Venous thromboembolism (VTE) in children is an important clinical concern for which risk factors include clinical conditions that incite venous stasis, endothelial damage, or thrombophilia (i.e., hypercoagulability) states. Acquired thrombophilia and markers of coagulation activation are common in pediatric VTE, while potent genetic thrombophilia states are less frequently encountered; nevertheless, the latter are more likely to present in the pediatric age than in older adulthood. Sequelae of VTE and its treatment in childhood survivors include bleeding, persistent or progressive thrombosis, recurrent VTE, and (when venous return from a limb is affected) the development of post-thrombotic syndrome (PTS). The focus of the present review is to discuss the role of tests of thrombophilia and coagulation activation as key predictors of outcome in this disease. Based upon this understanding, coupled with existing knowledge of clinical prognostic factors, new risk-stratified approaches of antithrombotic therapy have emerged for clinical investigation in the field of pediatric VTE.

Introduction
In neonates and children, greater than 90% of venous thromboembolism (VTE) have one or more identified risk factors. The etiology of pediatric VTE is often multifactorial, with risk factors comprising one or more components of Virchow’s triad of venous stasis, endothelial damage, and the hypercoagulable state (i.e., thrombophilia). Prevalent clinical prothrombotic risk factors in childhood include the presence of an indwelling central venous catheter, infection, dehydration, underlying malignancy or disorder for which bone marrow transplantation was undertaken, congenital cardiac disease and its corrective surgery, other surgery/trauma, and family history of VTE. Blood-based risk factors for VTE in children include both inherited and acquired thromboembolic conditions and markers of coagulation activation. As subsequently discussed in this review, acquired thrombophilia and markers of coagulation activation are common in pediatric VTE, while potent genetic thrombophilia states are less frequently encountered; nevertheless, the latter are more likely to present in the pediatric age than in older adulthood.

With regard to outcomes of pediatric VTE, acute complications consist of antithrombotic therapy–associated bleeding, thrombus progression, limb/organ infarction, pulmonary embolism, and death. Chronic sequelae have been recently reviewed and include persistent thrombosis following an appropriate course of anticoagulant therapy, recurrent VTE, and the development of PTS. In children with VTE onset beyond the neonatal period, VTE-specific mortality has ranged from 0 to 2%. The cumulative incidence of recurrent VTE at 1 to 2 years follow-up has been reported at 6% to 13%. By comparison, using Kaplan-Meier analysis, the Dutch pediatric VTE registry has indicated a probability of VTE recurrence-free survival of 84% at 1 year, 81% at 3 years and 77% at 7 years.

Persistent thrombosis has been associated with the development of venous valvular insufficiency, a key precursor to post-thrombotic syndrome. Persistent thrombosis despite adequate anticoagulant therapy, has been demonstrated in 12% of premature infants, as many as 62% of neonates, and between 37% and 68% of older children with VTE. The post-thrombotic syndrome has been documented in 33% of children at a median follow-up period of 1 year following acute venous thrombosis involving the limbs in a recent cohort study in the U.S. and in 70% of children at 2 years in the Dutch registry analysis. PTS has gained increasing attention in pediatrics in recent years, and a standardized pediatric PTS outcome instrument (em-
ployed in the former study\textdagger{\textdagger} has recently been validated.\textdagger{\textdagger} Given long-term risks for persistent thrombosis, recurrent VTE, and PTS, VTE may best be conceived not as an acute event, but as a chronic disease in children.

To date, few studies have rigorously investigated predictors of VTE outcome in children. While clinical factors such as obesity,\textdagger{\textdagger} persistence of thrombosis following a conventional duration of anticoagulation,\textdagger{\textdagger} use of graduated compression stockings,\textdagger{\textdagger} and acute thrombolytic therapy\textdagger{\textdagger} have each been established as outcome predictors with respect to PTS and/or recurrent VTE in adults, only thrombolytic therapy\textdagger{\textdagger} and complete veno-occlusion\textdagger{\textdagger} have been systematically studied and shown prognostic value within the framework of a cohort study or clinical trial of VTE in children. With regard to laboratory-based risk factors, as discussed in detail in this review, evidence has accumulated (albeit limited in some instances) for the association of potent inherited thrombophilia states (e.g., homozygous factor V Leiden or prothrombin polymorphisms, severe deficiency of intrinsic anticoagulants), persistent antiphospholipid antibodies (APA) and the APA syndrome (APAS), and markers of coagulation activation (specifically, elevated FVIII activity and D-dimer levels) with thrombotic outcomes such as PTS and recurrent VTE in children and/or adults. Further work remains in order to identify additional predictors as well as to focus assessment of predictors from the general VTE population to select VTE subgroups and risk strata of interest.

**Definition of Objective and Methods**

The purpose of this educational manuscript is to discuss the role of tests of thrombophilia and coagulation activation as key predictors of outcome in pediatric VTE, with comparison with evidence in adults. As an educational manuscript, this work does not reflect systematic review methodology, but rather serves as a survey of the literature. While efforts were taken to highlight the available evidence without bias, the interested reader is encouraged to conduct additional review of the literature.

**Outcome Predictors in VTE: Thrombophilia States and Markers of Coagulation Activation**

**Evidence in adults**

***Inherited deficiencies of, or resistance to, intrinsic anticoagulant function***

Severe congenital deficiencies of intrinsic anticoagulants (e.g., proteins C or S, antithrombin) are rare, but constitute powerful prothrombotic risk factors.\textdagger{\textdagger} Testing for protein C and antithrombin (AT) activities is typically performed by chromogenic assay, whereas that for protein S activity commonly employs ELISA for free (i.e., unbound to C4b binding protein) protein S antigen.

While inherited deficiencies of intrinsic anticoagulants are well-established as risk factors for a first VTE event, the magnitude of risk of recurrent VTE in these settings is less clearly defined. A retrospective cooperative European study reported in 1996 demonstrated a recurrence rate of greater than 60% over an unspecified duration of follow-up,\textdagger{\textdagger} which is nevertheless considerably higher than historical recurrence rates for non-deficient patients with first-episode VTE. Subsequently, a Dutch family cohort study of anticoagulant deficiencies revealed 1- and 5-year recurrent VTE risks of 10% (95% confidence interval, 1%-19%) and 23% (95% confidence interval, 10%-36%), respectively, and annual rates of recurrent VTE that were reduced by long-term anticoagulation as secondary prophylaxis;\textdagger{\textdagger} determination of whether these recurrence risks differ significantly from those of non-deficient patients with VTE is hindered by the lack of such a concomitant comparison group.

In 2005, a prospective cooperative European study was published that suggested a reduction in the risk of recurrent VTE among patients with inherited thrombophilias who did, versus did not, receive long-term anticoagulation following a first VTE episode;\textdagger{\textdagger} however, in that study, the annual incidence of recurrent VTE among patients who received standard-duration anticoagulation (at 5% per year) is not substantially different from historical data of similarly-treated, unselected adults with first-episode VTE. Recent retrospective analysis in patients with recurrent VTE has suggested a mildly increased risk of recurrent VTE over time in AT-deficient patients as compared to those without inherited thrombophilia.\textdagger{\textdagger} No increase in recurrence risk was detected for protein C and S deficiencies. However, no discrimination based upon severity of deficiency was reported, and it is possible that, because subjects treated longer than 6 months for the first VTE episode were excluded, the study may have been biased toward patients with mild deficiency states. Notably, in all of the aforementioned studies of recurrence risk associated with intrinsic anticoagulant deficiency, the proportion of the study population that was of pediatric age was unspecified; hence, the applicability of the findings to children is unclear.

The G1691A polymorphism in the factor V (FV) gene (FV Leiden),\textdagger{\textdagger} present in approximately 5% of healthy Caucasian individuals, is the leading cause of inherited activated protein C resistance (APCR) among Caucasians. Population-based and cohort-derived case-control studies in adults suggest that, when present in heterozygous form, this trait is associated with a 2- to 7-fold increased risk of first-episode VTE;\textdagger{\textdagger} pediatric findings are comparable.\textdagger{\textdagger} Other factors may magnify the prothrombotic risk; hence, the risk of recurrent VTE associated with FV Leiden. For example, the use of oral contraceptives by women who are FV Leiden heterozygotes is estimated to increase the risk of VTE by 35 times.\textdagger{\textdagger} The addition of standard-dose estrogen oral contraceptive pill to an underlying heterozygous
FV Leiden (in large part by virtue of a “double-hit” to the protein C pathway) can be estimated to increase the risk for VTE, for example, from a baseline risk of 15 per 10,000 U.S. females aged 15 to 17 years per year to a risk of over 500 per 10,000 (or 5%) per year.

The risk of recurrent VTE among patients heterozygous for FV Leiden remains unclear but may be modestly increased according to a recent meta-analysis. By comparison, early retrospective data with variable follow-up duration in a small number of FV Leiden homozygotes suggested a more substantial increase in risk of recurrent VTE relative to heterozygotes and non-carriers, and was subsequently confirmed by prospective findings of an approximately 2-fold increase in risk for recurrent VTE at 2 years (cumulative probability of recurrence at that time of 20% among homozygotes as compared to less than 10% in non-carriers).

**Increased procoagulant factor activity**

The factor II (i.e., prothrombin) G20210A polymorphism (PT G20210A), found in approximately 2% of Caucasians, is associated with elevated prothrombin levels and appears to confer a 2-fold increase in risk of first-episode VTE based upon epidemiologic studies. Currently, the risk of recurrent VTE among patients heterozygous or homozygous for PT G20210A polymorphism remains unclear; one prospective study found no increase in risk for recurrent VTE among prothrombin polymorphism heterozygotes as compared to non-carrier controls, and was not able to assess the recurrence risk for homozygotes due to their absence in the study population. While one recent meta-analysis found no increase in risk of recurrent VTE among PT G20210A homozygotes, another suggested a mild increase in recurrence risk of 1.4-fold.

Elevated plasma factor VIII (FVIII) activity has been defined in adult studies as a common thrombophilia state (found in approximately one-third of VTE patients) that in many instances appears to reflect constitutively increased expression not due to acute phase response, with a tendency to be familial. Currently, however, no prevalent polymorphism leading to elevated FVIII levels has been identified. Initial work established elevated FVIII activity as a risk factor for first-episode VTE. A pivotal study published in 2000 by Kyrle et al has established the association of elevated plasma levels of FVIII following completion of a conventional course of anticoagulation with recurrent VTE in adults, with an approximately 8% increase in risk of recurrence with each 10 U/dL increase in FVIII in the study population.

**Biochemical mediators of endothelial damage: hyperhomocysteinemia, APA, and the APAS**

Prompted by historical findings of a high prevalence of vascular events associated with severe hyperhomocysteinemia in patients with homocysteinuria, elevated plasma concentration of homocysteine has been identified as a mild risk factor for first-episode VTE, with a 3-fold increase in VTE risk defined via meta-analysis. Unfortunately, studies analyzed generally did not generally evaluate for an independent effect of hyperhomocysteinemia after adjustment for other thrombophilias, nor distinguish between acquired and congenital causes of hyperhomocysteinemia among evaluated subjects. Nevertheless, additional work has indicated that patients with hyperhomocysteinemia have a 2- to 3-fold increased risk of recurrent VTE.

When APA are identified in a patient with VTE on two venipuncture specimens 12 or more weeks apart, this meets recently-proposed consensus criteria for APAS. Predictors and correlates of APAS, especially when primary (i.e., not due to underlying chronic inflammatory condition), are poorly understood. By contrast, APAS is well established as a risk factor for recurrent thrombotic events. Early data from a prospective cohort study of patients with APAS and prior thrombotic events demonstrated that, in the absence of antithrombotic therapy, the cumulative probability of recurrent thrombotic events was approximately 50% at 2 years, and only approximately 2% at 2 years in patients treated with standard-intensity warfarin of variable duration. However, no concomitant non-APAS VTE control group was studied. A large prospective study in adults conducted by Schulman and colleagues and published in 1998 demonstrated a 2-fold risk of recurrent VTE at 4 years among patients with positive ACA testing following completion of a conventional course of anticoagulation for first-episode VTE, unfortunately, due to the single ACA testing time point, the APA-positive study subjects may have differed from those defined as having APAS by current consensus criteria. A more recent prospective cohort study of adults with a diagnosis of primary APAS (which included history of a first thrombotic episode or fetal loss, wherein patients with a history of VTE had been treated with anticoagulation for 3 to 12 months) demonstrated that high-titer ACA (i.e., > 40 GPL-U) was an independent risk factor for subsequent VTE or arterial thrombosis. However, inspection of the published data from this study reveals that, among patients with prior VTE, the cumulative incidence of recurrent VTE at 5 years was 13% (4/31), which is not substantially higher than historical recurrence rates for non-APAS adults with prior VTE; however, if lag time from prior VTE episode to study enrollment and cohort observation was substantial, this could have artifically reduced the perceived “5-year” recurrence risk, given that risk of recurrent VTE generally decreases with time following an initial VTE episode. Interestingly, recurrent VTE has most often occurred in APAS patients when off anticoagulation, as recently observed in a randomized controlled trial conducted by Crowther and group.
Multi-trait thrombophilia
Evidence for prognostic significance of multi-trait thrombophilia with respect to VTE recurrence has prompted some experts to espouse comprehensive thrombophilia testing among unselected individuals with first-episode VTE. In two Italian retrospective cohort studies of first-episode VTE, patients heterozygous for both FV Leiden and PT G20210A polymorphism exhibited a 2.6-fold increase in VTE recurrence risk relative to carriers of FV Leiden alone\(^5\) and a 5-fold increased recurrence risk when compared with patients with VTE without thrombophilia.\(^4\) A later retrospective nested case-control study of adult Dutch patients with VTE with FV Leiden demonstrated in 2001 that patients with recurrent VTE had a 9-fold increased odds of carrying the PT G20210A polymorphism, and an approximately 5-fold increased odds of hyperhomocysteinemia.\(^5\) While duration of anticoagulant therapy was not controlled in these retrospective studies, the Dutch study showed no significant difference in therapy duration between groups with and without recurrence. It is also notable that the number of patients with combined inherited thrombophilias in each of these studies (as expected based upon the prevalence of each trait) was rather small, such that risk estimates for recurrent VTE exhibited wide confidence intervals.

Markers of coagulation activation: D-dimer
D-dimer is a by-product of fibrin degradation that has been positively correlated with fibrin production and thrombin generation, and hence serves as a useful marker of coagulation activation. Several key prospective studies have established the prognostic role of D-dimer in adult VTE. In the 1990s, elevated plasma concentration of D-dimer following a conventional course of anticoagulation was associated with an increased risk of recurrent VTE, while normal values had a strong negative predictive value.\(^5\) More recently, the institution of extended anticoagulation in patients with persistently elevated D-dimer levels upon completion of a conventional course of anticoagulation was shown in a double-blind randomized controlled clinical trial of adult idiopathic VTE patients to decrease the risk of recurrent VTE relative to conventional-duration anticoagulation.\(^5\)

Evidence in children

Inherited deficiencies of, or resistance to, intrinsic anticoagulant function
Severe congenital deficiencies of intrinsic anticoagulants typically are manifest in neonatal purpura fulminans and VTE in early childhood.\(^6\) These inherited deficiencies must be distinguished from acquired anticoagulant deficiencies in children, which are especially common in clinical settings of severe infection or significant coagulation activation. For example, protein C may be consumed in disseminated intravascular anticoagulation,\(^6\) protein S activity may be reduced by inhibitory antibody production in acute varicella infection,\(^6\) and antithrombin may be reduced in veno-occlusive disease (i.e., sinusoidal obstruction syndrome) of the liver following bone marrow transplantation.\(^6\)

In 2001, Nowak-Göttl and colleagues published cohort findings of an increased risk of recurrent VTE among neonates and children with spontaneous VTE who had inherited protein C deficiency and resistance states.\(^6\) Protein C deficiency and heterozygous FV Leiden were each associated with approximately a 4-fold risk of recurrent VTE, while for homozygous FV Leiden, the increase in recurrence risk was 6-fold. In other work, Kenet and collaborators in Europe have recently shown in a multicenter cohort study of pediatric patients with cerebral sinovenous thrombosis (CSVT) that FV Leiden does not appear to be associated with an increased risk for recurrent VTE.\(^6\)

Biochemical mediators of endothelial damage: hyperhomocysteinemia, APA, and APAS
While hyperhomocysteinemia has been established as an important risk factor of a first VTE event stemming from pioneering outcomes research in cystathionine beta-synthase deficiency (wherein the likelihood of first-episode vascular event was estimated at 50% by 30 years of age),\(^6\) no studies have established the risk of recurrent VTE in children with hyperhomocysteinemia.

With regard to APA, these antibodies (and the lupus anticoagulant in particular) are perhaps the most common thrombophilic risk factor for VTE in children.\(^6\) The lupus anticoagulant is often present in association with acute infection and/or inflammation in children, and hence its presence in plasma is typically transient. Among children with systemic lupus erythematosus (SLE), patients with the lupus anticoagulant who demonstrate activated protein C resistance may be at heightened risk for thrombotic events.\(^6\) As in adults, despite some limitations in quality of evidence, studies in children have suggested that APAS is associated with a heightened risk of recurrent thrombotic events.\(^6,7\) An Israeli retrospective cohort study has shown recurrent thrombosis in 7 (nearly 30%) of 24 children with APAS who had a prior history of thrombosis, after an average follow-up of nearly 6 years.\(^7\) Whether APAS criteria and the associated risk of VTE established among adults (primarily those with SLE) applies equally to children merits devoted pediatric investigation, given the prevalence of this condition and its implications for extended anticoagulant management.

Multi-trait thrombophilia
The relationship between multi-trait thrombophilia and VTE outcome has not been well-studied in children. In the German spontaneous VTE cohort publication in 2001, an increased risk of recurrent VTE was found in neonates and...
older children who had 2 or more inherited thrombophilia traits when compared to 1 or none, with cumulative probabilities of recurrent VTE at 2 years of approximately 20%, 10%, and 0%, respectively. In multivariate analyses, the adjusted odds of recurrent VTE were increased markedly (specifically, 24-fold) among pediatric patients with multi-trait thrombophilia, relative to those without thrombophilia.

**Increased procoagulant factor activity and markers of coagulation activation**

In a collaborative European cohort study, Kenet et al evaluated predictors of recurrent VTE among pediatric patients with CSVT, demonstrating that the PT G20210A polymorphism was independently associated with VTE recurrence risk, which was increased approximately 4-fold in the presence of this trait. This study was also important in its finding of non-administration of anticoagulation as an additional independent predictor of recurrent VTE in pediatric patients with CSVT.

With regard to FVIII, it is likely that elevated activity of this procoagulant factor is frequently due to acute phase response, given the high prevalence of acute infection and other underlying pro-inflammatory states in pediatric VTE. As for markers of coagulation activation, D-dimer is often non-specifically elevated in the presence of infection and systemic inflammation. Nevertheless, prompted by the aforementioned evidence of an association with recurrent VTE for elevated plasma levels of FVIII and D-dimer in adult studies, the present author and colleagues evaluated the relationship between thrombotic outcomes and these laboratory markers in a pediatric cohort who underwent standardized long-term follow-up, including serial radiologic and PTS assessments.

In multivariate analysis, plasma levels of FVIII activity greater than 150 IU/dL, D-dimer greater than 500 ng/mL, or both, at diagnosis of thrombosis were associated with a nearly 9-fold risk (and following completion of 3 to 6 months of anticoagulant therapy, a 4-fold risk) of adverse thrombotic outcome, including persistent thrombosis, recurrent VTE and/or the development of PTS. It is worthy of note that, while this level of FVIII is not uniformly elevated across the pediatric age spectrum, and hence cannot be assumed to confer a risk of incident VTE, it was nevertheless informative with respect to risk of adverse outcomes of incident VTE. When both markers were above the threshold at diagnosis, this was 91% specific for a poor thrombotic outcome, and could increase the likelihood of a poor outcome from a pre-test probability of, for example, approximately 50% to a post-test probability of nearly 90%.

In 2006, Nowak-Göttl and colleagues published an analysis of FVIII in children of mixed study design in which FVIII activity was shown to be elevated among VTE cases relative to controls. While exploratory analyses did not demonstrate an increase in odds of PTS for each U/dL increase in FVIII activity, the frequency of PTS was low in this cohort, at 8%, such that a relationship between elevated FVIII activity and risk of PTS could not be definitively evaluated.

**Additional unresolved issues: Global hypercoagulability and hypofibrinolytic function**

Given evidence in both children and adults for a relationship between thrombotic outcomes and elevated FVIII and D-dimer levels following completion of a conventional course of anticoagulation for thrombosis, it may be more generally hypothesized that persistent hypercoagulability or hypofibrinolysis at the time of planned cessation of anticoagulant therapy may portend a poor prognosis, especially with respect to recurrent VTE. Similarly, patients with chronic hypofibrinolytic states may be at heightened risk for failure of thrombus resolution following a conventional course of anticoagulation as well as predisposed to recurrent VTE events. Present comprehensive thrombophilia testing approaches employed in routine care, however, do not evaluate overall coagulative function, and assessment of overall fibrinolytic potential by euglobulin lysis time is often omitted from an otherwise comprehensive thrombophilia evaluation. A few so-called “global” assays designed to detect both hypercoagulability and reduced fibrinolytic capacity have indeed been developed, including the thromboelastogram, the Overall Hemostasis Potential assay, and the Clot Formation and Lysis assay. The use of such assays in future prospective cohort studies and clinical trials may offer additional important information on prediction of VTE outcomes in children and adults alike.

**Conclusion: Risk-Stratified Approaches of Antithrombotic Therapy in Pediatric VTE**

As VTE and prothrombotic conditions are becoming increasingly recognized in children, the appropriate laboratory evaluation for thrombophilia has emerged as a frequent concern for the clinician. While no single battery of tests can be expected to apply equally to all children with VTE, comprehensive thrombophilia evaluation is recommended in these children. In the future, validated global assays of overall coagulative and fibrinolytic capacities may provide an initial diagnostic evaluation tool to direct more specific testing. Given that persistent thrombosis and the development of the post-thrombotic syndrome are demonstrated with high frequency during long-term follow-up, the conception of VTE in children has now evolved from that of an acute event to one of chronic disease. However, recent findings that some laboratory thrombophilia tests, such as plasma levels of FVIII and D-dimer, may be useful in predicting these pediatric thrombotic outcomes provides optimism that a risk-stratified approach to intensity and duration of antithrombotic therapy may soon be established.

Recently, the present author and colleagues applied prognostic indicators available at VTE diagnosis in chil-
Children (namely, veno-occlusiveness and FVIII and D-dimer biomarker status) toward the evaluation of intensity of acute antithrombotic therapy in a risk-stratified paradigm of pediatric VTE management. From within the aforementioned cohort study, 22 children with VTE perceived to have an a priori high risk of PTS by virtue of completely veno-occlusive DVT of a proximal lower extremity in association with elevated FVIII or D-dimer, and who were treated acutely either with a thrombolytic regimen followed by standard anticoagulation or via standard anticoagulation without initial thrombolysis, were evaluated for PTS outcomes at 18 to 24 months follow-up using a concomitantly validated pediatric PTS outcome instrument. The thrombolytic regimen was comprised of either local pharmacomechanical thrombolysis (LPMT) via an interventional radiologic approach or systemic low-dose (0.03-0.06 mg/kg/hr) tissue-type plasminogen activator (tPA) administered by extended (48-96 hours) infusion (with salvage LPMT for poor response).

Findings from this study demonstrated PTS in 85% (11) of 13 children in the standard anticoagulation group, as compared to only 22% (2) of 9 children in the thrombolytic group. After adjustment for age and lag time from symptom onset to initiation of therapy, the thrombolytic regimen was associated with a significant reduction in the odds of PTS (odds ratio: 0.018, 95% confidence interval: < 0.001-0.483; P = .02). Major bleeding episodes were infrequent, consisting of an episode of pulmonary hemorrhage associated with emergent pulmonary arterial thrombectomy in 1 child treated with systemic thrombolysis. Further clinical investigation in this area will be essential in order that these recent findings, along with prior knowledge (e.g., prognostic significance of APAS and complete veno-occlusion by DVT), may translate into future improved outcome of VTE in children.

Based upon recent advances in outcome prediction in pediatric VTE and the aforementioned cohort study-derived clinical evidence, two randomized controlled clinical trials (RCT) employing outcome predictors in risk-stratified approaches of antithrombotic therapy have recently been initiated or proposed. The Kids-DOTT trial (www.clinicaltrials.gov) is a national multicenter Phase III RCT of duration of therapy for pediatric DVT, which opened in 2008 with staged start-up at participating sites in the U.S., via the Hemophilia and Thrombosis Research Society (HTRS). This trial investigates the efficacy and safety of shortened-duration (6 weeks) versus conventional duration (3 months) anticoagulation for children with acute VTE who do not have evidence for a heightened risk of adverse thrombotic outcome, and in whom thrombus resolution is documented 6 weeks following diagnosis of DVT. The co-primary outcomes are recurrent VTE and development of PTS; the latter is assessed in blinded fashion, using a validated pediatric outcome instrument. Sub-analyses will evaluate for differences in outcomes among specific anticoagulant agents administered in subacute therapy.

The PHLO trial has recently been proposed by Manco-Johnson and colleagues as a national multicenter Phase II/III trial of the safety and efficacy of acute thrombolytic therapy followed by conventional anticoagulation versus conventional anticoagulation alone for completely veno-occlusive acute DVT of the proximal lower extremity in adolescents. The primary outcome in this trial, which is planned to be conducted via the HTRS at approximately 10 participating centers, is the development of PTS characterized by both physical (i.e., abnormal exam score) and functional (i.e., abnormal pain score) findings, using the aforementioned PTS outcome instrument. An appropriately powered secondary aim seeks to evaluate the relative safety and efficacy of a systemic thrombolytic regimen using low-dose, continuous infusion tPA versus LPMT via an interventional radiologic approach.

Through proper control of treatment factors not afforded by cohort studies, the conduct of these RCTs will, in turn, allow more valid estimation of associations between prognostic factors and VTE outcomes, and is likely to reveal additional important predictors to inform future RCTs. If this strategy is

Table 1. Summary of cited references for thrombophilia states and markers of coagulation activation as predictors of VTE outcome in children and adults.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Outcomes</th>
<th>Adult Literature</th>
<th>Pediatric Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic anticoagulant deficiencies</td>
<td>Recurrent VTE</td>
<td>20-23</td>
<td>63</td>
</tr>
<tr>
<td>Homozygous FV Leiden</td>
<td>Recurrent VTE</td>
<td>32, 37</td>
<td>63</td>
</tr>
<tr>
<td>Homozygous PT G20210A</td>
<td>Recurrent VTE</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PT G20210A (any)</td>
<td>Recurrent VTE</td>
<td>—</td>
<td>64</td>
</tr>
<tr>
<td>Elevated FVIII</td>
<td>Recurrent VTE, PTS, persistent thrombosis</td>
<td>44, 5</td>
<td>5</td>
</tr>
<tr>
<td>Elevated Hcy</td>
<td>Recurrent VTE</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td>APA(S)</td>
<td>Recurrent VTE</td>
<td>50-53</td>
<td>66, 69, 70</td>
</tr>
<tr>
<td>Multi-trait thrombophilia</td>
<td>Recurrent VTE</td>
<td>35, 54, 55</td>
<td>63</td>
</tr>
<tr>
<td>Acutely elevated D-dimer</td>
<td>Recurrent VTE, PTS, persistent thrombosis</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>Elevated D-dimer at 3-6 months post-event</td>
<td>Recurrent VTE, PTS, persistent thrombosis</td>
<td>56-58, 5</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: VTE, venous thromboembolism; OR, odds ratio; FV, factor V; PT, prothrombin; FVIII, factor VIII; PTS, post-thrombotic syndrome; Hcy, homocysteine; APA(S), antiphospholipid antibody (syndrome).
coupled with the establishment of an effective and adequately funded cooperative group for the conduct of VTE trials, substantial gains will be realized in optimizing outcomes of VTE in children and adults.

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