Improving evidence on anticoagulant therapies for venous thromboembolism in children: key challenges and opportunities

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Venous thromboembolism (VTE) is increasingly diagnosed in pediatric patients, and anticoagulant use in this population has become common, despite the absence of US Food and Drug Administration (FDA) approval for this indication. Guidelines for the use of anticoagulants in pediatrics are largely extrapolated from large randomized controlled trials (RCTs) in adults, smaller dose-finding and observational studies in children, and expert opinion. The recently FDA-approved direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban, provide potential advantages over oral vitamin K antagonists and subcutaneous low-molecular-weight heparins (LMWHs). However, key questions arise regarding their potential off-label clinical application in pediatric thromboembolic disease. In this Perspective, we provide background on the use of LMWHs such as enoxaparin as the mainstay of treatment of pediatric provoked VTE; identify key questions and challenges with regard to DOAC trials and future DOAC therapy in pediatric VTE; and discuss applicable lessons learned from the recent pilot/feasibility phase of a large multicenter RCT of anticoagulant duration in pediatric VTE. The challenges and lessons learned present opportunities to improve evidence for anticoagulant therapies in pediatric VTE through future clinical trials. (*Blood*. 2015; 126(24):2541-2547)

Background: LMWHs as the mainstay of pediatric VTE treatment

Low-molecular-weight heparins (LMWHs) such as enoxaparin have become the most commonly used anticoagulants for VTE treatment in children, particularly those with provoked venous thromboembolism (VTE), in whom duration of therapy is finite.[1,2] This can be explained by the observations that, compared with other agents such as vitamin K antagonists (VKAs), LMWHs require infrequent laboratory monitoring (and attendant need for venipuncture), demonstrate no drug or food interactions, and have an acceptable efficacy and safety profile—albeit based on indirect comparison in most published literature. With regard to safety, LMWHs also have a lower risk of heparin-induced thrombocytopenia compared with unfractionated heparin.[3] LMWHs are used in routine clinical care for pediatric VTE and arterial thrombosis treatment and in numerous other clinical settings for pediatric thromboprophylaxis (eg, status-post cardiac surgical repair or placement of ventricular assist device; peri-procedurally for diagnostic or therapeutic cardiac catheterization, as an alternative to unfractionated heparin),[4] although none of these uses are approved by the US Food and Drug Administration (FDA) in children for enoxaparin or dalteparin (the 2 LMWHs marketed in the United States and Canada). Over the last 20 years, enoxaparin has been the most widely studied anticoagulant in North American children, beginning with a dose-finding study involving infants and children mostly with VTE[5] and ultimately extending to multiple additional clinical uses across the pediatric age spectrum.[6-21]

Dose finding and pharmacodynamic (PD) information from these pediatric studies of enoxaparin have revealed important aspects unique to treating children, such as age-related dosing using PD end points (typically, targeted anti-Xa activity). When targeting anti-Xa activity ranges, younger patients require higher doses of enoxaparin on a per-kilogram basis than do older children: often much higher. Based on numerous PD end point-driven dose-finding studies,[5,6,8,11,15,17,18] current consensus- and evidence-based guidelines recommend a twice-daily dose of 1.5 mg/kg in infants vs 1.0 mg/kg in older children,[4,16] and some experts have further recommended that doses of 1.7 and 2.0 mg/kg be used in term and premature neonates, respectively.[19] However, it must be emphasized that a key limitation of this work is the paucity of evidence supporting a strong relationship between anti-Xa activity and clinical measures of efficacy and safety (eg, recurrent VTE, major bleeding).

Nevertheless, in contrast to the strictly weight-based dosing approach conventionally used in adult patients, the PD effect of LMWHs is typically targeted and monitored in pediatric patients. This is in large part due to a perception (and some evidence) of a high interindividual variability in dosing requirements to achieve a given anti-Xa activity.[20] Indeed, enoxaparin dosing requirements can vary as much as two- to threefold among pediatric patients, especially in younger infants and children.[17] Greater variation in PD response observed in certain patient pediatric patient subpopulations (eg, renal or cardiac disease) has also led some clinician-investigators to recommend an increased frequency of laboratory monitoring in these children.[21]

As an alternative to conventional twice-daily dosing of LMWH for VTE treatment beyond the first 1 to 2 weeks after diagnosis, some centers use once-daily dosing at 1.5 mg/kg,[4,14] for which published data suggest similar efficacy and safety to twice-daily dosing. Additionally,

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given that many of the advantages of LMWHs are also inherent in fondaparinux, this subcutaneously administered synthetic pentasaccharide agent is used routinely for VTE treatment at a few pediatric centers in the United States. Fondaparinux dose-finding data have been published.[22]

Key questions and challenges for current DOAC use in pediatric VTE treatment

The direct oral anticoagulants (DOACs) recently approved for antithrombotic indications in adults (Table 1), including dabigatran, rivaroxaban, apixaban, and edoxaban, provide potential advantages over VKAs and LMWHs. Principal among these are more consistent pharmacokinetic (PK)/PD (and hence perceived minimal need for laboratory monitoring) compared with VKAs and the avoidance of the parenteral administration necessitated by LMWHs. Although none of the DOACs has yet been FDA- or European Medicines Agency (EMA) approved for VTE treatment in children, the literature reflects published off-label use in this setting.[24] The following is a clinical scenario that typifies questions about DOAC use in pediatrics:

> A 16-year-old previously healthy boy with an unprovoked acute lower extremity deep venous thrombosis is started on anticoagulation with enoxaparin while in the hospital, with a planned duration of therapy of 6 to 12 months. You discuss options for further anticoagulant treatment with him and his parents. He will be going away to boarding school in ~3 months, and the parents have concerns regarding his future compliance with enoxaparin shots or with warfarin and laboratory monitoring. They have seen television advertisements for the new oral anticoagulants that do not need laboratory monitoring. The parents and the patient would like for him to be prescribed one of these medicines instead of enoxaparin or warfarin. What do you advise?

Although the lack of an FDA-approved indication does not by itself restrict its off-label use, the lack of information on safety and efficacy provided within the package insert of these marketed drugs and/or from published studies severely limits the ability to provide best clinical care with these agents. By contrast, numerous PD studies and safety experiences have been published for both warfarin and the LMWHs to inform their broad use in the standard of care for VTE treatment in children, despite the lack of FDA-approved pediatric VTE treatment indications. Although "indicated" in patients ≥18 years of age, the question of suitable evidence for DOACs in VTE treatment extends beyond pediatrics into the young adult setting. Young adults (even when defined as <40 years of age) comprised only a small proportion of the study population in DOAC registration trials (FDA/EMA) of VTE treatment; for example, mean (±standard deviation) age was 55.0 ± 15.8 years in dabigatran[25] vs warfarin in the treatment of venous thromboembolism (RE-COVER), 55.8 ± 16.4 years in oral direct factor Xa inhibitor rivaroxaban[26] in patients with acute symptomatic DVT and PE, and 57.2 ± 16.0 years in Apixaban[27] for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY). For these reasons, in cases such as that of the teenager described above, we typically advise warfarin therapy with "home"-based monitoring,[28,29] with close oversight from a hospital-based anticoagulant monitoring program, until such time as suitable data are available on dosing, safety, and efficacy of (and reliable reversal strategies for) DOACs. (These limitations are discussed further in the next section.) At the same time, perhaps more important than the choice of anticoagulant per se in this case scenario is the strategy for optimizing adherence. Indeed, adherence was the key concern underlying the parent's request, and is among the most critical issues in anticoagulant therapy for adolescents. To this end, anticoagulants that permit once-daily oral dosing without need for laboratory monitoring will be highly desirable.

A related key challenge to safe, effective, and convenient use of anticoagulants in children, which has not been uniformly met by previous postmarketing commitment trials for anticoagulants in pediatric VTE, lies in the availability of pediatric-appropriate formulations. Given that infancy (and the neonatal period in particular) is one of the bimodal peaks in VTE incidence during the pediatric age span, dosing formulations of liquids must be of suitable concentration for accurate measurement of comparatively minute dosing changes (eg, 10% increase or decrease in weight-based dose for a 3-kg neonate). By way of context, twice-daily enoxaparin for subcutaneous administration at this age must either be prepared by a specialty pharmacy in limited supply (eg, drawn up from a vial into tuberculin syringes) or this must be done from a multidose vial at home by the parent/guardian or a home health nurse. The oral VKA warfarin is not available in a liquid formulation but only in fixed tablet sizes, leading to difficulties both in providing a precise weight-based dose and in allowing children who cannot swallow pills a viable route for drug delivery. Warfarin tablets are often crushed and administered with water or spooned foods such as applesauce, creating increased potential for dosing errors and imprecision. It is critical that regulatory agencies require that anticoagulant formulations suitable for pediatric (indeed, infant) use be made available during and after completion of a postmarketing commitment or label-enabling trial in infants and children. To this end, it is gratifying to see that a number of DOAC development programs are pursuing formal pediatric indications (with pediatric formulations), rather than simply fulfilling postmarketing commitments with more limited resource allocation; it is vital to the field that future anticoagulant development programs continue the committed pursuit of formal pediatric indications.

Key questions and challenges for DOAC trials in pediatric VTE

The possibility exists that variability in PK/PD response to DOACs may be greater in children than in adults, in whom randomized trials have titrated solely to cohort-wide clinical effect, leading to a "one size fits all" dosing approach for these novel agents. A recent scientific statement from pediatric colleagues in the International Society on Thrombosis and Haemostasis[30] emphasizes that such a strategy is not suitable across a pediatric age spectrum that involves developmental changes in the hemostatic system, as well as age-related differences in PK parameters of, for example, elimination and volume of distribution. Hence, phase 2 trial designs in pediatric DOAC trial development programs have generally involved age-related dosing cohorts designed to proceed in serial, staged fashion after PK/PD modeling is complete for a given age cohort (typically starting with adolescents). Whether such an approach will obviate a real or perceived need for laboratory monitoring of DOACs in infants and children remains to be determined. Novel techniques have been proposed to address pediatric-specific challenges in PK/PD modeling[31-35] and should be evaluated before firm conclusions are drawn regarding the utility of laboratory monitoring. These techniques include modeling and simulation via a "physiologically based" PK/PD (PBPK/PD) approach that integrates

Table 1. Summary of FDA approvals for conventional anticoagulants and the DOACs and clinical trial experience/evidence in pediatric VTE treatment

Anticoagulant	Initial FDA approval (year)	FDA-approved indications in adults	Pediatric FDA approval	Pediatric VTE treatment trial experience
VKA				
Warfarin	1954	Prophylaxis and treatment of venous thrombosis and its extension, PE	None	PK/PD and safety/efficacy
		Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation/ cardiac valve replacement		No RCTs
		Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events after myocardial		
LMWH				
Enoxaparin	1993	Prophylaxis and treatment of DVT and PE	None	PD and safety/efficacy
		Prophylaxis of ischemic complications of unstable angina and myocardial infarction		No RCTs
Dalteparin	1994	Prophylaxis of DVT in abdominal surgery, hip replacement, and medical illness with immobility	None	PD and safety/efficacy (small, investigator-initiated)
Pentasaccaride				
Fondaparinux	2001	DVT and PE treatment and prophylaxis	None	PD and safety/efficacy (small, investigator-initiated)
DOAC				
Dabigatran	2010	Stroke prophylaxis in nonvalvular atrial fibrillation	None	None yet published
		VTE treatment		VTE treatment
		Reduction in risk of recurrence of VTE in patients previously treated		RCT started in 2013
Rivaroxaban	2011	DVT and PE prophylaxis in orthopedic surgery	None	None yet published
		Stroke prophylaxis in nonvalvular atrial fibrillation		VTE treatment RCT started in 2015; phase 1 study published (Abstract)[23]
Apixaban	2012	Stroke prophylaxis in nonvalvular atrial fibrillation	None	None yet published
		DVT and PE prophylaxis in orthopedic surgery (2014)		VTE prevention
		VTE treatment and reduction in risk of recurrence		RCT anticipated to start in 2015
Edoxaban	2015	Stroke prophylaxis in nonvalvular atrial fibrillation	None	None yet published
		VTE treatment		

DVT, deep venous thrombosis; PE, pulmonary embolism.

physiologic changes into a multicompartment PK/PD model, wherein each relevant organ system and physiologic space (eg, adipose, muscle, blood) is treated as a compartment. PK/PD data from adult data are initially used, and the model is further developed via integration of PK/PD-related data from preclinical species, in vitro experiments, and any pilot studies or prior pediatric age cohorts (eg, adolescents). The model is then refined via the integration of physicochemical characteristics and metabolic (including pharmacogenetically enhanced) profiles of the drug, as well as developmentally driven physiologic changes in drug absorption, distribution, metabolism, and elimination across the pediatric age spectrum.[31,33] Support for the use of PBPK/PD modeling and simulation techniques has come from academia, industry, and regulatory agencies (eg, FDA), and the approach has provided a pragmatic solution to the challenge of establishing a Pediatric Investigation Plan, including the required PK/PD studies, early in the course of a drug development program, before extensive data are available from adult trials. Nevertheless, for oral drug administration, such as with the DOACs, the PBPK/PD approach remains limited by a paucity of data on the ontogeny of drug transporters in the gastrointestinal tract, resulting in uncertainty regarding developmental changes in drug absorption.[31]

As in adults, it will be critical in new anticoagulant trials in pediatrics to address dose-finding and monitoring needs in special populations that are well represented among VTE cases, such as infants and older children with obesity, renal insufficiency, or congenital cardiac disease (especially those undergoing Fontan procedures, as also emphasized in a recent position statement from the National Heart Lung and Blood Institute[36]). In addition, pediatric DOAC trials must recognize that the pediatric population has different comorbidities compared with adults, which often necessitate reversal of anticoagulation.[4,16] Consequently, if safety and efficacy of DOACs is demonstrated in pediatric VTE treatment trials, subsequent studies of safety and efficacy of DOAC reversal strategies in infants and older children must also be conducted, prior to broad uptake of these agents in the routine care of pediatric VTE.

Given the challenges in conducting randomized controlled trials (RCTs) in patients with rare diseases, whether in hematology or pediatrics (perhaps magnified by the intersection of the 2 disciplines, in the case of pediatric VTE), an important question arises from the academic and broader clinical community of pediatric hematologists: "Should we expect anything more than to rely on data from PK/PD end point-driven phase 2 studies of anticoagulants in pediatric VTE

treatment?" This question was indeed raised at a recent panel discussion involving the authors of this manuscript, convened by the Division of Hematology Products at FDA in the Center for Drug Evaluation and Research's Office of New Drugs, on challenges in the design of anticoagulant trials in pediatrics. Our perspective is that the answer is, definitively, "Yes." Clinical end point-driven trials, particularly those adequately powered to evaluate comparative efficacy and safety, are critically lacking. The children with VTE for whom we care deserve far better than the historically low-quality evidence on which their treating clinicians base management decisions, particularly because they are a vulnerable population and because the stakes are high (including risks of life-threatening/disabling bleeding and pulmonary embolism). We therefore must partner with our industry colleagues and regulatory agencies to commit to the design and execution of adequately powered, clinical end point-driven phase 3 trials, as well as effective phase 4 postmarketing surveillance studies, and to take the opportunity, in the latter case, to approach well-characterized patient populations from successfully completed phase 3 trials for participation in long-term follow-up (prospective cohort) studies. In circumstances where phase 3 RCTs are not undertaken, are deemed infeasible, or are prematurely terminated due to poor accrual, such prospective observational registries with quality-assured data collection on efficacy and safety outcomes that use standardized pediatric end point definitions[37] can provide next-highest quality evidence derived from real-world use in pediatrics, albeit with limitations in data quality and potential biases.

The use of efficient trial designs and continued emphasis on methodologic advances in efficient RCT design and analysis will also be vital to future success in pediatric end point-driven trials, particularly in conditions with relatively low incidence/prevalence. Efficiency of pediatric trials can be improved with interim analyses that allow trials to be shorter when early differences clearly establish efficacy or lack thereof. In anticoagulant trials of VTE prevention and treatment, study designs and interim analysis plans that consider treatment effects on both VTE and bleeding risks can improve trial efficiency by structuring the clinical trade-off between VTE and bleeding risks by assessing for superiority on one and noninferiority on the other. Such a bivariate design has reduced the sample size requirements for the randomized arms of the Multicenter Evaluation of the Duration of Therapy for Thrombosis in Children (Kids-DOTT trial).[38]

Because pediatric trials commonly involve evaluation of established adult therapies, further efficiency gains for event-driven trials in pediatric VTE can be realized by using designs that formally incorporate established effects in adult populations in an empirical Bayesian framework.[39] This Bayesian approach to the design of end point-driven trials has the potential to better reflect the clinical utility of the comparison between treatment approaches, but must recognize regulatory agency guidance on the use of Bayesian trial design.[40] Given that outcome event rates are often not well established in pediatric rare/infrequent disease (eg, due to paucity of prior RCTs or multi-institutional prospective cohort studies), methods that allow adaptive alteration of the trial sample size to reflect observed event risk during the trial can also be useful to potentially reduce sample size requirements compared with nonadaptive designs but should adhere to established guidelines.[41] One example of efficient adaptive design is the internal (ie, nested) pilot phase 3 trial (as exemplified by Kids-DOTT[2]), wherein findings of the pilot phase are used to refine the sample size for the overall trial, and the study population enrolled during the pilot is counted toward the final sample size required for the definitive trial.[42]

Lessons learned from the recent pilot/feasibility phase of a large multicenter RCT in pediatric VTE, in historical context

Recently, the findings of the pilot/feasibility phase of the multicenter Kids-DOTT RCT on shortened vs conventional duration of clinically prescribed anticoagulants of choice for treatment of venous thrombosis in neonates, older children, and young adults (age <21 years) were published.[2] Interestingly, in >90% of patients on a predominantly US multicenter trial basis, the anticoagulant of choice administered in the treatment of provoked VTE was enoxaparin. This observation strongly suggests that in future RCTs of treatment of provoked VTE (which represents the vast majority of VTE overall) in children, the most appropriate comparator for new anticoagulants (whether orally or parenterally administered) is LMWH.

In Kids-DOTT, substantial emphasis during the pilot/feasibility phase was placed on accrual, which has historically plagued RCTs in pediatric VTE. Indeed, Kids-DOTT only achieved an appropriate pace of accrual in the final year of its pilot/feasibility phase. The prophylactive LMWH compared to standard cure for the prevention of CVL-related VTE during childhood trial (PROTEKT) and open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of VTE in children (REVIVE) performed in the 1990s in pediatric VTE prevention and treatment, respectively, were hindered by lack of robust preliminary data on incidence and outcomes by which to power the trials[43]: a limitation that led in part to the design of a pilot/feasibility phase within the Kids-DOTT trial. A problem of overly extensive exclusion criteria in PROTEKT and REVIVE,[43] which significantly hampered accrual in those trials, was also experienced early in the prespecified pilot/feasibility component of Kids-DOTT; relaxation of these exclusion criteria was then effected during this phase, via input from the Investigators and the active engagement of the Steering and Data and Safety Monitoring Committees overseeing the trial.[2] These experiences underscore the importance of substantiating key trial assumptions, particularly with regard to recruitment, protocol (including randomization) adherence, and retention, to optimize the successful completion of an RCT in pediatric VTE.

As alluded to above, a key ingredient for pediatric multicenter trial success is a highly engaged Steering Committee that actively monitors the trial's progress, works directly with site investigators and their teams to identify and overcome site-based barriers to recruitment, and fosters motivation in the trial. The enhanced responsibilities of the modern steering committee for actively monitoring and managing progress on the trial have also been emphasized and further described in a prior *Blood* Perspectives article.[44] Appropriate site selection is an additional important measure. The pilot dose-finding, pharmacokinetic, and safety study of fondaparinux in children (FondaKIDS) and Utilization of Bivalirudin On Clots in Kids (UNBLOCK) trials on dose-finding and preliminary safety and efficacy of fondaparinux[22] and bivalirudin[45] in children focused the selection of participating sites on large-volume pediatric VTE centers highly experienced in pediatric VTE trials, as a key strategy for successful patient recruitment and protocol execution.

Another important facilitator of optimal accrual as learned in Kids-DOTT was the implementation of recruitment tools and surveillance methods typical of industry-sponsored registration trials. These approaches

included regular collection and review of screening logs, frequent e-mail contact to acknowledge key site-based milestones, and individual enrollments. In addition, the use of investigator meetings and study coordinator conference calls throughout the course of the trial permitted continuous sharing of strategies for successful recruitment and retention, regular discussion of trial progress, and the ability to sustain a high level of enthusiasm among participating centers. Importantly, current DOAC pediatric trial programs appear to incorporate many of the above factors important for success. At first glance, the simultaneous execution of 4 distinct DOAC pediatric trial programs might seem to undermine these beneficial measures, threatening successful accrual on any given trial. Yet, it is encouraging that these pediatric programs have included nonoverlapping indications, such as VTE prevention (eg, apixaban) and VTE treatment (eg, rivaroxaban) and/or nonoverlapping populations (eg, children with acute lymphoblastic leukemia [apixaban] and those with congenital heart disease [edoxaban]). For this reason, we are optimistic that much-needed efficacy and safety data will be gained from clinical end point-driven trials in each of these key pediatric groups and settings.

Perhaps the most critical success factor in increasing overall accrual rate on Kids-DOTT was the ability to increase the number of participating centers during the most recent years of the pilot phase. The financial imperative for rapid completion of industry-sponsored trials often leads to a strategy of rapid engagement of a large number of centers from study onset, taking into account historically informed, realistic enrollment rates. Although the same approach is highly advantageous for academically driven RCTs, this is very difficult to consistently achieve from one trial to the next, in the absence of a large clinical trials network of pediatric centers. For example, despite matching grants from the Medical Research Council of Canada and Pharmaceutical Manufacturers Association of Canada, the experiences of the PROTEKT and REVIVE RCTs highlighted the need for better resourcing of pediatric trials.[43] A historical approach that might be described as "small patients, smaller budgets" will only perpetuate failure. We therefore believe that the establishment and maintenance of a pediatric clinical trials meta-network that encompasses a broad array of therapeutic areas not currently addressed by funded cooperative networks is critically necessary, and is a prerequisite for sustainable success in the execution of end point-driven pediatric trials in conditions of relatively low prevalence/incidence. This meta-network should ideally be comprised of large pediatric centers of excellence and expertise in clinical trial operations, administration, quality assurance, and regulatory compliance. Furthermore, the meta-network must be financially sustained through investments made not only from the federal government but also from the pharmaceutical industry (either directly or indirectly via a portion of pediatric pharmaceutical sales) and via philanthropy. Within this meta-network, individual networks for specific therapeutic areas (eg, thrombosis and hemostasis) must be developed to best address the needs of specific pediatric disease populations and trials. With such a paradigm shift, we could look forward to an era in which successfully conducted RCTs in pediatric VTE and many other therapeutic areas in children become the rule rather than the exception.

Conclusions

LMWHs have become the most commonly used and widely studied anticoagulants for pediatric VTE treatment, based on relatively small dose-finding, PD, and nonrandomized safety and efficacy studies. However, like other anticoagulants (including oral VKAs, such as warfarin), LMWHs lack FDA- or EMA-approved indications for VTE treatment in children. Successfully completed clinical end point-driven trials, particularly those adequately powered to evaluate comparative efficacy and safety, are critically lacking in the pediatric VTE field. DOACs, recently indicated in adult antithrombotic settings, provide potential advantages over LMWHs and VKAs that are particularly relevant to children, including noninvasive administration and a perceived minimized need for laboratory monitoring. Pediatric VTE treatment trials with DOACs are ongoing, and include age-specific dose-finding and PK/PD studies, as well as phase 3 RCTs in some cases. Emphasis has been placed on pediatric formulations for use beyond the trial programs, which has not been consistently the case with prior anticoagulant trials performed in children as part of postmarketing commitments. As in adults, it will be critical in pediatrics to address dose-finding and monitoring needs in special populations that are well represented among VTE cases, such as infants and older children with obesity, renal insufficiency, or congenital cardiac disease. Until these trials are completed, the lack of information on safety and efficacy provided within the package insert of these marketed drugs and/or from published studies severely limits the ability to provide best clinical care with these agents.

Despite the challenges in conducting RCTs in patients with rare diseases, the children with VTE for whom we care deserve far better than the historically low-quality evidence on which their treating clinicians base management decisions; therefore, we must commit to the design and execution of adequately powered, clinical end point-driven phase 3 trials, as well as effective postmarketing surveillance studies. The key challenge to success, as experienced in pediatric VTE RCTs both historically and recently, has been recruitment. Success factors discerned in recent academically driven pediatric VTE trials have included a highly engaged steering committee and the use of recruitment tools and surveillance metrics conventionally used in industry-driven trials. Perhaps most important for RCT success is a strategy of rapid initiation of a large number of participating centers based on historically informed, realistic accrual estimates. Given the difficulty in achieving this consistently in the absence of a large clinical trials network of pediatric centers, the establishment and maintenance of such a pediatric trials network (achieved via sustainable investments derived from the federal government, the pharmaceutical industry, and philanthropy) is an urgent priority to permit the successful conduct of RCTs in pediatric VTE and other therapeutic areas in children. In addition, future success of RCTs in pediatric diseases of relatively low prevalence/incidence must rely on continued methodological advances in efficient trial design and analytic approaches.

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References

1. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics.* 2009;124(4):1001-1008.
2. Goldenberg NA, Abshire T, Blatchford PJ, et al; Kids-DOTT Trial Investigators. Multicenter randomized controlled trial on Duration of Therapy for Thrombosis in Children and Young Adults (the Kids-DOTT trial): pilot/feasibility phase findings. *J Thromb Haemost.* 2015;13(9):1597-1605.
3. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood.* 2005;106(8):2710-2715.
4. Monagle P, Chan AK, Goldenberg NA, et al; American College of Chest Physicians. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e737S-e801S.
5. Massicotte P, Adams M, Marzinotto V, Brooker LA, Andrew M. Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr.* 1996;128(3):313-318.
6. Dix D, Andrew M, Marzinotto V, et al. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr.* 2000; 136(4):439-445.
7. Trame MN, Mitchell L, Krümpel A, Male C, Hempel G, Nowak-Göttl U. Population pharmacokinetics of enoxaparin in infants, children and adolescents during secondary thromboembolic prophylaxis: a cohort study. *J Thromb Haemost.* 2010;8(9):1950-1958.
8. Malowany JI, Knoppert DC, Chan AK, Pepelassis D, Lee DS. Enoxaparin use in the neonatal intensive care unit: experience over 8 years. *Pharmacotherapy.* 2007;27(9):1263-1271.
9. Bontadelli J, Moeller A, Schmugge M, et al. Enoxaparin therapy for arterial thrombosis in infants with congenital heart disease. *Intensive Care Med.* 2007;33(11):1978-1984.
10. Revel-Vilk S, Sharathkumar A, Massicotte P, et al. Natural history of arterial and venous thrombosis in children treated with low molecular weight heparin: a longitudinal study by ultrasound. *J Thromb Haemost.* 2004;2(1):42-46.
11. Streif W, Goebel G, Chan AK, Massicotte MP. Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. *Arch Dis Child Fetal Neonatal Ed.* 2003;88(5):F365-F370.
12. Burak CR, Bowen MD, Barron TF. The use of enoxaparin in children with acute, nonhemorrhagic ischemic stroke. *Pediatr Neurol.* 2003;29(4):295-298.
13. Elhasid R, Lanir N, Sharon R, et al. Prophylactic therapy with enoxaparin during L-asparaginase treatment in children with acute lymphoblastic leukemia. *Blood Coagul Fibrinolysis.* 2001;12(5): 367-370.
14. Schobess R, Düring C, Bidlingmaier C, Heinecke A, Merkel N, Nowak-Göttl U. Long-term safety and efficacy data on childhood venous thrombosis treated with a low molecular weight heparin: an open-label pilot study of once-daily versus twice-daily enoxaparin administration. *Haematologica.* 2006;91(12):1701-1704.
15. Michaels LA, Gurian M, Hegyi T, Drachtman RA. Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. *Pediatrics.* 114(3)703-707.

    Michaels LA, Gurian M, Hegyi T, Drachtman RA. Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. *Pediatrics.* 2004;114(3):703-707.
16. Giglia TM, Massicotte MP, Tweddell JS, et al; American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Stroke Council. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. *Circulation.* 2013; 128(24):2622-2703.
17. Ignjatovic V, Najid S, Newall F, Summerhayes R, Monagle P. Dosing and monitoring of enoxaparin (Low molecular weight heparin) therapy in children. *Br J Haematol.* 2010;149(5):734-738.
18. Bauman ME, Belletrutti MJ, Bajzar L, et al. Evaluation of enoxaparin dosing requirements in infants and children. Better dosing to achieve therapeutic levels. *Thromb Haemost.* 2009; 101(1):86-92.
19. Malowany JI, Monagle P, Knoppert DC, et al; Canadian Paediatric Thrombosis and Hemostasis Network. Enoxaparin for neonatal thrombosis: a call for a higher dose for neonates. *Thromb Res.* 2008;122(6):826-830.
20. Trame MN, Mitchell L, Krümpel A, Male C, Hempel G, Nowak-Göttl U. Population pharmacokinetics of enoxaparin in infants, children and adolescents during secondary thromboembolic prophylaxis: a cohort study. *J Thromb Haemost.* 2010;8(9):1950-1958.
21. Ho SH, Wu JK, Hamilton DP, Dix DB, Wadsworth LD. An assessment of published pediatric dosage guidelines for enoxaparin: a retrospective review. *J Pediatr Hematol Oncol.* 2004;26(9):561-566.
22. Young G, Yee DL, O'Brien SH, Khanna R, Barbour A, Nugent DJ. FondaKIDS: a prospective pharmacokinetic and safety study of fondaparinux in children between 1 and 18 years of age. *Pediatr Blood Cancer.* 2011;57(6):1049-1054.
23. Young G, Kubitza D, Chan A, et al. Development of a rivaroxaban dosing regimen for treatment of VTE in children aged 12 to 18 years. *J Thromb Haemost.* 2015;13(Suppl 2):37-38.
24. Lyle CA, Sidonio RF, Goldenberg NA. New developments in pediatric venous thromboembolism and anticoagulation, including the target-specific oral anticoagulants. *Curr Opin Pediatr.* 2015; 27(1):18-25.
25. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24): 2342-2352.
26. Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510.
27. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808.
28. Christensen TD, Larsen TB, Hjortdal VE. Self-testing and self-management of oral anticoagulation therapy in children. *Thromb Haemost.* 2011;106(3):391-397.
29. Bauman ME, Bruce AK, Buchholz H, Kuhle S, Massicotte MP. Accuracy of the CoaguChek XS® for POC INR in warfarinised children and adults with ventricular assist devices. *Thromb Haemost.* 2013;110(3):616-617.
30. Male C, Monagle P, Chan AK, Young G; Subcommittee on Pediatric/Neonatal Hemostasis and Thrombosis. Recommendations for the

development of new anticoagulant drugs for pediatric use: communication from the SSC of the ISTH. *J Thromb Haemost.* 2015;13(3):481-484.

31. Barrett JS, Della Casa Alberighi O, Läer S, Meibohm B. Physiologically based pharmacokinetic (PBPK) modeling in children. *Clin Pharmacol Ther.* 2012;92(1):40-49.

32. Meibohm B, Läer S, Panetta JC, Barrett JS. Population pharmacokinetic studies in pediatrics: issues in design and analysis. *AAPS J.* 2005;7(2): E475-E487.

33. Läer S, Barrett JS, Meibohm B. The *in silico* child: using simulation to guide pediatric drug development and manage pediatric pharmacotherapy. *J Clin Pharmacol.* 2009;49(8): 889-904.

34. Zhao P, Rowland M, Huang SM. Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. *Clin Pharmacol Ther.* 2012;92(1):17-20.

35. Willmann S, Becker C, Burghaus R, et al. Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. *Clin Pharmacokinet.* 2014;53(1):89-102.

36. McCrindle BW, Li JS, Manlhiot C, et al. Challenges and priorities for research: a report from the National Heart, Lung, and Blood Institute (NHLBI)/National Institutes of Health (NIH) Working Group on thrombosis in pediatric cardiology and congenital heart disease. *Circulation.* 2014;130(14):1192-1203.

37. Mitchell LG, Goldenberg NA, Male C, Kenet G, Monagle P, Nowak-Göttl U; Perinatal and Paediatric Haemostasis Subcommittee of the SSC of the ISTH. Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary embolism in children. *J Thromb Haemost.* 2011;9(9):1856-1858.

38. Kittelson JM, Spyropoulos AC, Halperin JL, et al; Antithrombotic Trials Leadership and Steering (ATLAS) Group. Balancing risk and benefit in venous thromboembolism trials: concept for a bivariate endpoint trial design and analytic approach. *J Thromb Haemost.* 2013;11(8): 1443-1448.

39. Goodman SN, Sladky JT. A Bayesian approach to randomized controlled trials in children utilizing information from adults: the case of Guillain-Barré syndrome. *Clin Trials.* 2005;2(4):305-310, discussion 364-378.

40. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf. Accessed October 7, 2015.

41. http://www.fda.gov/downloads/Drugs/Guidances/ucm201790.pdf. Accessed October 7, 2015.

42. van der Lee JH, Wesseling J, Tanck MW, Offringa M. Efficient ways exist to obtain the optimal sample size in clinical trials in rare diseases. *J Clin Epidemiol.* 2008;61(4):324-330.

43. Massicotte MP, Sofronas M, deVeber G. Difficulties in performing clinical trials of antithrombotic therapy in neonates and children. *Thromb Res.* 2006;118(1):153-163.

44. Goldenberg NA, Spyropoulos AC, Halperin JL, et al; Antithrombotic Trials Leadership and Steering Group. Improving academic leadership and oversight in large industry-sponsored clinical trials: the ARO-CRO model. *Blood.* 2011;117(7): 2089-2092.

45. O'Brien SH, Yee DL, Lira J, Goldenberg NA, Young G. UNBLOCK: an open-label, dose-finding, pharmacokinetic and safety study of bivalirudin in children with deep vein thrombosis. *J Thromb Haemost*. 2015;13(9): 1615-1622.