Published in final edited form as:

J Thromb Thrombolysis. 2013 April ; 35(3): 352–358. doi:10.1007/s11239-013-0895-y.

Sickle cell disease and venous thromboembolism: what the anticoagulation expert needs to know

Rakhi P. Naik, Michael B. Streiff, and Sophie Lanzkron

Division Hematology, Department of Medicine, Johns Hopkins University, 1830 E. Monument Street, Suite 7300, Baltimore, MD 21205, USA

Abstract

Venous thromboembolism (VTE) is common in patients with sickle cell disease (SCD). The etiology of increased risk of VTE in SCD patients is multifactorial and is related to both traditional factors and SCD-specific factors. Traditional risk factors such as central venous catheters, frequent hospitalization, orthopedic surgeries for avascular necrosis, and pregnancy may lead to increased incidence of VTE in the SCD population. In addition, SCD itself appears to be a hypercoagulable state, and many SCD-specific factors such as thrombophilic defects, genotype and splenectomy may modify the risk of VTE. SCD complications such as acute chest syndrome and pulmonary hypertension may also be related to VTE. Anticoagulation experts should be aware of these factors to help inform prophylaxis and treatment decisions.

Keywords

Sickle cell disease; Venous thromboembolism; Deep venous thrombosis; Pulmonary embolism; Anticoagulation

Introduction

Sickle cell disease (SCD) is an inherited disorder resulting in the production of abnormal hemoglobin (hgb S) that polymerizes in hypoxic conditions to form sickle-shaped red blood cells (RBCs). While historically the pathophysiology of the clinical complications of SCD was attributed solely to direct entrapment of deformed RBCs in the microcirculation [1], it is now recognized that various complex mechanisms, and importantly hypercoagulability, contribute considerably to disease pathology. The mechanisms of hypercoagulability in SCD are vast, including enhanced platelet function [2–4], activation of the coagulation cascade [5, 6], and impaired fibrinolysis [7]. These perturbations are partly due to alterations in sickled RBC structure leading to intravascular hemolysis and externalization of highly procoagulant phosphatidylserines on the RBC membrane [8]. Circulating free hemoglobin in the setting of hemolysis also causes nitric oxide depletion, which leads to chronic vasoconstriction and platelet activation [9]. In addition, vaso-occlusion of sickled RBCs contributes to decreased blood flow and local vascular ischemic injury. In fact, every aspect of Virchow's triad—

increased coagulability, endothelial dysfunction, and impaired blood flow—is present in patients with SCD and results in a highly thrombogenic environment [10].

Despite the known association between hypercoagulability and SCD, venous thromboembolism (VTE) is often overlooked as a major complication of SCD [11]. Thrombotic complications such as stroke in pediatric SCD patients have been more robustly characterized, in part, because VTE is primarily a complication of adults and has only been recently recognized with advances in therapies and increased survival of SCD patients. In addition, risk of VTE in SCD patients is influenced by factors outside the disease itself such as hospitalization and catheter use. However, VTE affects nearly one-quarter of adult patients and appears to be a risk factor for death in SCD [11, 12]; therefore, management by anticoagulation experts is an essential part of care for the SCD population.

Incidence/prevalence of VTE in SCD

Several studies have evaluated the prevalence of VTE in SCD patients and provide some insight into the burden of this complication in adult SCD patients. The largest study performed using the National Hospital Discharge Survey evaluated 1,804,000 SCD admissions from 1979 to 2003 and found that the prevalence of pulmonary embolism (PE) in hospitalized SCD patients <40 years of age was approximately 3.5 times higher than African-American controls [13]. Notably, the mean age of PE in SCD patients was 28 years compared to 57 years among controls, reflecting a high thrombotic risk among young SCD patients. Although the prevalence of deep venous thrombosis (DVT) was not found to be significantly increased in SCD compared to controls in that study, SCD patients with DVT were similarly much younger than controls, with a mean age of 31 years at diagnoses of DVT in patients with SCD compared to 54 years in controls. A second inpatient study demonstrated a nearly 50–100-fold increased annual incidence of PE in hospitalized SCD patients compared to non SCD patients <50 years old [12]. In our institution, we have noted that 25 % of our adult SCD patients have a history of VTE with a median age at first VTE of 30 years [11]. These prevalence and age data are similar to those observed in family cohorts of patients with high-risk thrombophilias such as anti-thrombin III, protein C, and protein S deficiency [14], and underscore the potent thrombophilic environment of SCD.

Risk factors for VTE in SCD patients

Although SCD itself is associated with underlying hyper-coagulability, several factors modify the risk of VTE in this population. Traditional risk factors such as high use of central venous catheters, frequent hospitalization, high-risk surgeries such as orthopedic surgery for avascular necrosis (AVN), and pregnancy significantly influence VTE risk in SCD patients. Furthermore, SCD-related factors such as an increased prevalence of certain thrombophilic defects, genotype, and history of splenectomy can also alter VTE risk. These factors are summarized in Table 1.

Traditional risk factors

Central venous catheters

Central venous catheters (CVC) are commonly used in SCD, and therefore are a significant trigger for VTE. Approximately 30 % of adult SCD patients have experienced a CVC-related VTE, 80 % of which occur in patients with hemoglobin SS or S β^0 , reflecting the high use of catheters in more severe genotypes [11]. Reasons for CVC use in SCD include poor venous access, chronic transfusion therapy, recurrent complications, and long-term antibiotics [15, 16]. While partially implantable tunneled and non-tunneled lines are still frequently used for acute complications, totally implantable venous access devices (TIVAD) are being increasingly utilized in SCD patients as a more sterile and convenient alternative in patients who require frequent intravenous access or transfusion therapy [15–19]. As summarized in Table 2, the incidence of symptomatic CVC-related VTE in SCD patients appears to be high in both adult and pediatric populations. Studies including adult SCD patients have demonstrated that 12–30 % of TIVADs are complicated by VTE with an incidence ranging from 0.18 to 0.99 VTE events per 1,000 catheter days. Pediatric-only studies have also shown high incidence of thrombotic complications (15–16 % per CVC) in SCD patients [16, 18]. In contrast, studies investigating clinically symptomatic CVC-related VTE in cancer patients report VTE incidence ranges of 0.3–28.3 % per catheter in adult patients, with substantially lower VTE rates in pediatric populations (0–3.1 % in most studies) [20]. The high CVC–VTE rates in SCD pediatric patients may be due to the significant underlying hypercoagulability in SCD or differences in CVC-related factors such as type of catheter or duration of CVC implantation [18, 20]. Furthermore, the observed high incidence of catheter-related VTE in pediatric SCD patients is seen in other chronic inheritable diseases such as cystic fibrosis, and may reflect increased coagulability in the setting of chronic illness and inflammation [21].

Hospitalization

Frequent hospitalization is often required in patients with SCD secondary to vaso-occlusive pain crisis and complications such as acute chest syndrome (ACS). A large database study using identified records found that SCD patients had a average of 1.5 hospitalizations per year, with rates as high as 2.0 average inpatient stays per year in the 18–30 year old group. In addition, among those hospitalized, 33 % of SCD patients required re-hospitalization within 30 days [22]. However, despite high average hospitalization rates, hospital utilization differs significantly among SCD patients, with 20 % of patients accounting for over 50 % of hospital days [23]. Intensive care unit (ICU) admissions are also common in SCD secondary to severe complications such as ACS, multiorgan failure, and neurologic sequelae such as stroke. One study found that 38/500 SCD patients (8 %) required at least one ICU admission within an 8 year follow-up period [24]. In addition, in SCD patients with ACS, nearly 13 % require an ICU admission for mechanical ventilation during their course [25].

Surgery

SCD patients are predisposed to many disease-specific complications that require surgical intervention and may be associated with post-surgical VTE risk. Chronic hemolysis leads to the development of pigment stones and gallbladder disease necessitating cholecystectomy in

nearly 50–70 % of patients by adulthood. AVN occurs in SCD in 20–50 % of SCD patients [26, 27], and ultimately necessitates total hip arthroplasty in 10 % of patients [28]. Other orthopedic surgeries such as hip core decompression, debridement, and shoulder replacement are also common, and as SCD patients survive longer, the need for orthopedic interventions secondary to AVN will likely increase [27].

Pregnancy

Pregnancy-related thrombotic complications in SCD patients have been demonstrated to be higher than that of controls. In one study of nearly 18,000 SCD deliveries, both cerebral vein thrombosis and DVT were more common in women with SCD than those without SCD [29]. A second large database study of over 14,000 pregnancy-related VTE events found that SCD was a significant risk factor for VTE, with a similar degree of risk as lupus [30].

SCD-specific risk factors

Thrombophilic defects

SCD is associated with several thrombophilic defects that may contribute to hypercoagulability. Antiphospholipid antibodies, which have known prothrombotic properties, are commonly identified in SCD patients. The high frequency of antiphospholipid antibodies is thought to be secondary to structural changes in sickled red cell membranes, such as phosphatidylserine exposure, and lipid degradation in the setting of oxidative stress [6, 31]. One study that measured IgG, IgA, and IgM titers of various antiphospholipid antibodies, including phosphatidylserine and cardiolipin, found that the patients with SS disease had elevated IgG levels of all measured antiphospholipid antibodies. A subset of patients were noted to have thrombotic complications such as stroke, though none had a history of VTE by report [6]. In addition, a functional assay (Kaolin clotting time) was evaluated in one study and found that nearly 20 % of SCD patients with chronic leg ulcers demonstrated the presence of a lupus anticoagulant [32].

In addition to antiphospholipid antibodies, decrease in protein C and protein S activity and antigen levels have been noted in SCD patients [6, 33, 34]. The low circulating protein C and S levels may be due to chronic consumption in the setting of increased tissue factor expression and activation of coagulation on the surface of sickled red blood cells with phosphatidylserine externalization [7]. The degree of deficiency does not correlate with incidence of vaso-occlusive pain crisis [33]; however, protein S and C activity does appear to be correlated to a history of stroke in pediatric patients [35, 36]. Mean baseline activity levels in patients with prior stroke have been noted to be as low as 47 % for protein S and 52 % for protein C [35, 36].

Given the baseline changes in antiphospholipid antibodies and protein S and C levels, these thrombophilia studies should be interpreted with caution in patients with SCD. Other thrombophilic states such as antithrombin III deficiency is not generally found in SCD patients [37]. Similarly, inherited thrombophilic mutations such as Factor V Leiden and the prothrombin G20210A mutation are not prevalent in patients with SCD, likely secondary to low allele frequency in African populations [7].

Splenectomy

Surgical splenectomy is a significant risk factor for VTE in hereditary hemolytic conditions such as β -thalassemia and hereditary spherocytosis [38, 39]. While the observed association between splenectomy and VTE may be related in part to disease severity, a pathophysiologic basis for an increase in post-splenectomy thrombotic risk has been hypothesized. Splenectomy is thought to contribute to hypercoagulability by resulting in elevated levels of circulating abnormal red blood cells, increase in intravascular hemolysis, and post-splenectomy thrombocytosis [40]. In a large study of 8,860 adult patients with β -thalassemia, 1 % of β -thalassemia major patients and 4 % of patients with β -thalassemia intermedia reported a history of VTE. In that series, 93 % of patients with VTE had an antecedent history of surgical splenectomy [38]. In a subsequent cohort study of 584 patients with β -thalassemia intermedia, the rate of prior splenectomy was significantly higher in patients with VTE (22 %) compared to those who had not developed venous thrombosis (4 %) [41]. In patients with hereditary spherocytosis, a similarly high incidence of VTE has been observed in post-splenectomy patients compared to those with intact spleens and, interestingly, the risk of VTE appears to persist for years to decades following splenectomy [39].

In patients with SCD, splenic auto-infarction affects the majority of children with hemoglobin SS disease by age 1 year and a large proportion of patients with SC disease by mid-childhood [42, 43]. While it is hypothesized that functional asplenia may contribute to underlying hypercoagulability in SCD [40], no formal studies have evaluated the role of functional asplenia on thrombotic risk in SCD patients. At our institution, we have evaluated the prevalence of surgical splenectomy to VTE in our patients with sickle variant genotypes (SC and S β +thalassemia) and have found that 27 % of patients with VTE had a history of splenectomy compared to 6 % without VTE, which may suggest that splenic dysfunction results in increased VTE risk in SCD as is seen with other hemolytic disorders.

Genotype

Sickle cell genotype has been shown to modify the risk of SCD complications and may reflect a balance between hemolytic rate, endothelial dysfunction, vaso-occlusion, and viscosity [44]. While patients with hemoglobin SS genotype demonstrate a high prevalence of hemolysis-related vascular complications such as leg ulcers and pulmonary hypertension [44], patients with hemoglobin SC experience an increased frequency of viscosity-related events such as retinopathy and renal papillary necrosis [45]. The relationship between genotype and VTE has not been fully defined; however, non-catheter-related VTE does appear to be more common in adult patients with sickle cell variant genotypes such as SC and S β +thalassemia compared to those with hemoglobin SS or S β^0 thalassemia [11, 45]. Autopsy studies have also verified a higher prevalence of PE in patients with SC and S β^0 thalassemia compared to those with hemoglobin SS [46]. Therefore, elevated baseline hemoglobin and increased viscosity may play a role in the development of VTE in SCD.

Relationship of VTE to SCD complications

Acute chest syndrome

ACS is a leading cause of morbidity and mortality in patients with SCD. While the etiology of respiratory dysfunction in SCD is multifactorial, pulmonary fat embolism and infection contribute to ACS in a significant proportion of cases [25]. Although PE is not often cited as a cause of ACS, there is some evidence that pulmonary arterial thrombi are frequently found in SCD patients with ACS. One study of 144 ACS events found that 17 % of cases had pulmonary thrombi on computed tomography, with most cases demonstrating filling defects in the main pulmonary artery or segmental branches [47]. In that report, density of the thrombi, measured in Hounsfield units, were measured to differentiate pulmonary thrombi from fat embolism. Lower extremity compression ultrasonography performed at the time of the ACS episode did not detect DVT in any of the cases, although two patients were noted to have infra-popliteal thrombosis. This may suggest that pulmonary thrombosis during ACS is an in situ, rather than embolic phenomenon in some cases [47]. In addition, the largest study of ACS in predominantly pediatric patients, noted that pulmonary emboli were the most common cause of death in ACS, although differentiation between VTE and fat embolism could not be determined [25]. Given the uncertainty of the etiology of pulmonary arterial thrombosis in ACS, anticoagulation practices vary widely. Pediatric physicians do not commonly prescribe anticoagulation in ACS [48], whereas treatment-dose anticoagulation is frequently used in adult patients with positive radiography [47].

Pulmonary hypertension

Pulmonary hypertension has been increasingly recognized as a prevalent complication in adults with SCD, affecting approximately 10 % of patients and resulting in an increased risk of death [49]. Although not generally considered a major cause of pulmonary hypertension, chronic thromboembolic pulmonary hypertension has been noted in patients with SCD. One study found that 6/27 of SCD patients with pulmonary hypertension had a high probability ventilation-perfusion scans, three (12 %) of which were consistent with patterns observed in chronic thromboembolic pulmonary hypertension [50]. In addition, one small autopsy study demonstrated that up to 50 % of patients with pulmonary hypertension defined by right ventricular hypertrophy had evidence of proximal vessel pulmonary thrombi [51]. Successful pulmonary endarterectomy has also been described in a patient with hemoglobin SC disease and known chronic thromboembolic pulmonary hypertension [52].

Underlying hypercoagulability may also contribute to the pathogenesis of elevated pressures in pulmonary hypertension patients without chronic thromboembolic disease. Autopsy studies of SCD patients have demonstrated diffuse in situ thrombi in the pulmonary vessels of a majority of patients with pulmonary hypertension [51, 53]. Markers of coagulation also appear to be increased in SCD patients with echocardiography-defined pulmonary hypertension [54]. Echocardiography-defined pulmonary hypertension also appears to be more common in SCD patients with a history of VTE [11], which may suggest a pathogenic link between the small vessel thrombi seen in SCD patients with pulmonary hypertension and VTE.

VTE management

Anticoagulation

To date, there have been no studies to inform anticoagulation practices in patients with SCD. Small pilot studies have investigated anticoagulant agents such as warfarin, acenocoumarol, and heparin to prevent complications such as vaso-occlusive crisis in SCD [55], but trials evaluating anticoagulation for VTE treatment and prevention are lacking. Anticoagulation management of symptomatic VTE, therefore, currently relies on established general guidelines for VTE management [56]. Because VTE recurrence is common in SCD [11], care should be taken to elicit a comprehensive history of prior VTE to inform treatment duration decisions.

Similar to treatment of VTE, there are no disease-specific guidelines for VTE prophylaxis for high-risk situations in SCD patients. Because frequent hospitalization and ICU admissions are a significant problem in SCD, decisions to prescribe VTE prophylaxis for inpatients should be tailored to the SCD population. Current recommendations rely on individual assessment of thrombotic and bleeding risk factors to determine the need and mode of VTE prophylaxis for hospitalized patients [57]. Characteristics such as age are often used to determine VTE risk but, because VTE risk appears to be high at a young age in SCD, strict age cut-offs may not be appropriate. In addition, because degree of anemia may also influence decisions regarding the risk of bleeding, awareness of baseline hemoglobin values for SCD patients, which often range from 7 to 8 g/dL in hemoglobin SS patients, should be considered so that the risk of bleeding is not overestimated. Prophylactic anticoagulation for orthopedic surgery or pregnancy should similarly be prescribed based on general current practices [58, 59]. For pregnancy, a targeted history of prior VTE is imperative since many women with SCD may have had a history of VTE prior to their pregnancy and prophylaxis decisions often rely on prior events [60].

Current recommendations regarding VTE treatment monitoring with d-dimer levels cannot be reliably applied to patients with SCD. Because people with SCD have chronic activation of the coagulation cascade [55], baseline d-dimer levels are increased compared to controls and have been found to fluctuate with complications such as vasoocclusive crisis [34, 61]; therefore, at this time, d-dimer should not be used to guide VTE diagnosis or treatment decisions in SCD.

Other therapies

Although transfusion appears to decrease the risk of VTE in patients with β -thalassemia [41], chronic transfusion therapy is not currently used for VTE management in SCD patients. Similarly, hydroxyurea, which is a mainstay of treatment in SCD patients, appears to be associated with decreased markers of coagulation [62], however, its effect on VTE risk is not known.

Conclusions

VTE is a significant cause of morbidity and mortality in SCD patients. Anticoagulation experts should be aware of the risk factors and complications of VTE in patients with SCD to ensure that appropriate prophylaxis and treatment decisions are made.

Acknowledgments

Funding: National Heart, Lung, and Blood Institute (NHLBI), National Institute of Health (NIH) 2K12 HL087169-06 (RPN) and K23HL083089-03 (SL).

References

1. Bunn HF. Pathogenesis and treatment of sickle cell disease. *N Engl J Med*. 1997; 337(11):762–769. [PubMed: 9287233]
2. Famodu AA, Oduwa D. Platelet count and platelet factor 3 (PF-3) availability in sickle cell disease. *Br J Biomed Sci*. 1995; 52(4):323–324. [PubMed: 8555788]
3. Foulon I, Bachir D, Galacteros F, Maclouf J. Increased in vivo production of thromboxane in patients with sickle cell disease is accompanied by an impairment of platelet functions to the thromboxane A2 agonist U46619. *Arterioscler thromb*. 1993; 13(3):421–426. [PubMed: 8443146]
4. Kenny MW, George AJ, Stuart J. Platelet hyperactivity in sickle-cell disease: a consequence of hyposplenism. *J Clin Pathol*. 1980; 33(7):622–625. [PubMed: 7430367]
5. Westerman M, Pizzey A, Hirschman J, et al. Microvesicles in haemoglobinopathies offer insights into mechanisms of hypercoagulability, haemolysis and the effects of therapy. *Br J Haematol*. 2008; 142(1):126–135. [PubMed: 18422994]
6. Westerman MP, Green D, Gilman-Sachs A, et al. Anti-phospholipid antibodies, proteins C and S, and coagulation changes in sickle cell disease. *J Lab Clin Med*. 1999; 134(4):352–362. [PubMed: 10521081]
7. Ataga KI, Orringer EP. Hypercoagulability in sickle cell disease: a curious paradox. *Am J Med*. 2003; 115(9):721–728. [PubMed: 14693325]
8. Chiu D, Lubin B, Roelofsen B, van Deenen LL. Sickled erythrocytes accelerate clotting in vitro: an effect of abnormal membrane lipid asymmetry. *Blood*. 1981; 58(2):398–401. [PubMed: 7248527]
9. Villagra J, Shiva S, Hunter LA, Machado RF, Gladwin MT, Kato GJ. Platelet activation in patients with sickle disease, hemolysis-associated pulmonary hypertension, and nitric oxide scavenging by cell-free hemoglobin. *Blood*. 2007; 110(6):2166–2172. [PubMed: 17536019]
10. Ataga KI. Hypercoagulability and thrombotic complications in hemolytic anemias. *Haematologica*. 2009; 94(11):1481–1484. [PubMed: 19880774]
11. Naik RP, Streiff MB, Haywood C, Nelson JA, Lanzkron S. Venous thromboembolism in adults with sickle cell disease: a serious and under-recognized complication. *Am J Med*. doi: 10.1016/j.amjmed.2012.12.016.
12. Novelli EM, Huynh C, Gladwin MT, Moore CG, Ragni MV. Pulmonary embolism in sickle cell disease: a case-control study. *J Thromb Haemost*. 2012; 10:760–766. [PubMed: 22417249]
13. Stein PD, Beemath A, Meyers FA, Skaf E, Olson RE. Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease. *Am J Med*. 2006; 119(10):897.e7–897.e11. [PubMed: 17000225]
14. Lijfering WM, Brouwer JL, Veeger NJ, et al. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2,479 relatives. *Blood*. 2009; 113(21):5314–5322. [PubMed: 19139080]
15. Jeng MR, Feusner J, Skibola C, Vichinsky E. Central venous catheter complications in sickle cell disease. *Am J Hematol*. 2002; 69(2):103–108. [PubMed: 11835345]

16. Abdul-Rauf A, Gauderer M, Chiarucci K, Berman B. Long-term central venous access in patients with sickle cell disease. incidence of thrombotic and infectious complications. *J Pediatr Hematol Oncol*. 1995; 17(4):342–345. [PubMed: 7583391]
17. Alkindi S, Matwani S, Al-Maawali A, Al-Maskari B, Pathare A. Complications of PORT-A-CATH((R)) in patients with sickle cell disease. *J Infect Public Health*. 2012; 5(1):57–62. [PubMed: 22341844]
18. Raj A, Bertolone S, Bond S, Burnett D, Denker A. Cath-link 20: a subcutaneous implanted central venous access device used in children with sickle cell disease on long-term erythrocytapheresis—a report of low complication rates. *Pediatr Blood Cancer*. 2005; 44(7):669–672. [PubMed: 15700248]
19. Phillips G, Slingluff C, Hartman J, Thomas P, Akwari O. Totally implantable intravenous catheters in the management of sickle cell anemia. *Am J Hematol*. 1988; 29(3):134–138. [PubMed: 3189307]
20. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *J Clin Oncol*. 2003; 21(19):3665–3675. [PubMed: 14512399]
21. Takemoto CM. Venous thromboembolism in cystic fibrosis. *Pediatr Pulmonol*. 2012; 47(2):105–112. [PubMed: 22006666]
22. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA*. 2010; 303(13):1288–1294. [PubMed: 20371788]
23. Epstein K, Yuen E, Riggio JM, Ballas SK, Moleski SM. Utilization of the office, hospital and emergency department for adult sickle cell patients: a five-year study. *J Natl Med Assoc*. 2006; 98(7):1109–1113. [PubMed: 16895280]
24. Gardner K, Bell C, Bartram JL, et al. Outcome of adults with sickle cell disease admitted to critical care - experience of a single institution in the UK. *Br J Haematol*. 2010; 150(5):610–613. [PubMed: 20560967]
25. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. national acute chest syndrome study group. *N Engl J Med*. 2000; 342(25):1855–1865. [PubMed: 10861320]
26. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1,056 patients. *Medicine (Baltimore)*. 2005; 84(6):363–376. [PubMed: 16267411]
27. Vichinsky EP, Neumayr LD, Haberkern C, et al. The perioperative complication rate of orthopedic surgery in sickle cell disease: report of the national sickle cell surgery study group. *Am J Hematol*. 1999; 62(3):129–138. [PubMed: 10539878]
28. Adam S, Jonassaint J, Kruger H, et al. Surgical and obstetric outcomes in adults with sickle cell disease. *Am J Med*. 2008; 121(10):916–921. [PubMed: 18823864]
29. Villers MS, Jamison MG, De Castro LM, James AH. Morbidity associated with sickle cell disease in pregnancy. *Am J Obstet Gynecol*. 2008; 199(2):125.e1–125.e5. [PubMed: 18533123]
30. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol*. 2006; 194(5):1311–1315. [PubMed: 16647915]
31. Kucuk O, Gilman-Sachs A, Beaman K, Lis LJ, Westerman MP. Antiphospholipid antibodies in sickle cell disease. *Am J Hematol*. 1993; 42(4):380–383. [PubMed: 8493989]
32. Olayemi EE, Bazuaye GN. Lupus anticoagulant and leg ulcers in sickle cell anemia. *Indian J Dermatol*. 2009; 54(3):251–254. [PubMed: 20161857]
33. Schnog JB, Mac Gillavry MR, van Zanten AP, et al. Protein C and S and inflammation in sickle cell disease. *Am J Hematol*. 2004; 76(1):26–32. [PubMed: 15114593]
34. Piccin A, Murphy C, Eakins E, et al. Protein C and free protein S in children with sickle cell anemia. *Ann Hematol*. 2012; 91(10):1669–1671. [PubMed: 22434279]
35. Tam DA. Protein C and protein S activity in sickle cell disease and stroke. *J Child Neurol*. 1997; 12(1):19–21. [PubMed: 9010791]
36. Khanduri U, Gravell D, Christie BS, Al Lamki Z, Zachariah M, Cherian E. Reduced protein C levels—a contributory factor for stroke in sickle cell disease. *Thromb Haemost*. 1998; 79(4):879–880. [PubMed: 9569210]

37. Porter JB, Young L, Mackie IJ, Marshall L, Machin SJ. Sick cell disorders and chronic intravascular haemolysis are associated with low plasma heparin cofactor II. *Br J Haematol.* 1993; 83(3):459–465. [PubMed: 8485052]
38. Taher A, Isma'eel H, Mehio G, et al. Prevalence of thromboembolic events among 8,860 patients with thalassaemia major and intermedia in the mediterranean area and iran. *Thromb Haemost.* 2006; 96(4):488–491. [PubMed: 17003927]
39. Schilling RF, Gangnon RE, Traver MI. Delayed adverse vascular events after splenectomy in hereditary spherocytosis. *J Thromb Haemost.* 2008; 6(8):1289–1295. [PubMed: 18485083]
40. Cappellini MD. Coagulation in the pathophysiology of hemolytic anemias. *Hematol Am Soc Hematol Educ Program.* 2007; 2007:74–78.
41. Taher AT, Musallam KM, Karimi M, et al. Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the optimal care study. *Blood.* 2010; 115(10):1886–1892. [PubMed: 20032507]
42. Rogers ZR, Wang WC, Luo Z, et al. Biomarkers of splenic function in infants with sickle cell anemia: baseline data from the baby hug trial. *Blood.* 2011; 117(9):2614–2617. [PubMed: 21217080]
43. Lane PA, O'Connell JL, Lear JL, et al. Functional asplenia in hemoglobin SC disease. *Blood.* 1995; 85(8):2238–2244. [PubMed: 7718896]
44. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. *Blood Rev.* 2007; 21(1):37–47. [PubMed: 17084951]
45. Ballas SK, Lewis CN, Noone AM, Krasnow SH, Kamarulzaman E, Burka ER. Clinical, hematological, and biochemical features of hb SC disease. *Am J Hematol.* 1982; 13(1):37–51. [PubMed: 7137165]
46. Mancini EA, Culbertson DE, Yang YM, et al. Causes of death in sickle cell disease: an autopsy study. *Br J Haematol.* 2003; 123(2):359–365. [PubMed: 14531921]
47. Mekontso Dessap A, Deux JF, Abidi N, et al. Pulmonary artery thrombosis during acute chest syndrome in sickle cell disease. *Am J Respir Crit Care Med.* 2011; 184(9):1022–1029. [PubMed: 21836136]
48. Miller ST. How I treat acute chest syndrome in children with sickle cell disease. *Blood.* 2011; 117(20):5297–5305. [PubMed: 21406723]
49. Mehari A, Gladwin MT, Tian X, Machado RF, Kato GJ. Mortality in adults with sickle cell disease and pulmonary hypertension. *JAMA.* 2012; 307(12):1254–1256. [PubMed: 22453563]
50. Anthi A, Machado RF, Jison ML, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *Am J Respir Crit Care Med.* 2007; 175(12):1272–1279. [PubMed: 17379852]
51. Adedjeji MO, Cespedes J, Allen K, Subramony C, Hughson MD. Pulmonary thrombotic arteriopathy in patients with sickle cell disease. *Arch Pathol Lab Med.* 2001; 125(11):1436–1441. [PubMed: 11697998]
52. Jerath A, Murphy P, Madonik M, Barth D, Granton J, de Perrot M. Pulmonary endarterectomy in sickle cell hemoglobin C disease. *Eur Respir J.* 2011; 38(3):735–737. [PubMed: 21885420]
53. Haque AK, Gokhale S, Rampy BA, Adegboyega P, Duarte A, Saldana MJ. Pulmonary hypertension in sickle cell hemoglobinopathy: a clinicopathologic study of 20 cases. *Hum Pathol.* 2002; 33(10):1037–1043. [PubMed: 12395378]
54. Ataga KI, Moore CG, Hillery CA, et al. Coagulation activation and inflammation in sickle cell disease-associated pulmonary hypertension. *Haematologica.* 2008; 93(1):20–26. [PubMed: 18166781]
55. Ataga KI, Key NS. Hypercoagulability in sickle cell disease: new approaches to an old problem. *Hematol Am Soc Hematol Educ Program.* 2007; 2007:91–96.
56. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest.* 2012; 141(2 Suppl):e419S–e494S. [PubMed: 22315268]
57. Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P. Clinical guidelines committee of the American college of physicians. venous thromboembolism prophylaxis in hospitalized patients: a

- clinical practice guideline from the american college of physicians. *Ann Intern Med.* 2011; 155(9): 625–632. [PubMed: 22041951]
58. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest.* 2012; 141(2 Suppl):e278S–e325S. [PubMed: 22315265]
59. Bates SM. Pregnancy-associated venous thromboembolism: prevention and treatment. *Semin Hematol.* 2011; 48(4):271–284. [PubMed: 22000093]
60. Naik RP, Lanzkron S. Baby on board: what you need to know about pregnancy in the hemoglobinopathies. *Hematol Am Soc Hematol Educ Program.* 2012; 2012:208–214.
61. Kabrhel C, Mark Courtney D, Camargo CA, et al. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. *Acad Emerg Med.* 2010; 17(6):589–597. [PubMed: 20624138]
62. Colella MP, De Paula EV, Conran N, et al. Hydroxyurea is associated with reductions in hypercoagulability markers in sickle cell anemia. *J Thromb Haemost.* 2012; 10(9):1967–1970. [PubMed: 22817333]

Table 1

Factors influencing development of VTE in SCD patients

Traditional risk factors	SCD-related factors
Central venous catheters (CVCs) for poor venous access, transfusion therapy	Increased prevalence of thrombophilic defects
<ul style="list-style-type: none"> • Totally implantable CVCs (port) • Partially implantable CVCs (tunneled and nontunneled lines) 	<ul style="list-style-type: none"> • Anti-phospholipid antibodies • Protein C/S deficiency
Frequent hospitalization for pain and complications	Genotype (SS/S ⁰ vs. SC/S ⁺)
Surgery	Splenectomy
<ul style="list-style-type: none"> • Orthopedic surgery (hip, shoulder avascular necrosis) • Cholecystectomy 	<ul style="list-style-type: none"> • Surgical • Functional asplenia?
Pregnancy	

VTE venous thromboembolism, SCD sickle cell disease

Table 2

Symptomatic VTE associated with TIVADs in patients with SCD

Reference	No of patients	No of catheters	Mean age (years)	Total catheter days/ mean days per catheter	VTE events per total catheters (%)	Incidence of VTE per 1,000 TIVAD days
Alkindi et al. [17]	16	24	31	16,523/688	3 (12.5)	0.18
Raj et al. [18]	15	20	14	19,230/962	3 (15.0)	0.16
Jeng et al. [15]	15	41	18 (median)	12,120/296	12 (29.3)	0.99
Abdul-Rauf et al. [16]	25	31	12	17,444/563	5 (16.1)	0.29
Phillips et al. [19]	8	10	30	4,308/431	2 (20.0)	0.46

VTE venous thromboembolism, TIVADs totally implantable venous access devices, SCD sickle cell disease