |

<sup>a</sup> Percentage reflects denominator specific to each treatment group. <sup>d</sup> Defined as a major bleeding event plus clinically relevant nonmajor bleeding event within 1 year.

<sup>b</sup> The Kaplan-Meier curves appear in eFigures 1 and 2 in Supplement 2.

<sup>c</sup> Calculated according to Fay et al<sup>20</sup> and used the R package exact2x2. The negative values denote benefit for the 6-week regimen compared with the 3-month regimen, whereas the positive values denote harm.

female. The predominant anticoagulant therapies used were low-molecular-weight heparins, which were administered to 84% of participants during the acute treatment period (ie, first week) after diagnosis of index venous thromboembolism and to 86% of patients during the subacute treatment period. eTable 5 in Supplement 2 provides details on anticoagulant class among all randomized patients by treatment group.

### Primary Outcomes

The adjudicated primary efficacy and safety outcomes in the per-protocol population and in all randomized patients appear in Table 2. The times to occurrence of the primary efficacy and safety outcomes are shown as Kaplan-Meier plots in Supplement 2 (eFigure 1 for the per-protocol population and eFigure 2 for all randomized patients). In the per-protocol population, the primary efficacy outcome (adjudicated symptomatic recurrent venous thromboembolism within 1 year) occurred in 1 patient (0.65%) in the 6-week group and in 2 patients (1.40%) in the 3-month group. The primary safety outcome (adjudicated clinically relevant bleeding events [defined by the International Society on Thrombosis and Hemostasis] within 1 year) occurred in 1 patient (0.65%) in the 6-week group and in 1 patient (0.70%) in the 3-month group. The Kaplan-Meier estimate of the 1-year cumulative incidence of symptomatic recurrent venous thromboembolism in the per-protocol population was 0.66% (95% CI, 0% to 1.95%) for the 6-week group and 0.70% (95% CI, 0% to 2.07%) for the 3-month group; this yielded an absolute risk difference of -0.04% (95% CI, -3.81% to 3.56%) for the primary efficacy outcome. The Kaplan-Meier estimate of the 1-year cumulative incidence of clinically relevant bleeding events in the per-protocol population was 0.65% (95% CI, 0% to 1.91%) for the 6-week group and 0.70% (95% CI, 0% to 2.06%) for the 3-month group, yielding an absolute risk difference of -0.05% (95% CI, -3.78% to 3.54%) for the primary safety outcome.

Among all randomized patients, the primary efficacy outcome occurred in 2 patients (0.97%) in the 6-week group and in 4 patients (1.91%) in the 3-month group; the primary safety

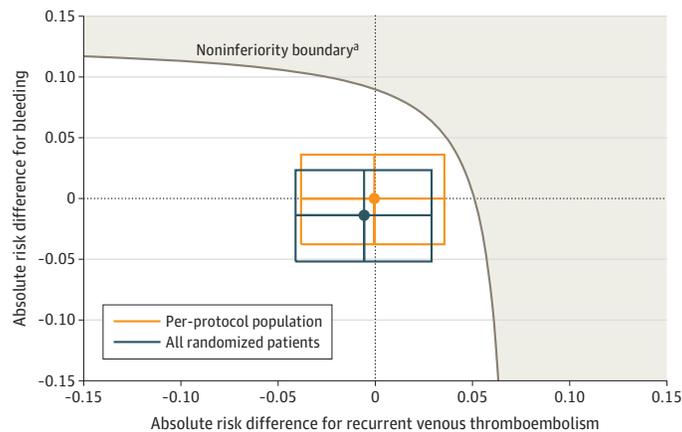
outcome occurred in 2 patients (0.97%) in the 6-week group and in 5 patients (2.38%) in the 3-month group. Kaplan-Meier estimates of the 1-year cumulative incidence of symptomatic recurrent venous thromboembolism among all randomized patients was 1.03% (95% CI, 0% to 2.43%) in the 6-week group and 1.60% (95% CI, 0% to 3.38%) in the 3-month group; this yielded an absolute risk difference of -0.57% (95% CI, -4.10% to 2.90%) for the primary efficacy outcome. The Kaplan-Meier estimate of the 1-year cumulative incidence of clinically relevant bleeding events among all randomized patients was 1.06% (95% CI, 0% to 2.53%) in the 6-week group and 2.47% (95% CI, 0.31% to 4.59%) in the 3-month group, yielding an absolute risk difference of -1.41% (95% CI, -5.19% to 2.28%) for the primary safety outcome.

In the primary analysis, noninferiority was demonstrated in the per-protocol population, and confirmed among all randomized patients, given that the 95% confidence rectangle of the absolute risk differences for the 1-year risk of symptomatic recurrent venous thromboembolism and clinically relevant bleeding events excluded the prespecified noninferiority boundary (Figure 2).

### Secondary Outcomes

The findings for the composite secondary efficacy outcome, which consisted of the development of chronic venous insufficiency (postthrombotic syndrome) or adjudicated symptomatic recurrent venous thromboembolism within 1 year among patients with index DVT of the limbs, appear in eTable 6 in Supplement 2. In the per-protocol population, the composite secondary efficacy outcome occurred in 36 patients (30.0%) in the 6-week group and in 32 patients (29.6%) in the 3-month group (absolute risk difference, 2.75% [95% CI, -10.4% to 15.7%]). Among all randomized patients, the composite secondary efficacy outcome occurred in 42 patients (26.3%) in the 6-week group and in 42 patients (26.9%) in the 3-month group (absolute risk difference, 2.6% [95% CI, -9.2% to 14.4%]). The findings for the additional secondary outcome of the 1-year risk of postthrombotic syndrome by itself, by treatment group,

**Figure 2. Bivariate Noninferiority Analysis Reflecting the Trade-off Between Adjudicated Symptomatic Recurrent Venous Thromboembolism (Primary Efficacy End Point) and Clinically Relevant Bleeding Events (Primary Safety End Point)**



The absolute risk differences (anticoagulant therapy for 6 weeks minus anticoagulant therapy for 3 months) for both primary end points yield point estimates in a 2-dimensional plane. The 95% CIs for the 2-dimensional point estimates form 95% confidence rectangles.

<sup>a</sup> Constructed using the following points for between-group absolute risk differences in symptomatic recurrent venous thromboembolism and clinically relevant bleeding events, respectively: 1% and -12%; 0% and -4%; -5% and

4%. Noninferiority is demonstrated in the per-protocol population and confirmed among all randomized patients by the fact that in each case the entire 95% confidence rectangle lies within the noninferiority zone (white background) to the southwest of the noninferiority boundary. Additional details on the bivariate end point methods appear in [Supplement 3](#) and have been described by Hu et al.<sup>7</sup>

in the per-protocol population, and among all randomized patients appear in eTable 7 in [Supplement 2](#).

In the descriptive secondary analyses of noninferiority, the 1-year incidence of the composite secondary efficacy outcome was similar in the 2 treatment groups for both the per-protocol population and all randomized patients (eTable 6 in [Supplement 2](#)). The findings excluded an absolute risk increase of greater than 15.7% (upper limit of the 95% CI of the absolute risk difference) for the composite secondary outcome in association with abbreviated anticoagulant therapy. In addition, the 1-year incidence of postthrombotic syndrome itself among patients with index DVT of the limbs was similar in the 2 treatment groups for both the per-protocol population and all randomized patients (eTable 7 in [Supplement 2](#)), and excluded an absolute risk increase of greater than 14.7% for the postthrombotic syndrome in association with shortened anticoagulant therapy.

### Adverse Events

In the safety population, adverse events occurred in 26% of patients in the 6-week treatment group and in 32% of patients in the 3-month group. The frequency of each adverse event diagnosis was less than 4% and did not differ appreciably between the 2 treatment groups (eTable 8 in [Supplement 2](#)). The most common event was fever (1.9% of patients in the 6-week treatment group and 3.4% in the 3-month group). There were no episodes of heparin-induced thrombocytopenia. Among 49 serious adverse events, only 2 were judged as possibly related to the study intervention; both were bleeding events in the 3-month group. Four deaths each occurred in the 6-week group (1.9%) and in the 3-month group (1.9%); none was deemed related to the study intervention (eTable 9 in [Supplement 2](#)).

## Discussion

In this multinational RCT among patients younger than 21 years of age with acute provoked venous thromboembolism who had neither persistent antiphospholipid antibodies nor complete occlusion on repeat imaging at 6 weeks, a 6-week total course of anticoagulant therapy was noninferior to a 3-month course based on the trade-off between risks of recurrent venous thromboembolism and clinically relevant bleeding events within 1 year.

Among all 417 patients randomized, the Kaplan-Meier 1-year risk estimates for symptomatic recurrent venous thromboembolism were similar to those recently reported in the EINSTEIN-Junior phase 3 trial<sup>22</sup> of the direct oral anticoagulant rivaroxaban for pediatric venous thromboembolism treatment (n = 500) at 1% for rivaroxaban and 3% for standard anticoagulants at a median follow-up time of 3 months (noninfants, n = 463) or 1 month (infants, n = 37). In the DIVERSITY phase 2b/3 trial<sup>23</sup> (n = 267), the rates of venous thromboembolism recurrence were 4% for treatment with the direct oral anticoagulant dabigatran and 8% with standard anticoagulants. Whereas the present RCT enrolled pediatric patients with provoked venous thromboembolism, 23% of the cases of index venous thromboembolism in the DIVERSITY trial and 11% in the EINSTEIN-Junior trial were unprovoked; among adults, unprovoked venous thromboembolism is associated with an increased risk of recurrence.<sup>9</sup>

In the present study, the Kaplan-Meier 1-year risk estimate for the clinically relevant bleeding event rates among all randomized patients in the conventional (3-month) duration group was consistent with the bleeding event rates reported in the EINSTEIN-Junior trial (3% for rivaroxaban and 2% for

standard anticoagulants) and in the DIVERSITY trial (3% with either dabigatran or standard anticoagulants).<sup>22,23</sup> Taken together, data from these recent RCTs suggest that the risks of recurrent venous thromboembolism and clinically relevant bleeding events in young patients receiving anticoagulation for the treatment of acute venous thromboembolism are lower than previously reported from observational studies—particularly among patients with provoked venous thromboembolism. This may reflect experience gained in pediatric venous thromboembolism management and improved ability to distinguish provoked from unprovoked venous thromboembolism in children and young adults.

### Limitations

This study has several limitations. First, given that the study population was characterized by a small proportion of patients with cancer or pulmonary embolism (which were excluded from the protocol until a protocol modification in 2017 at the data and safety monitoring committee's recommendation), caution should be exercised in applying these trial results to such patients. Second, the anticoagulant therapies prescribed were predominantly low-molecular-weight heparins, whereas direct oral anticoagulant therapies are increasingly used for pediatric venous thromboembolism treatment.

Nevertheless, the rates of recurrent venous thromboembolism and clinically relevant bleeding events were similar to those in recent direct oral anticoagulant trials of pediatric venous thromboembolism treatment. In those trials, the rates of recurrent venous thromboembolism and clinically relevant bleeding events were similar between the direct oral anticoagulant and standard anticoagulant groups.

Third, the points representing the trade-offs between recurrent venous thromboembolism and clinically relevant bleeding events that were used to define the bivariate noninferiority

boundary were selected by consensus of the executive steering committee rather than by a process of utility assessment. Formal utility assessment may have resulted in a different boundary, potentially altering the study findings.

Fourth, unlike the primary noninferiority analyses, the secondary noninferiority analyses involving chronic venous insufficiency (postthrombotic syndrome) were solely descriptive.

Fifth, findings from a trial conducted in a low-frequency pediatric disease starting in 2008 might have limitations for informing current clinical care. Although evaluation for an interaction of the outcomes by time was not possible given the low rate of outcome events, the standard of care for pediatric venous thromboembolism has minimally changed over the past few decades, apart from the recent increase in use of direct oral anticoagulants.

Sixth, there was a small number of primary efficacy and safety events in the trial, precluding a random-effects model that would include participating site as a variable; however, the observed cumulative incidences of the outcome events in the randomized population were accounted for in the sample size and power calculations of the analytic design. The low rates observed for recurrent venous thromboembolism serve to further support the clinical appropriateness of shortening the duration of anticoagulant therapy for provoked venous thromboembolism in patients younger than 21 years of age.

### Conclusions

Among patients younger than 21 years of age with provoked venous thromboembolism, anticoagulant therapy for 6 weeks compared with 3 months met noninferiority criteria based on the trade-off between recurrent venous thromboembolism risk and bleeding risk.

### ARTICLE INFORMATION

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**Author Contributions:** Drs Goldenberg and Bonaca had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Acquisition, analysis, or interpretation of data:** Goldenberg, Schulman, Kittelson, Bonaca, Dale, Halperin, Hamblin, Kessler, Manco-Johnson, Sidonio, Steg.

**Drafting of the manuscript:** Goldenberg, Kittelson, Bonaca, Casella, Hamblin, Spyropoulos.

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**Administrative, technical, or material support:**

Goldenberg, Bonaca, Casella, Sidonio.

**Supervision:** Kittelson, Abshire, Bonaca, Halperin.

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**Group Information:** A list of the Kids-DOTT Trial Investigators and the ATLAS Group members appears in [Supplement 4](#).

**Data Sharing Statement:** See [Supplement 5](#).

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