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Multicenter Randomized Controlled Trial on Duration of Therapy for Thrombosis in Children and Young Adults (Kids-DOTT): Pilot/Feasibility Phase Findings

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AUTHORSHIP CONTRIBUTIONS

N. A. Goldenberg designed and performed the research, provided scientific oversight, collected data, interpreted findings, drafted the manuscript, revised the manuscript, and approved its submission.

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W. R. Hiatt and M. J. Manco-Johnson contributed to the research design, provided scientific oversight, interpreted findings, reviewed and revised the manuscript, and approved its submission.

L. Z. Fenton contributed to the research design, analyzed data, interpreted findings, reviewed and revised the manuscript, and approved its submission.

N. V. Stence analyzed data, interpreted findings, reviewed and revised the manuscript, and approved its submission.

All other authors provided scientific oversight to the research, interpreted the findings, reviewed and revised the manuscript, and approved its submission.

In addition, S. Schulman served as Chair of the Steering Committee and N. A. Goldenberg served as Overall Principal Investigator.

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Abstract

BACKGROUND—Randomized controlled trials (RCTs) in pediatric venous thromboembolism (VTE) treatment have been challenged by unsubstantiated design assumptions and/or poor accrual. Pilot/feasibility (P/F) studies are critical to future RCT success.

METHODS—Kids-DOTT is a multicenter RCT investigating non-inferiority of a 6-week (shortened) vs. 3-month (conventional) duration of anticoagulation in patients <21 years old with provoked venous thrombosis. Primary efficacy and safety endpoints are symptomatic recurrent VTE at 1 year and anticoagulant-related, clinically-relevant bleeding. In the P/F phase, 100 participants were enrolled in an open, blinded endpoint, parallel-cohort RCT design.

RESULTS—No eligibility violations or randomization errors occurred. Of enrolled patients, 69% were randomized, 3% missed the randomization window, and 28% were followed in pre-specified observational cohorts for completely occlusive thrombosis or persistent antiphospholipid antibodies. Retention at 1 year was 82%. Inter-observer agreement between local vs. blinded central determination of venous occlusion by imaging at 6 weeks post-diagnosis was strong (κ-statistic=0.75; 95% confidence interval [CI] 0.48–1.0). Primary efficacy and safety event rates were 3.3% (95% CI 0.3–11.5%) and 1.4% (0.03–7.4%).

CONCLUSIONS—The P/F phase of Kids-DOTT has demonstrated validity of vascular imaging findings of occlusion as a randomization criterion, and defined randomization, retention, and endpoint rates to inform the fully-powered RCT.

Keywords

thrombosis; child; anticoagulants; clinical trial; pilot study; reliability and validity

INTRODUCTION

Venous thromboembolism (VTE) has become a major pediatric health concern, largely as a consequence of invasive support and intensive care of ill children and improved survival of children with chronic illnesses. Of VTE in children, 90–95% is considered provoked, based on association with an identifiable, typically-transient risk factor such as surgery, central

venous catheterization, or hospitalization for exacerbation of a medical condition. The occurrence of VTE in hospitalized children has risen by 70% over 6 years to approximately 1 in 200 [1], and the epidemic of obesity in children is anticipated to continue to amplify the problem and impact of VTE.

In both children and adults, treatment of VTE typically involves anticoagulation. However, none of the anticoagulants used in the routine clinical care of children with VTE is approved by federal regulatory agencies for this indication. Comorbidities and outcomes differ between children and middle-aged/elderly adults with VTE, yet recommendations for a 3-month course of anticoagulation for pediatric patients with provoked VTE [2] have been based on results of clinical trials in adults [3]. Pediatric guidelines also suggest that consideration be given to a shorter, 6-week course of anticoagulation in certain scenarios, albeit without evidence.[2] Prolonged anticoagulation poses a considerable risk of bleeding complications in children, while inadequate treatment duration is associated with a risk of recurrent VTE. The net clinical benefit of a given duration of anticoagulation compared with another has not been evaluated in a pediatric population.

To address this issue in a generalizable fashion that will inform future guidelines and care in pediatric and young-adult VTE requires large, multicenter RCTs. In the past, investigator-initiated trials involving prevention and/or treatment of pediatric venous or arterial thromboembolism were terminated due to futility or feasibility concerns [4–6]. This underscores the critical need for P/F studies to be conducted in order to validate design assumptions before executing fully-powered, definitive trials. Accordingly, the objective of the P/F phase of the Kids-DOTT trial was to evaluate, while maintaining the blind, key feasibility metrics and design assumptions on inter-observer reliability of radiological determination of venous occlusion, as well as recruitment, randomization, retention, protocol deviation, and endpoint rates.

PATIENTS AND METHODS

Study Design

The Kids-DOTT trial employs a parallel-cohort, randomized, open-label, blinded-endpoint (PROBE) design (www.clinicaltrials.gov NCT00687882) [7]. The primary aim of the trial is to compare the efficacy and safety of a three-month course versus a six-week course of anticoagulation for first-episode, provoked venous thrombosis in patients <21 years of age. A multicenter P/F phase was pre-specified to consist of the first 100 participants enrolled, with metrics described below. The Kids-DOTT trial was initially opened in 2007 at the University of Colorado (Aurora, CO, USA) with Institutional Review Board (IRB) approval as a limited, single-center pilot, with staged addition of further participating centers based upon Data and Safety Monitoring Committee reviews. From 2012–2013 the trial's Clinical Coordinating Center was transitioned to All Children's Hospital Johns Hopkins Medicine (ACH JHM, St. Petersburg, FL, USA). The study was approved by the local IRB at each participating site, with signed informed consent/assent required for patient participation. Recruitment in the P/F phase continued through December 2014, at which time the 100th participant was enrolled.

Subject Eligibility

Inclusion criteria for the P/F phase were the same as for the main trial, and included: (1) age from birth (post-conceptional age ≥36 weeks) to <21 years; (2) radiologic evidence of venous or right atrial thrombosis within 30 days, and 3) identification of a provoking clinical factor at time of diagnosis or symptom onset (e.g.: recent hospitalization, immobilization, or traumatic injury; central venous catheterization; oral contraceptive pill administration; major infection). The inclusion of young adults <21 years old along with children was based on the appreciation that many pediatric hospitals and thrombosis centers (particularly in the U.S.) take responsibility for the management of these young adult patients; in addition, the protocol utilized the National Institute of Health age definition for pediatrics (e.g., Policy on Inclusion of Children) as <21 years of age, consistent with the trial's early funding from the National Heart Lung and Blood Institute.

Exclusion criteria were: (1) prior VTE; (2) history of cancer; (3) congenital heart disease with history of single ventricle physiology or intra-cardiac shunt procedure; (4) known pulmonary embolism (other than septic embolism as in Lemierre's syndrome, which was allowed); (5) thrombolytic therapy; (6) plasma antithrombin activity <30 IU/dL or protein C or S activity <20 IU/dL. Of note, prior to 2013 the exclusion criteria also included the presence of ≥3 thrombophilia traits (or 2 in the presence of a first-degree family history of young-onset VTE); given evolution of the standard of care at participating sites toward no longer performing comprehensive thrombophilia testing in provoked VTE, it was recommended at the annual Investigator Meeting that this exclusion criterion be removed from the protocol. Considering the absence of screen failures due multi-trait thrombophilia, as well as the opportunity to optimize trial design during the pre-specified P/F phase, the Steering Committee subsequently adopted (and Data and Safety Monitoring Committee endorsed) this recommendation.

Treatment and Observations

All participants received anticoagulant therapy in accordance with American College of Chest Physician guidelines [2,8]. The schedule of assessments is provided in Table 1. Randomization occurred at the 6 +/− 1 week follow-up visit given that the study intervention consists of stopping versus continuing anticoagulation after an initial 6 weeks of therapy, and in order to afford determination at the time of study intervention as to complete occlusion by repeat imaging and persistence of antiphospholipid antibodies (APA) by follow-up testing of previously positive APA values. Patients in whom flow was demonstrated in the previously-involved venous segment(s) and who were without persistent APA (APA) were randomized to stop anticoagulation after 6 weeks of therapy, versus continue anticoagulation for a total of 3 months. Randomization was executed via the trial's vendor-hosted electronic data capture system (DATATRAK), utilizing a randomization code generated by a primary biostatistician and validated by an independent secondary biostatistician. Randomization was stratified by age group (<12 months, 12 months–<13 years, 13–<21 years) and anatomic site of thrombosis (lower extremity DVT, upper extremity DVT, cerebral sinovenous thrombosis, other). As previously described for the trial design [7], patients not eligible for randomization at the 6 week visit were subsequently followed in non-randomized parallel observational cohorts defined by occlusive thrombosis

or persistent APA, due to lack of equipoise among prospective investigators for these subpopulations to potentially receive shortened-duration anticoagulation (i.e., perceived heightened risk of recurrent VTE).

All participants were followed for the primary safety endpoint of anticoagulant-associated clinically-relevant bleeding and primary efficacy endpoint of symptomatic recurrent VTE at 1 year, in accordance with International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) definitions for endpoints in pediatric VTE research [9]. A secondary endpoint of post-thrombotic syndrome (PTS) using the Manco-Johnson instrument, as also described by the ISTH SSC [10,11].

Of note, the primary efficacy endpoint was initially defined at 2 years. However, in early 2014, the Data and Safety Monitoring Committee noted an increasing trend in loss-to-follow-up after the 1 year visit, and the Steering Committee then conducted a root cause analysis via survey of the participating site investigators. The principal cause was determined to be evolution in the standard of care toward discharge from follow-up after 1 year among pediatric and young adult patients with provoked venous thrombosis. Given the opportunity to optimize trial design afforded by the pre-specified P/F phase, the Steering Committee then recommended (and the Data and Safety Monitoring Board endorsed) modification of the protocol to capture the primary and secondary efficacy endpoints at 1 year. Endpoint definitions *per se* remained unchanged.

Quality Assurance

Quality assurance measures during the P/F phase included eligibility-type quality assurance and measurement-type quality assurance procedures. With regard to eligibility, the overall principal investigator performed real-time, remote source document verification of radiologic and laboratory reports from each subject's medical record. This procedure was utilized to minimize the risk of protocol deviations pertaining to eligibility, enrollment and subsequent randomization. As for measurement-type quality assurance, participating sites obtained brief video files to document dynamically (rather than via static images alone) the apposition of the walls of the vein during compression ultrasonography with Doppler. This quality assurance measure was designed to optimize the reliability of, and inter-observer agreement in, the determination of complete venous occlusion by ultrasound.

P/F Metrics

P/F metrics were as follows: 1) screened: enrolled ratio; 2) accrual rate; 3) frequency of protocol violations pertaining to eligibility criteria and randomization procedures; 4) inter-observer agreement in mutually blinded central versus local radiologist determination of presence/absence of complete veno-occlusion at 6 weeks post-diagnosis (a key randomization criterion); 5) proportion of the enrolled population comprising the non-randomized parallel cohorts; 6) retention rate for primary endpoint assessment at 1 year post-diagnosis; and 7) estimates of endpoint rates in the RCT population.

Key protocol assumptions tested in the pilot/feasibility phase related to sample size and endpoint rates. For the definitive trial, a target sample size of 750 had been estimated to

achieve 285 participants retained to the 1-year primary endpoint in each randomized arm (accounting for per-protocol assignment of patients with occlusive thrombosis or persistent APA at 6 weeks to non-randomized parallel cohort arms, as well as for withdrawals/drop-outs prior to 1 year [including withdrawals for eligibility violations or randomization errors]). Beyond their impact upon a feasibility metric of attrition, assessment of individual rates of randomization errors and protocol violations was left to the discretion of the Steering Committee toward its conclusion of trial feasibility. With respect to the analyzable RCT population, the protocol assumed a 25% attrition (non-randomizable proportion plus non-retention rate); these rate estimates had been developed and substantiated through early discussions of physician-investigator opinions and experiences at Investigators Meetings. Primary efficacy and safety endpoint rates were projected at 10% each, based upon evaluation of cumulative evidence from prior prospective research in the field, and estimation of clinically-relevant bleeding rate from published rates of major vs. minor bleeding. The Steering Committee determined that feasibility would be concluded if these protocol assumptions were upheld; in the case of endpoint rates, given the sample size of the pilot, we hypothesized that the 95% confidence interval of the observed rate for the primary efficacy and safety endpoints includes 10% each. (Formal net clinical benefit comparison of primary efficacy and safety endpoint rates between randomized arms was specified to occur at two formal interim analyses, conducted when n=200 and n=500 subjects reach the 1-year primary outcome assessment.) To conclude feasibility, the Steering Committee also required that the observed κ value for inter-observer agreement in radiological determination of occlusiveness exceed 0.7, based on a desire to indicate strong (“substantive”) agreement by Landis-Koch criteria [12].

Statistical analyses

Average recruitment rate was calculated based on the trial opening and closing dates at each clinical site. Descriptive analyses summarized frequencies with corresponding 95% confidence intervals (CIs), calculated by the Wald method. Inter-observer agreement was assessed by κ statistic.

RESULTS

Demographic characteristics, VTE-provoking factors, and distribution of thrombotic events by anatomic site in the 100 enrolled participants are shown in Table 2. The ratio of patients screened to enrolled was approximately 6:1, including declined consent in 4%. Sixty-nine percent of enrolled participants were randomized at the 6 +/− 1 week post-diagnosis visit (updated data at time of manuscript submission, 78%); 3% missed the randomization window. The remainder met criteria for non-random allocation at 6 weeks to parallel observational cohorts of complete veno-occlusion or persistent APA.

Following completion of an investigational drug sub-study of dalteparin [13], the average accrual was 0.18 (range: 0–0.76) participants per site per month, equivalent to an average accrual of 3.25 subjects per site per year. During this period of the trial, an average of 20 participating centers were open. There were no eligibility violations or randomization errors.

Protocol deviations due to missed randomization were infrequent, occurring in 3% of children.

Anticoagulation therapy is summarized in Table 3 for the acute (first week) and sub-acute (beyond one week) periods prior to the randomization visit. During the acute phase, unfractionated heparin (UFH) or low molecular weight heparin (LMWH, mainly enoxaparin, but occasionally dalteparin under an investigator-held Investigational New Drug application with the U.S. Food and Drug Administration),[13]) were most often employed. In the sub-acute period, LMWH was principally administered, with the vitamin K antagonist (VKA) warfarin used in 3%.

In 86 participants, radiological images obtained at 6 weeks post-diagnosis were suitable for blinded central adjudication; images were not available from a small number of participating centers due to technical limitations in complying with IRB requirements pertaining to the transfer of these imaging files. Inter-observer agreement in the determination of complete veno- occlusion was 97% (95% CI, 89–99%). κ-statistic for inter-observer agreement was 0.75 (95% CI, 0.48–1.0).

At the time of enrollment of the 100th patient on the trial (i.e., the pre-specified end of the pilot/feasibility phase), 73 participants had come due for the one-year endpoint visit, and the remaining 27 were not yet due for this visit. Among these 73, 60 completed a 1-year follow-up visit, resulting in a retention of 82% to the primary endpoint. The primary efficacy endpoint, symptomatic recurrent VTE at 1 year, was 3.3% (95% CI: 0.3–11.5%) in the randomized population. Anticoagulant-associated clinically-relevant bleeding, the primary safety endpoint, occurred in 1.4% (0.03–7.4%). Two percent (95% CI: 0.1–11.5%) of patients (1/46) with limb DVT were diagnosed with clinically-significant PTS (a secondary efficacy endpoint) upon assessment at 1 year, and an additional 13% (6/46) had non-clinically-significant PTS.

DISCUSSION

Our findings reported here from the P/F phase of the Kids-DOTT trial demonstrate the feasibility of identifying, enrolling, randomizing, and retaining pediatric and young adult patients in a multicenter RCT of VTE treatment, consisting of differing durations of anticoagulation. Protocol violations pertaining to eligibility or randomization were rare, confirming the effectiveness of the trial's quality assurance measures. Additionally, we found strong inter-observer agreement in the radiologic assessment of complete venous occlusion 6-weeks following initial diagnosis of VTE. Lastly, we determined primary efficacy and safety endpoint rates of 3.3% and 1.4% for symptomatic recurrent VTE and anticoagulant-associated bleeding, respectively, during the first year.

These findings confirm the Kids-DOTT design, based on a total sample size of approximately 800 patients (originally specified as 750, now revised with these data to 815), whose recruitment at 42 participating sites will be completed over a 4-year accrual period (enrollment of final patient estimated to be Summer 2019), to test the hypothesis of non-inferiority of a 6 week vs. 3 month duration of anticoagulation for provoked venous

thrombosis in patients <21 years old. Expansion to include international sites will enhance external validity (generalizability) and the potential to influence the standard of care for duration of anticoagulation in this population. As of early April 2015, 150 patients have been enrolled.

While awaiting the findings from the definitive trial, the P/F phase of Kids-DOTT provides among the most extensive RCT experience reported to date in the management of pediatric VTE, both in terms of the number of participating sites and size of the study population. In addition, the P/F findings from Kids-DOTT provide unique data on validity of radiologic assessment of complete venous occlusion, with implications for future research in the field. Given prior knowledge that the compression maneuver is critical to the diagnostic performance of compression ultrasonography for DVT [14], it is likely that the capture of brief dynamic video imaging during compression ultrasonography with Doppler contributed substantively to our findings of high inter-rater reliability. Similarly, we attribute the paucity of protocol deviations related to eligibility violations at least in part to the real-time, remote source document verification as an additional key quality assurance measure that will be maintained during the main Kids-DOTT trial.

Though bounded by wide confidence intervals, preliminary observations of symptomatic recurrent VTE and clinically-relevant bleeding event rates in this P/F phase of the Kids-DOTT trial are low in comparison with findings in the Canadian REVIVE trial conducted in the 1990s--the only other published RCT of pediatric VTE treatment. REVIVE evaluated the LMWH reviparin, versus UFH followed by VKA, in the three-month treatment of a first VTE (provoked or unprovoked) in children aged >3 months and <18 years. Among 78 children enrolled prior to early closure of the trial for poor accrual, the cumulative incidences of recurrent VTE (including both symptomatic and asymptomatic events) and major bleeding at 6 months post-diagnosis were each approximately 6% for reviparin, as compared to nearly 13% each for UFH/VKA. A number of non-randomized, uncontrolled trials have been reported, predominantly phase 2 studies of specific anticoagulants [15–18], providing additional insight about short-term risks of recurrent VTE and major/clinically-relevant bleeding that were concordant with the one-year risks reported here for Kids-DOTT. Notably, given that neither REVIVE nor non-randomized trials to date have employed PTS as an additional endpoint, the PTS findings from the P/F phase of Kids-DOTT represent unique trial-derived data on PTS in children.

Limitations of the present work include the fact that recruitment assessment is limited to this the most informative time period during the P/F phase when the investigational drug sub-study had been completed and most but not all of the planned centers were open and active. This may have led to an imprecise estimate of future accrual. In addition, the low event rates present a limitation and challenge for the main trial. While the 95% CI for the observed risk of recurrent VTE from the P/F phase included a value of 10% (the assumption in the protocol), the upper bound of the 95% CI for the observed risk of clinically relevant bleeding was a bit lower than 10%. Despite this finding, and recognizing that this was the only assumption not met in the P/F study and that this endpoint estimate was still imprecise due to the relatively small sample size to date, the Steering Committee determined that the trial should proceed directly into the “rest-of-trial” phase. However, as a consequence of the

low event rates, the Steering Committee and lead trial biostatistician (JMK) are working with the Data and Safety Monitoring Committee to develop additional stopping criteria pertaining to low event rates in the statistical analysis plan for the two pre-specified interim analyses, should these event rates continue to be low as the main trial expands. These stopping criteria will employ the bivariate endpoint analysis model described previously for the Kids-DOTT trial interim analyses [19]. A third limitation of the study is participant retention to the primary endpoint, which (at 82%) should be improved. Accordingly, the Clinical Coordinating Center is working with sites to adopt additional quality assurance measures, including heightened surveillance of enrolled subjects' electronic health record for events that should prompt study endpoint visits, and approaches to enhanced adherence to long-term follow-up visits (including participant remuneration for travel/time). Lastly, the fact that a few of the eligibility criteria, as well as the long-term follow-up visit selected for the primary endpoint, were refined over time may be construed as a weakness of the trial. However, these adaptations were carefully reviewed by the Steering Committee and the Data and Safety Monitoring Committee prior to implementation, in order to assure that they did not substantively alter the enrolled population, and we believe that this ability to refine the trial is a key advantage of having pre-specified this P/F phase within the overall trial design.

Notwithstanding these limitations, the P/F phase of the Kids-DOTT trial provides a key contribution to the VTE field in demonstrating validity of vascular imaging findings of occlusion. It has also defined recruitment, randomization, retention, and endpoint rates to inform the fully-powered trial on duration of anticoagulation for provoked venous thrombosis in patients <21 years old. Regardless of its results, successful completion of the main trial will inform the standard of care for this growing population, toward achieving optimal outcomes.

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CONFLICT OF INTEREST DISCLOSURES:

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C. M. Kessler receives consulting fees for advisory, data and safety monitoring board and/or steering committee activities from Baxter Immuno, Bayer Healthcare, CSL Behring, Eisai, NovoNordisk, Octapharma, Pfizer and sanofi-aventis, and honoraria from CPC Clinical Research for academic thought-leadership via the ATLAS Group. Georgetown University receives research support on his behalf from the National Institutes of Health, the Maternal and Child Health Bureau and the Centers for Disease Control and Prevention, as well as from Amgen, Baxter Immuno, Eisai, Genentec, GlaxoSmithKline, Griffols, NovoNordisk, Octapharma and sanofi-aventis.

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S. Carpenter reports affiliations with Bayer, Bristol-Meyers Squibb and Eisai as multi-centre trial sites, outside the submitted work.

M. Rajpurkar reports consultancy work for Bayer and Pfizer.

APPENDIX

Kids-DOTT participating site Principal Investigators who contributed data on enrolled patients during the P/F phase were as follows (alphabetically by site): *All Children's Hospital Johns Hopkins Medicine* (N. Goldenberg), *Blood Center of Wisconsin* (R. Punzalan), *Children's Hospital Colorado/University of Colorado Denver* (M. Wang/N. Goldenberg), *Children's Hospital of Los Angeles* (J. Jaffray/G. Young), *Children's Hospital of Michigan/Wayne State University* (M. Rajpurkar), *Children's Mercy Hospitals* (S.

Carpenter), *Children's National Medical Center/George Washington University* (Y. Diab/N. Verdun), *Cincinnati Children's Hospital Medical Center* (C. Tarango), *Cohen Children's Medical Center* (S. Acharya), *Cook Children's Medical Center* (M. Torres), *New York-Presbyterian/Weill Cornell Medical Center* (N. Kucine/B. Mitchell), *Duke University Medical Center* (N. Shah/C. Thornburg), *Johns Hopkins Bloomberg Children's Center* (C. Takemoto), *Michigan State University* (R. Kulkarni), *Nationwide Children's Hospital* (S. O'Brien), *Oregon Health & Science University* (K. Haley/M. Recht), *Phoenix Children's Hospital* (C. Knoll), *Rady Children's Hospital* (C. Thornburg/A. Geddis), *Rainbow Babies and Children's Hospital* (S. Ahuja), *Rush University Medical Center* (M. Simpson), *Texas Children's Hospital/Baylor University* (L. Srivaths), and *University of Texas Southwestern/ Children's Medical Center Dallas* (J. Journeycake/A. Zia).

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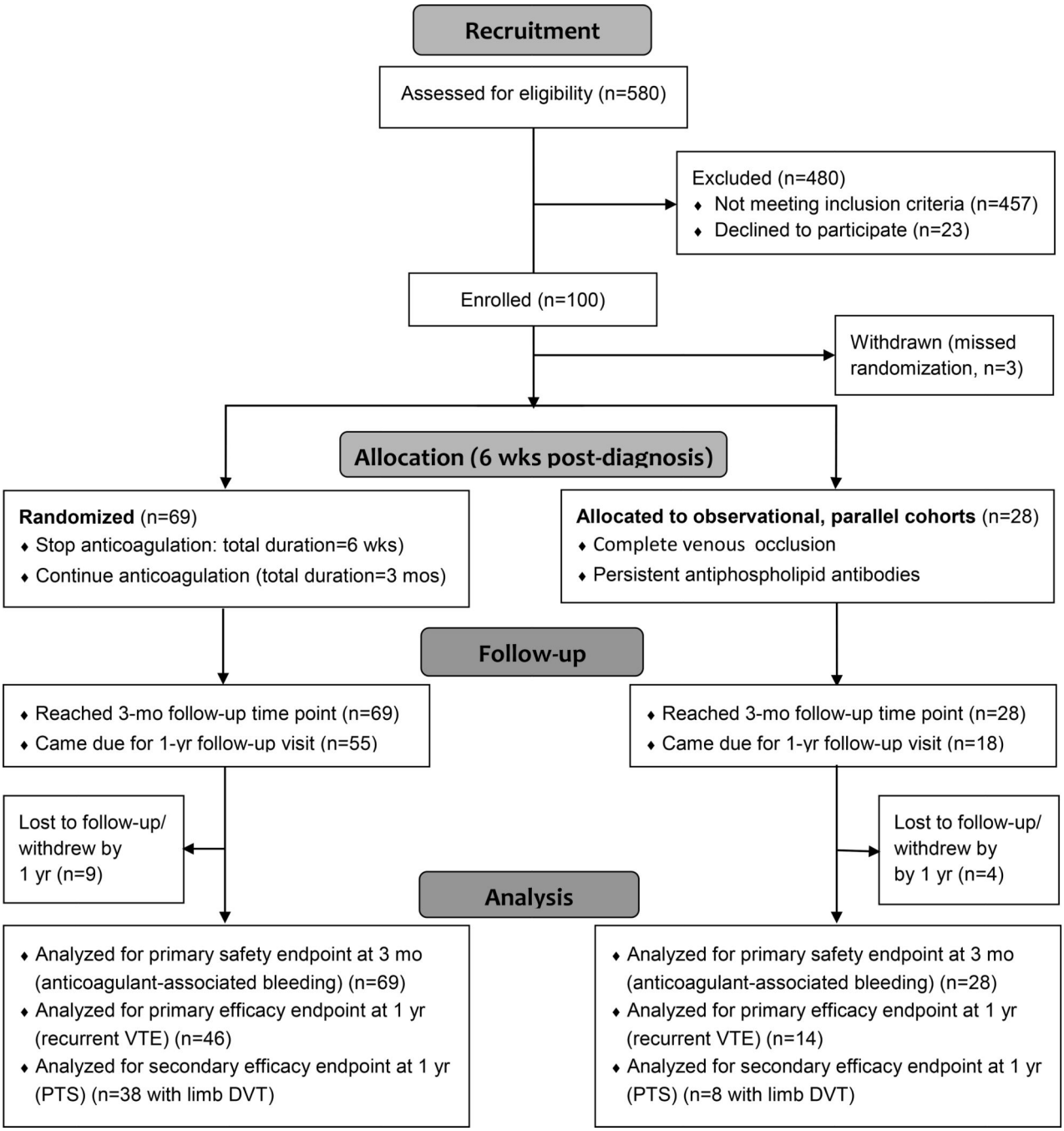

Figure 1.

Flow-diagram reflecting screened and enrolled populations and disposition of enrolled subjects over the course randomization and follow-up.

Table 1

Schedule of assessments.

Assessment Performed	Screening Visit 1	Clinic Follow-up Visit 2	Telephone Follow-up Visit 3	Clinic Follow-up Visit 4	Telephone Follow-up Visits 5, 6	Clinic Follow-up Visit 7	Clinic Follow-up Visits 8, 9
	Within 30 days diagnosis	6 weeks +7 / −5 days post-diagnosis	8 weeks +/− 7 days post-diagnosis	12 weeks +/− 10 days post-diagnosis	4 months and 5 months +/− 10 days post-diagnosis	6 months +/− 14 days post-diagnosis	1 year and 2 years +/− 30 days post-diagnosis
Informed consent	X						
Full medical history	X	X		X		X	X
Physical exam	X	X		X		X	X
Laboratory testing	X[a]	X[b,c]		X[b,c]			
Web-based data collection	X	X	X	X	X	X	X
Recurrent VTE history		X	X	X	X	X	X
Bleeding history	X	X	X	X	X	X	X
PTS evaluation						X	X*
AEs assessment		X	X	X			
Eligibility Review		X					
Randomization		X					

[a] Protein C; protein S; antithrombin; antiphospholipid antibodies (APA) as follows: lupus anticoagulant; anticardiolipin IgM, beta-2-glycoprotein-1 IgG and IgM

[b] Blood sampling for research (global assays and prognostic biomarker discovery/validation) as well as plasma and DNA/RNA biobanking (for patients who consent).

[c] Repeat testing of antiphospholipid antibody testing, if positive at the previous time point.

Table 2

Demographic characteristics, distribution of index venous thrombotic events by anatomic site, and relationship of thrombosis to central venous catheterization in the randomized and non-randomized (parallel cohort) study populations.

Variable		Randomized (N=69)	Not Randomized (N=31)	Total (N=100)
Sex				
Male	N (%)	39 (56.5)	20 (64.5)	59 (59.0)
Female		30 (43.5)	11 (35.5)	41 (41.0)
Ethnicity				
Hispanic	N (%)	12 (17.4)	7 (22.6)	19 (19.0)
Non-Hispanic		56 (81.2)	21 (67.7)	77 (77.0)
Unknown		1 (1.4)	3 (9.7)	4 (4.0)
Race				
White	N (%)	50 (72.5)	24 (77.4)	74 (74.0)
Black		10 (14.5)	5 (16.1)	15 (15.0)
Other Race		6 (8.7)	1 (3.2)	7 (7.0)
Asian		2 (2.9)	0 (0.0)	2 (2.0)
American Indian		0 (0.0)	1 (3.2)	1 (1.0)
Unknown		1 (1.4)	0 (0.0)	1 (1.0)
Age at Enrollment				
Years*	N	69	31	100
	Mean (SD)	7.9 (7.0)	7.8 (7.6)	7.9 (7.1)
Index Thrombosis Anatomical Site				
LE DVT	N (%)	27 (39.1)	19 (61.3)	46 (46.0)
UE DVT		17 (24.6)	5 (16.1)	22 (22.0)
CSVT		18 (26.1)	2 (6.5)	20 (20.0)
Other		7 (10.1)	5 (16.1)	12 (12.0)
Index Thrombosis Catheter-Related				
Yes	N (%)	32 (46.4)	14 (45.2)	46 (46.0)
No		37 (53.6)	17 (54.8)	54 (54.0)

* Data were parametrically (i.e., normally) distributed.

Table 3

Anticoagulant agent use in the randomized population, by acute (first week) and sub-acute (after first week) period post-diagnosis of index venous thrombotic event.

Acute period		
LMWH	N (%)	43 (67.2)
UFH		20 (31.3)
Other*		1 (1.6)
Sub-acute period		
LMWH	N (%)	62 (95.4.9)
Warfarin		2 (3.1)
Other*		1 (1.5)

Abbreviations: LMWH, low molecular weight heparin; UFH, unfractionated heparin.

*Consisted of fondaparinux.