Published in final edited form as:
Am J Med. 2013 May ; 126(5): 443–449. doi:10.1016/j.amjmed.2012.12.016.

Venous thromboembolism in adults with sickle cell disease: A serious and under-recognized complication

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Abstract

BACKGROUND—Sickle cell disease is recognized as a hypercoagulable state; however the frequency and characteristics of venous thromboembolism in sickle cell patients have not been well-defined.

PURPOSE—To establish the prevalence and risk factors for venous thromboembolism in a large cohort of patients with sickle cell disease and determine the relationship between venous thromboembolism and mortality.

METHODS—We performed a cross-sectional study of 404 sickle cell disease patients cared for at the Sickle Cell Center for Adults at Johns Hopkins. Demographic, sickle cell disease-specific comorbidity, and venous thromboembolism data were collected on all patients.

RESULTS—101 patients (25%) had a history of venous thromboembolism with a median age at diagnosis of 29.9 years. A history of non-catheter-related venous thromboembolism was found in 18.8% of patients. Sickle variant genotypes conferred a higher risk of non-catheter-related venous thromboembolism compared to sickle cell anemia genotypes (SS/Sβ^0) (relative risk (RR) 1.77, 95% confidence interval (CI) 1.18–2.66). Tricuspid regurgitant jet velocity ≥ 2.5 m/s was also associated with non-catheter-related venous thromboembolism (RR 1.65, CI 1.12–2.45). Thirty patients (7.4%) died during the study period. Adjusting for all variables, non-catheter-related venous thromboembolism was independently correlated with death (RR 3.63, CI 1.66–7.92).

CONCLUSION—Venous thromboembolism is common in adults with sickle cell disease. Sickle variant genotypes and tricuspid regurgitant jet velocity ≥ 2.5m/s are associated with non-catheter-related venous thromboembolism. In addition, non-catheter-related venous thromboembolism appears to be an independent risk factor for death in our cohort. These results suggest that disease-specific prophylaxis and treatment strategies for venous thromboembolism should be investigated in sickle cell disease patients.

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Authorship: All authors had access to the data and played a role in writing this manuscript.

Conflict of Interest: MBS has provided consulting services to Sanofi-Aventis, Daiichi-Sakyo, Eisai, and Janseen HealthCare; has received honoraria from Sanofi-Aventis and Ortho-McNeil; has received funding from Bristol-Myers-Squibb; and has provided expert testimony relating to thrombosis. SL serves on the scientific advisory board for Hemaquest.

Introduction

Microvascular and small-vessel arterial thrombosis is common in sickle cell disease contributing to severe complications such as pulmonary hypertension, osteonecrosis, and stroke.[1–3] Various mechanisms have been hypothesized to contribute to thrombogenesis in sickle cell disease patients including erythrocyte adhesion,[4] endothelial dysfunction,[5] leukocyte activation in the setting of chronic inflammation,[6] platelet aggregation,[7–10] coagulation defects, [11] and free hemoglobin-induced oxidative damage. [10, 12] Nitric oxide scavenging secondary to intravascular hemolysis also results in hypercoagulability in sickle cell disease and may be an important mediator of thrombotic complications.[10] While it is widely recognized that sickle cell disease is associated with a hypercoagulable state, most research has focused on *in-situ* thrombosis as the primary clinical manifestation, and previous reports investigating the risk and characteristics of venous thromboembolism have yielded conflicting results. Prior studies using large databases with de-identified records found the prevalence of pulmonary embolism in hospitalized sickle cell patients younger than 40 years of age to be significantly higher than African-American controls,[13] but did not find the overall prevalence of pulmonary embolism to be higher in sickle cell disease.[13, 14] In addition, the risk of deep venous thrombosis was not found to be increased in patients with sickle cell disease.[13] In contrast, autopsy studies have demonstrated pulmonary emboli in 20–50% of sickle cell patients,[15–18] and studies evaluating thrombotic complications in pregnancy have demonstrated an increased risk of deep venous thromboses in sickle cell disease patients compared to controls.[19, 20] Furthermore, because sudden death accounts for a significant proportion of mortality in adult sickle cell disease patients,[21] venous thromboembolism may be an important and unrecognized cause of morbidity and mortality in the sickle cell population.

We hypothesized that venous thromboembolism is more common in sickle cell disease than previously reported. We performed a retrospective analysis of a large cohort of adult sickle cell patients to assess the prevalence and mortality associated with venous thromboembolism in sickle cell disease. In addition, we sought to identify traditional and sickle cell disease-specific risk factors for venous thromboembolism in our cohort.

Methods

We conducted a retrospective cross-sectional study of sickle cell patients cared for at the Sickle Cell Center for Adults at Johns Hopkins between August 2008 and January 2012. Inclusion criteria included an age ≥18 years and a known genotype. Patients who had undergone successful bone marrow transplant prior to the study period were not included. The study was approved by the Institutional Review Board and was determined to be exempt from informed consent.

Data was collected via review of electronic charts. Information on genotype, age, sex, relevant comorbidities, and date of death were recorded for all patients. We defined sickle cell anemia genotypes as SS or $S\beta^0$ and sickle cell variant genotypes as all other sickle compound heterozygous states, such as SC or $S\beta^+$. As part of routine health maintenance, we collect information on sickle cell disease-specific co-morbidities including a history of venous thromboembolism, stroke, avascular necrosis, end-stage-renal disease, and leg ulcer on all patients with sickle cell disease. In addition, we refer all patients for screening echocardiograms to determine baseline tricuspid regurgitant jet velocity values. Patients who did not have complete data for the health maintenance evaluation were excluded from the study. Death was verified by available chart records and the Social Security Death Index.

Venous thromboembolism events were defined as those that were symptomatic and were subsequently recommended to be treated with full-dose anticoagulation. A diagnosis of venous thromboembolism was defined by a history of a positive Duplex ultrasound, ventilation-perfusion scan, or computed tomography angiography in most cases. When radiology reports were not available, only patients who had a documented history of anticoagulation treatment were included as venous thromboembolism cases. This criterion has previously been verified as having high specificity for a history of venous thromboembolism.[22] For thromboembolism cases, data was collected on the date of diagnosis, first recurrence, site of thrombosis, and central venous catheter-related status. Additional triggering factors, including oral contraceptive use, pregnancy, active cancer, hospitalization, and surgery, were also recorded. Hospitalization-associated clots were defined as any venous thromboembolism occurring >24 hours after admission or within 90-days after discharge.

T-test and chi-square statistics were used for bi-variate analyses. Poisson regression with a robust estimate of variance was used to identify independent risk factors associated with venous thromboembolism and death, and results are presented as relative risk (RR) and 95% confidence interval (CI). Regression models were performed using genotype, age, sex, and relevant comorbidities. Because of the high rate of central-line use in the sickle cell population, the variability in indication for central-line use including chronic transfusions, recurrent vaso-occlusive crisis and poor venous access, and the high incidence of catheter-triggered thrombosis in sickle cell disease,[23] patients who had only experienced a catheter-related event were excluded from the regression analyses in order to identify factors associated with venous thromboembolism and death, rather than factors associated with catheter use. In addition, because age was not normally distributed, it was analyzed as a categorical variable. Tricuspid regurgitant jet velocity ≥ 2.5 m/s was also used as a categorical variable. Patients who had an un-measurable tricuspid regurgitant jet velocity by echocardiogram were assumed to have values less than 2.5 m/s. All statistics were performed using STATA Data Analysis and Statistical Software (Version 10, College Station, TX). Statistical significance was defined as a p-value <0.05.

Results

Patient Characteristics

Five hundred and three patients were seen in the Sickle Cell Center for Adults at Johns Hopkins from August 2008 to January 2012. Of those patients, 4 had unknown genotype and 2 had undergone successful bone marrow transplant and therefore were excluded. Of the remaining 497 patients, 404 patients (81.3%) had complete data on venous thromboembolism history and relevant comorbidities for analysis. Within our cohort, 69% (279/404) had sickle cell anemia genotypes. Of the 125 patients with sickle variant genotypes, 84 had SC disease, 39 had $S\beta^+$ genotype, and 4 had other documented sickle cell variants. Women comprised 58.9% (238/404) of our cohort. Median age at follow-up was 35.8 years (19–83 years), and 147 patients (36.4%) were >40 years of age.

Prevalence of Venous Thromboembolism

A history of venous thromboembolism was confirmed in 101 (25%) patients. The median age at diagnosis of first venous thrombosis was 29.9 years. Seventy-four (18.3%) patients had a documented history of deep venous thrombosis and 53 (13.1%) patients had experienced a pulmonary embolism. Prevalence and characteristics of venous thromboembolism by genotype status are summarized in table 1. Seventy-six (18.8%) patients had a history of at least one non-catheter-related venous thromboembolism. The prevalence of non-catheter-related venous thromboembolism was significantly higher in

patients with sickle variant genotypes than those with sickle cell anemia genotypes (26.4% vs. 15.4%, p=0.009). Similarly, the prevalence of pulmonary embolism was higher in the sickle variant group (19.2% vs. 10.4%, p=0.015). Sickle variant patients were also older at diagnosis than patients with sickle cell anemia (34.2 years vs. 28.0 years, p=0.006).

Venous Thromboembolism Recurrence and Provoking Factors

With a median follow-up of 4.8 years (range 0–34 years) after initial venous thromboembolism, twenty-five patients (24.8%) had a documented recurrent event. The median time to recurrence was 1.8 years (range 0.1–12 years). Eighteen out of 25 (72.0%) patients with recurrent venous thromboembolism experienced a recurrence >1 year after their first event. Thirty-one patients (30.7%) developed a catheter-related venous thromboembolism as their initial clot event, 1 of whom developed a subsequent catheter-related clot, and 6 of whom later experienced a non-catheter-related venous thromboemboli. In addition, 25/31 (80.6%) catheter-related clots occurred in patients with sickle cell anemia genotypes, which likely reflects the high use of catheters in those patients.

Seventy-six patients experienced at least one non-catheter-related venous thromboembolism. Table 2 lists identifiable provoking factors for first non-catheter-related venous thromboembolism in these patients. Of the 238 women in our cohort, 10 (4.2%) had a history of venous thromboembolism during pregnancy or after delivery, 2 of whom experienced a recurrence during a subsequent pregnancy. Surgery (excluding cesarean-section) was identified as a provoking factor in 4 patients. Because of the retrospective nature of our study, hospitalization status could not be definitively assessed for 15 patients. However, hospitalization was known to be the sole provoking factor in 18 patients. No patients had active cancer at the time of their VTE. Of the 60 patients with non-catheter-related venous thromboembolism who had complete records for all provoking factors including hospitalization status, 25 (41.7%) had a history of idiopathic VTE.

Risk Factors for Non-Catheter-Related Venous Thromboembolism

Demographic and clinical risk factors for patients with sickle cell disease according to history of non-catheter-related venous thromboembolism are summarized in table 3. There was no significant difference in age or sex between patients with and without non-catheter-related venous thromboembolism. Sickle variant genotype was strongly correlated with non-catheter-related thrombosis on bivariate analysis (p =0.014). Among the sickle cell disease-specific comorbidities, a tricuspid regurgitant jet velocity ≥ 2.5 m/s was also significantly associated with a history of non-catheter-related venous thromboembolism (p=0.020).

Table 4 shows the Poisson regression model for non-catheter-related venous thromboembolism. Patients with sickle variant genotypes were more likely to develop a non-catheter-related venous thrombosis compared to those with sickle cell anemia genotypes, with a relative risk of 1.8 (RR 1.77, CI 1.18–2.66). Tricuspid regurgitant jet velocity ≥ 2.5 m/s (RR 1.65, CI 1.12–2.45) was also found to be associated with a history of non-catheter-related venous thromboembolism. Although our primary analysis was performed with non-catheter-related events, it is important to note that the tricuspid regurgitant jet velocity association was still observed when all clots (both catheter and non-catheter-related) were included in the analysis (RR 1.56, CI 1.12–2.16). Similarly, sickle variant genotype demonstrated a trend toward significance in the all-venous thromboembolism model (RR 1.49, CI 0.98–1.99), though true statistical significance could not be seen given the high proportion of sickle cell anemia genotype patients in the catheter-related group.

Mortality

During our study period of August 2008 to January 2012, 30 (7.4%) patients died. Four patients had a history of only catheter-related clots and, therefore, were excluded from risk factor analysis. Of the patients who died, 12 had a history of non-catheter-related venous thromboembolism and died a median of 1.8 years (0–11 years) after their first thrombotic event. Mortality in patients with a history of non-catheter-related venous thromboembolism was statistically higher than in patients without prior venous thromboembolism on bi-variate analysis (15.8% vs. 4.6%, p=0.001). On regression analysis adjusting for all variables (Table 5), end-stage renal disease (RR 3.03, CI 1.16–7.93) and tricuspid regurgitant jet velocity ≥ 2.5 m/s (RR 3.40, CI 1.47–7.87) were independently associated with mortality, as has been described previously.[21, 24, 25] In addition, patients with a history of non-catheter-related venous thromboembolism were 3.6 times more likely to die than those without a history of venous thromboembolism on multivariate analysis (RR 3.63, CI 1.66–7.92). This association with mortality did not substantially change when all clots (catheter and non-catheter-related) were included in the model (RR 3.46, CI 1.65–7.25).

Discussion

Venous thromboembolism is not generally recognized as a common comorbidity in sickle cell patients. In fact, venous thromboembolism has not been included in comprehensive reviews of complications associated with sickle cell disease.[24, 26] We found that 25% of adult patients with sickle cell disease have a history of a venous thromboembolism, a prevalence that is similar to that seen at baseline in family studies of patients with strong thrombophilic defects such as antithrombin, protein C and protein S deficiency (21%).[27] We also found that the median age for first thromboembolism was 29.9 years, which is significantly younger than noted for the general population (65 years),[28] but is comparable to the age observed in families with high-risk thrombophilia (29 years).[27] Furthermore, it has been suggested that high hospitalization rates may influence the assessment of sickle cell disease as an independent risk factor for venous thromboembolism.[29] However, although our study lacked complete traditional risk factor data for all case patients, we were able to verify that at least 32.9% (25/76) of patients with non-catheter-related venous thromboembolism experienced an idiopathic event. These findings underscore the potent thrombophilic stimulus associated with sickle cell disease and suggest that sickle cell disease is an independent risk factor for venous thromboembolism.

Not surprisingly, we found that catheters were a significant trigger for venous thrombosis, an observation that has been made previously.[23] Catheter-related venous thromboembolism was more likely to occur in patients with sickle cell anemia ($SS/S\beta^0$) genotypes, consistent with the high use of catheters for treatment in this subgroup.[23, 30] In contrast, we found that non-catheter-related venous thromboembolism was significantly more common in adult patients with sickle variant genotypes than in patients with sickle cell anemia. We suspect that increased whole blood viscosity may underlie this genotypic difference. Higher blood viscosity has also been hypothesized to contribute to the higher incidence of proliferative retinopathy and osteonecrosis observed in patients with SC or $S\beta^+$ compared to patients with SS genotype.[31–33] A similar phenotypic phenomenon has been noted in β-thalassemia where the prevalence of venous thromboembolism has been noted to be higher in patients with β-thalassemia intermedia compared to those with β-thalassemia major.[34] Unfortunately, we were not able to reliably record and analyze baseline hematologic parameters for all patients in our current retrospective evaluation, and further investigation will be necessary to validate this relationship.

Another major finding of our study is that a history of non-catheter-related venous thromboembolism was an independent risk factor for death in sickle cell patients. While the

etiology of death of each individual patient in our cohort cannot be determined, the increased mortality risk implies that underlying hypercoagulability may lead to death in patients with sickle cell disease. The Cooperative Study of Sickle Cell Disease, a natural history study of 3764 patients, found that sudden death accounted for a majority of mortality in sickle cell disease patients.[21] Given the uncertainty about cause of death in sickle cell patients, a few recent autopsy studies have been performed in select groups. In one autopsy study of sickle cell disease patients with sudden death, pulmonary embolism was thought to have contributed to fatality in 38.1% of cases.[16] In another post-mortem study in sickle cell patients with pulmonary hypertension, large-vessel pulmonary emboli contributed to death in 6 out of 9 patients.[15] In both of these studies, pulmonary embolism was differentiated from fat emboli and microvascular pulmonary thrombi to reflect the contribution of true macrovascular thrombosis to death.

The pathogenesis of pulmonary thrombosis in patients with sickle cell disease has been debated given the difficulty in differentiating between *in-situ* arterial thrombosis and thromboembolic disease in both autopsy and clinical studies.[15, 35] A large database study in hospitalized patients with sickle cell disease demonstrated an increased prevalence of pulmonary embolism compared to African-American controls but failed to show a corresponding increase in deep venous thrombosis risk.[13] In contrast, we found that sickle cell patients had equally high rates of both deep venous thrombosis and pulmonary embolism, with a prevalence of 18.3% and 13.1% respectively, and that 52.8% of the sickle cell disease patients diagnosed with pulmonary embolism also had a history of deep venous thrombosis. A prior report of unselected patients with acute pulmonary embolism found that 60% had ultrasound-diagnosed deep venous thrombosis at the time of presentation, which is similar to the rate we found in our patients.[36] The high prevalence of deep venous thrombosis alone as well as the high rate of concomitant deep venous thrombosis and pulmonary embolism suggests that thromboembolism is the primary mechanism of radiology-defined pulmonary thrombosis in sickle cell disease.

Our finding that a tricuspid regurgitant jet velocity ≥ 2.5 m/s is associated with a history of venous thromboembolism may suggest a pathogenic link between large-vessel venous thrombosis and the small-vessel thrombi observed in autopsied sickle cell patients with pulmonary hypertension. [15, 37, 38] Prior studies have concluded that chronic thromboembolic disease as defined by V/Q scan[39] or magnetic resonance angiography[40] is not common in sickle cell disease patients with tricuspid regurgitant jet velocity ≥ 2.5 m/s. However, studies in sickle cell disease patients with catheterization-confirmed pulmonary hypertension will be needed to definitively determine the contribution of chronic thromboemboli to pulmonary hypertension and to evaluate the relationship between venous thromboembolism and high pulmonary pressures.

Our study has a number of strengths and limitations. A significant strength of the study is the availability of a dedicated sickle cell center with access to inpatient and outpatient records of a large cohort of sickle cell patients who survived to adulthood. This structure allowed us to collect sickle cell disease-specific data that would not be available in an administrative database. In addition, because previous database studies have relied on records that lacked patient identifiers, they may have underestimated pulmonary embolism and deep venous thrombosis risk in the sickle cell population that has known high hospitalization rates.[41] The data in our study, on the other hand, were collected from known sickle cell disease patients with identified patient records and, therefore, more accurately reflect the true prevalence of venous thromboembolism in adult sickle cell patients.

The retrospective nature of our study is its major limitation. Our analysis was restricted to data collected during the routine care and, therefore, patient comorbidities and risk factors

may not have been recorded in some cases. Another limitation is that we lacked data for administered prophylactic anticoagulation for hospitalized inpatients and for compliance with anticoagulation treatment in patients with venous thromboembolism. We also lacked cause of death data for the patients who died during the study period. In addition, because our institution is an academic medical center, our data may have been subject to some degree of referral bias; however, given the rarity of sickle cell disease, tertiary centers are often the main providers of sickle cell care and, therefore, often reflect a heterogeneous and representative population of sickle cell patients.

In summary, our study is the first to systematically analyze venous thromboembolism data in a large cohort of adult sickle cell disease patients. Our findings indicate that venous thromboembolism is a common and under-recognized cause of morbidity and mortality in sickle cell disease. Patients with sickle variant genotypes appear to be at the greatest risk of VTE. Prospective investigation is warranted to identify the optimal approach for treatment and prevention of venous thromboembolism in sickle cell disease.

Acknowledgments

Funding: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH) 2K12 HL087169-06 (RPN), 1K01HL108832-01 (CH), K23HL083089-03 (SL).

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Table 1

Prevalence and characteristics of venous thromboembolism among 404 patients with sickle cell disease by genotype

Variable	All patients (n = 404)	Sickle cell anemia (n = 279)	Sickle variant (n = 125)	*p* value
Median age at 1st venous thromboembolism (years)	29.9 (15.9–81.0)	28.0 (15.9–63.5)	34.2 (16.9–81.0)	0.006
Any venous thromboembolism	101 (25.0)	63 (22.6)	38 (30.4)	0.093
Deep venous thrombosis	74 (18.3)	51 (18.3)	23 (18.4)	0.977
Pulmonary embolism	53 (13.1)	29 (10.4)	24 (19.2)	0.015
Other venous thrombosis *	4 (1.0)	2 (0.7)	2 (1.6)	0.055
Non-catheter-related venous thromboembolism	76 (18.8)	43 (15.4)	33 (26.4)	0.009

All results expressed as number (percent) or number (range). Percentages do not add up to 100 because of overlap of groups.

* Includes 3 patients with abdominal vein thrombosis and 1 patient with cerebral vein thrombosis.

Table 2

Identifiable provoking factors for first non-catheter-related venous thromboembolism in 76 patients with sickle cell disease

Provoking Factor	Number (percent)
Hormone-related	
Pregnancy or post-partum	10 (13.2)
Oral Contraceptives	3 (3.9)
Surgery *	4 (5.3)
Hospitalization Status	
Hospitalization -associated †	18 (23.7)
Unknown hospitalization status	16 (21.1)
No Provoking Factors Identified (Idiopathic) ‡	25 (32.9)

Provoking factors are listed as mutually exclusive variables.

* Surgery does not include cesarean section. Venous thromboembolism that occurred after cesarean section were listed as pregnancy-related.

† Defined as venous thromboembolism occurring > 24 hours after admission or occurring within 90 days post-discharge. Does not include surgery or pregnancy-related admissions.

‡ Includes only patients who had complete information about all provoking factors.

Table 3

Demographics and clinical co-morbidities in 379 sickle cell disease patients with no history of venous thromboembolism verses patients with a history of non-catheter-related venous thromboembolism

Variable	No Venous Thromboembolism (n = 303)	Non-Catheter-Related Venous Thromboembolism (n = 76)	*p* value
Demographics			
Age* (years)			
18–30	117 (38.6)	21 (27.6)	0.144
31–40	84 (27.7)	21 (27.6)	
41–50	68 (22.4)	19 (25.0)	
51–60	20 (6.6)	11 (14.5)	
>60	14 (4.6)	4 (5.3)	
Female	171 (56.4)	52 (68.4)	0.058
Sickle variant genotype	87 (28.7)	33 (43.4)	0.014
Co-morbidities			
End-stage renal disease	7 (2.3)	3 (3.9)	0.426
Avascular necrosis	103 (34.0)	35 (46.1)	0.051
Stroke	37 (12.2)	10 (13.2)	0.823
Leg Ulcer	28 (9.2)	9 (11.8)	0.495
Tricuspid regurgitant jet velocity ≥ 2.5 m/s	93 (30.7)	34 (44.7)	0.020

All results expressed as number (percent).

*Age refers to age at last follow-up.

Table 4

Poisson regression model of risk factors for non-catheter-related venous thromboembolism among adults with sickle cell disease

Variable	RR	CI
Age * (years)		
31–40	1.26	0.74–2.13
41–50	1.27	0.74–2.19
51–60	1.85	0.98–3.51
> 60	0.87	0.32–2.41
Female	1.52	1.00–2.34
Sickle variant genotype	1.77‡	1.18–2.66
Avascular necrosis	1.46	0.98–2.17
Tricuspid regurgitant jet velocity ≥2.5 m/s	1.65†	1.12–2.45

RR = relative risk, CI = 95% confidence interval

*Reference age category is 18–30 years.

†p < 0.05,

‡p < 0.01

Table 5

Poisson regression model of risk factors for mortality among adults with sickle cell disease

Variable	RR	CI
Age* (years)		
31–40	1.08	0.42–2.77
41–50	1.55	0.65–3.69
51–60	0.52	0.06–4.77
> 60	1.03	0.16–6.55
Female	0.56	0.27–1.18
Sickle variant genotype	0.57	0.21–1.58
Venous thromboembolism**	3.63‡	1.66–7.92
End-stage renal disease	3.03†	1.16–7.93
Avascular necrosis	0.58	0.26–1.28
Stroke	1.47	0.62–3.45
Leg ulcer	1.00	0.29–3.49
Tricuspid regurgitant jet velocity ≥ 2.5 m/s	3.40‡	1.47–7.87

RR = relative risk, CI = 95% confidence interval.

*Reference age category is 18–30 years.

†$p < 0.05$,

‡$p < 0.01$

**Does not include catheter-related events.