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## The Excess Burden of Stroke in Hospitalized Adults with Sickle Cell Disease

John J. Strouse, MD<sup>1,2</sup>, Lori C. Jordan, MD<sup>3</sup>, Sophie Lanzkron, MD<sup>2</sup>, and James F. Casella, MD<sup>1</sup>

<sup>1</sup>Division of Pediatric Hematology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

<sup>2</sup>Division of Hematology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

<sup>3</sup>Division of Pediatric Neurology, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

### Abstract

**Objective**—To compare the relative rates and risk factors associated with stroke in adults vs. children with sickle cell disease (SCD) in the U.S. over the last decade.

**Methods**—We identified incident strokes in patients with SCD using ICD-9 codes for acute stroke and SCD and the California Patient Discharge Databases. We estimated SCD prevalence by using the incidence of SCD at birth with adjustment for early mortality from SCD.

**Results**—We identified 255 acute strokes (70 primary hemorrhagic and 185 ischemic) among 69,586 hospitalizations for SCD-related complications from 1998–2007. The rate of stroke in children [ $<18$  years old (310/100,000 person-years)] was similar to young adults [18 to 34 years old (360/100,000 person-years)], but much higher in middle-aged [35 to 64 years old (1160/100,000 person-years)] and elderly adults [ $\geq 65$  years old (4700/100,000 person-years)]. Stroke was associated with hypertension in children and hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and renal disease in adults. Most acute strokes (75%) and in-hospital deaths from stroke (91%) occurred in adults.

**Interpretation**—Our results suggest that the rate of stroke in SCD peaks in older adults and is 3-fold higher than rates previously reported in African-Americans of similar age (35 to 64 years) without SCD. Stroke in SCD is associated with several known adult risk factors for ischemic and hemorrhagic stroke. Studies for the primary and secondary prevention of stroke in adults with SCD are urgently needed.

### Keywords

Stroke; sickle cell disease; epidemiology; transfusion

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Corresponding author: John Strouse, MD, Division of Pediatric Hematology, 200 N. Wolfe Street, Rubenstein Building, Rm 3006, Baltimore, MD 21287, 410-614-6102 (office) 410-502-5114 (fax), jstrous1@jhmi.edu.

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## Introduction

Sickle cell disease (SCD) confers a greatly increased risk of ischemic and primary hemorrhagic stroke. The association with stroke was first described by Sydenhimer in a three-year-old child with left hemiparesis and presumably sickle cell anemia (HbSS) (1). The predisposition to stroke in early childhood has been confirmed in multiple case series (2) and cohort studies, with an incidence of first stroke of 500 to 1000 per 100,000 person-years in those with HbSS (3–5) and 400 to 800 for all patients with SCD (3,5). The high rate of first and recurrent stroke (3) have been the impetus for multiple studies of primary (6–8) and secondary (9–12) prevention of stroke in children with SCD. However, there have not been rigorous studies of stroke prevention in adults with SCD. The few studies describing the epidemiology of stroke in adults with HbSS have been limited by small size and provide imprecise and likely biased estimates of the incidence and prevalence of stroke, and associated outcomes (3,5,13,14). We hypothesize that both the number and incidence rate of stroke in adults with SCD has increased from earlier reports since the widespread use of interventions to prevent early mortality from SCD (15).

## RESULTS

### Stroke Incidence

From 1998 to 2007, there were 255 discharges for acute stroke (70 primary hemorrhagic and 185 ischemic) among 69,586 discharges (including in-hospital deaths) from acute care hospitals for patients with SCD. Discharged patients with stroke had the diagnosis of homozygous sickle cell (51.8%), SCD, not otherwise specified (40.4%), other SCD (2.8%), sickle-hemoglobin C disease (2.4%), or sickle-thalassemia (2.8%). Information on age was masked in 12% of the records of patients with SCD. We estimated that there were 43,542 person-years of observation, including 19,616 for children and 23,926 for adults. Rates of stroke were similar for children <18 years old (310/100,000 person-years, 95% CI 230–390) and young adults 18 to 34 years old (360/100,000 person-years, 95% CI 270–480); however, they increased significantly in middle-aged adults 35 to 64 years old (1160/100,000 person-years, 95% CI 950–1,390,  $p<0.001$ ) and older adults  $\geq 65$  years old (4700/100,000 person-years, 95% CI 2,700–7,600,  $p<0.001$ ) compared to children. Adults 35 to 64 years old had the greatest absolute number of ischemic strokes and the highest incidence rates of ischemic stroke were in these middle-aged (740/100,000 person-years) and older adults [3500/100,000 person-years (Table 1)]. The variation in rates and associated confidence intervals for incident stroke were greater for incidence by 5 year-age groups than for other sub-analyses, since there were relatively few events within each age group (Table 2, Figure 1).

Primary hemorrhagic stroke accounted for 13% of pediatric (32/100,000 person-years) and 34% of adult acute stroke, with a peak in both absolute numbers and incidence in adults 35 to 64 (330/100,000 person-years) and  $\geq 65$  years old [1100/100,000 person-years (Table 1, Figure 1)]. Rates of hemorrhagic stroke were similar by calendar year for children and adults <65 years of age, but, on average, decreased 19% (95% CI 1–38%,  $p<0.05$ ) per year for adults  $\geq 65$  years old.

### Case Fatality Rates

Thirty-four (7%, 95% CI 5.1–10.0) of the 467 deaths in hospitalized patients with SCD were associated with acute stroke. Deaths were seen in all age groups, with an overall case fatality rate of 13% for acute stroke. The case fatality rate per SCD admission (other than for acute stroke) was significantly lower (0.7%, 95% CI 0.6–0.72) than that of ischemic (7%, 95% CI

3.8–11.7) or hemorrhagic stroke (30%, 95% CI 19.6–42.1,  $p < 0.0001$  for pair wise comparisons). Case fatality rates were similar across age groups (Table 1).

### Length of Stay and Hospital Costs

Mean length of stay was similar for ischemic (9 days, median 6, IQR 3–10) and hemorrhagic stroke (10 days, median 7, IQR 2–15,  $p > 0.5$ ) but on average significantly longer than for other diagnoses in patients with SCD (6 days, median 4, IQR 2–7,  $p < 0.001$  for ischemic and hemorrhagic stroke). Hospital charges were significantly higher for hemorrhagic stroke (median \$79,307, IQR 24,301–153,405) compared to ischemic stroke (median \$32,216, IQR 19,214–63,704,  $P < 0.005$ ) or other diagnoses (\$16,005, IQR 8,519–30,815,  $p < 0.0001$ )

### Comorbid Conditions and Treatments

Acute stroke in SCD was strongly associated with ICD-9 codes for a number of comorbid conditions that are known risk factors for stroke. In adults, we identified a significantly increased odds ratio for hypertension, hyperlipidemia, renal disease, and atrial fibrillation for ischemic stroke and for hypertension, renal disease and coagulopathy for hemorrhagic stroke (Table 3). Hypertension was associated with hemorrhagic and ischemic stroke in children and adults. The association with hypertension was significantly stronger for hemorrhagic than ischemic stroke (Table 3). A diagnosis of renal failure (OR 3.6, 95% CI 1.3–9.4  $p < 0.005$ ) or coagulopathy [OR 7.2 (1.2–40,  $p < 0.005$ )] was associated with an increased risk of death from acute stroke. There were no significant differences in mortality for patients with other risk factors for stroke. A diagnosis of asthma was not significantly associated with all acute stroke, but was less frequent in patients with hemorrhagic stroke. A diagnosis of sickle cell crisis was significantly less frequent (37%) in patients with stroke compared to those without (72%). Transfusion was more frequent in patients with ischemic (48%) vs. hemorrhagic stroke (26%) and in children (53%) vs. adults (39%,  $P < 0.05$ ). Only 26% of transfusions for ischemic stroke and 6% for hemorrhagic stroke were coded as exchange transfusions.

### Discussion

We provide, to our knowledge, the first population-based incidence of stroke in adults with SCD. By using a large database of discharge diagnoses and a stringent administrative definition of acute stroke, we were able to estimate the incidence of stroke in all patients in California with a known diagnosis of SCD. These results suggest that older adults have the greatest absolute number and rate of both hemorrhagic and ischemic stroke in patients with SCD. We found that the rate of stroke in patients with SCD was 3 fold higher than that of stroke in African-Americans of similar age (35 to 64 years). We conclude that SCD is an important risk factor for stroke in older adults with SCD as it is in young adults (approximately 20 fold increased risk) (24).

Our estimates of the incidence of stroke in children with SCD (310/100,000 person-years) were substantially lower than those reported from a large cohort study in southern California (800/100,000 person-years for initial stroke) (3), but similar to those reported in the Cooperative Study of Sickle Cell Disease (CSSCD, 400/100,000) and the Baltimore-Washington Cooperative Study of Stroke (285/100,000) (5,25). They are also lower than those reported by Fullerton *et al.* in a study of first stroke in children with HbSS that also used the California Patient Discharge Databases for 1991 to 1998 (880 per 100,000 person years) (22). This may reflect their exclusion of other genotypes of SCD with lower stroke incidence than HbSS or our exclusion of ICD-9 codes with poor specificity for acute stroke, including codes for transient ischemic attacks, late effects of stroke, and occlusion of the precerebral arteries. An alternative explanation is that the incidence of stroke has truly

decreased during the late 1990's. Fullerton *et. al* reported much lower rates of stroke for 1999 and 2000 (500 and 170/100,000 person-years) and postulated that this was the result of widespread screening for elevated cerebral blood flow velocities by transcranial Doppler ultrasound and treatment of those at high risk with regular blood transfusions (22).

Our estimates of stroke incidence are higher than those reported from the CSSCD for older adults (26), but a four-decade cohort study of patients with SCD from a single institution also demonstrated a higher rate of hemorrhagic stroke in patients 35 to 54 years old (13). The CSSCD may have underestimated stroke rates in older adults because of survival or enrolment bias, since patients with more severe SCD were less likely to survive to the 5<sup>th</sup> and 6<sup>th</sup> decade of life. In addition, both cohorts had fewer person-years of observation for adults  $\geq 35$  years old, resulting in much less precise estimates of stroke rates than this study (5,13).

We also found differences in case fatality rates. We found similar overall hospital mortality to the CSSCD [13% (34/255) vs. 8% (11/133, P=NS) after acute stroke with higher hospital mortality for ischemic [7% (13/185) vs. 0% (0/96, P<0.01)] but not hemorrhagic stroke [30% (21/70) vs. 26% (9/35, P=NS). We propose that the case fatality rate for ischemic stroke in SCD may be higher outside formal cohort studies or dedicated centers that provide comprehensive care for SCD. We also identified potentially higher overall stroke mortality in children (5%) than an earlier study using the same California discharge data and limited to first stroke in children with SCD (1.1%, p=0.14) (22). This may reflect an increased risk of death with recurrent stroke or our more stringent definition of stroke. Case fatality rates for primary hemorrhagic stroke in SCD are similar to the general population (20–45%) (27), but significantly lower than those reported for ischemic stroke in children (15%) (28) or adults (10–20%) in the general population (27) .

We evaluated several previously identified risk factors for stroke, including hypertension (29) obesity, tobacco use, diabetes mellitus, hyperlipidemia, renal disease, history of myocardial infarction, atrial fibrillation, and coagulopathy (23,30), as well as asthma, and concomitant crisis. We found a strong relationship between stroke and hypertension and also identified new risk factors for stroke in SCD, including diabetes mellitus, hyperlipidemia, renal disease, and atrial fibrillation. Hypertension and coagulopathy were more strongly associated with hemorrhagic than ischemic stroke; however, the temporal relationship between hypertension and stroke cannot be established from this study, since hypertension may be secondary to increased intracranial pressure from stroke. High blood pressure has been associated with an increased volume of hemorrhage (31) and increased mortality (32) in stroke, but we identified an increased risk of death only in those with concomitant renal failure or coagulopathy. End-stage renal failure is associated with a greatly increased risk of both ischemic and hemorrhagic stroke in the general population. This risk has been attributed to both the accelerated atherosclerotic vascular disease and the bleeding diathesis associated with renal failure. In addition, patients on dialysis for end stage renal failure have an increased risk of death after both intracranial hemorrhage (56% vs. 16%) and ischemic stroke (28% vs. 17%) than the population overall (33). One potential strategy to decrease stroke incidence and mortality in patients with SCD might be to aggressively treat known risk factors for stroke.

It is surprising that only about half of children with acute ischemic stroke had a transfusion documented during their hospital admission. This is higher than the 33% of children that received transfusion in an earlier study which used the California discharge database(22), and may reflect incomplete ascertainment of transfusion, errors in the coding, or lower rates of transfusion at certain facilities. Immediate transfusion remains the standard treatment for acute ischemic stroke in children with SCD (34). The relative benefit of an immediate

simple transfusion versus the delay often required to coordinate an exchange transfusion remains an area of controversy; however, a retrospective study from 14 pediatric sickle cell centers demonstrated a substantial decrease in risk of recurrent stroke in children initially treated with exchange transfusion when compared to those receiving simple transfusion (35). For adults with SCD, treatment recommendations for acute ischemic stroke include urgent consultation with a hematologist about the utility of transfusion, aspirin, and thrombolytics, if strict eligibility criteria are met (34,36).

This study had several limitations. We used an administrative dataset to identify stroke and other diagnoses, based on ICD-9 coding that may not have accurately reflected the actual diagnoses. However, we limited the ICD-9 codes for stroke to those most reliably associated with acute stroke in adults (17,18). Similar strategies have only been evaluated for all (acute and prevalent) stroke in children (37). In addition, we only included hospitalized patients and some patients (with severe hemorrhagic stroke) may die before admission while patients with mild stroke may not seek medical attention or be treated as outpatients. Our conservative assumptions likely resulted in an underestimate of the number of strokes and co-morbid conditions and may have decreased the power to detect associations between stroke and other conditions.

Our estimates of the number of patients alive with SCD depends on several assumptions, such as the prevalence of SCD at birth, the population of California by age and ethnicity, and the age-specific survival of people with SCD and African-Americans overall. The first two assumptions were based on high-quality data sources (the 2000 Census and the published newborn screening results for California), but survival was calculated based on the age of death for all patients with a diagnosis of SCD who died in non-federal hospitals in California. We assumed that the age of death was similar for people with SCD who died outside of a hospital setting and that the age of death had not changed over time. Our estimates of survival were similar to those obtained for sickle cell anemia from the CSSCD (38) and a large Californian cohort study (13), but about 10 years less than a Jamaican cohort study that adjusted for excess mortality before registration in the cohort (39). An increase in estimated survival would result in a decrease in our estimates of stroke incidence particularly in the older age groups. This is unlikely, because our population-based estimates likely underestimate mortality in the patients born before newborn screening and other advances in care for SCD and reflect a broad range of patients with SCD (not just those enrolled at referral centers).

In this study of SCD, the burden of acute stroke was significantly greater in adults than in children, with 75% of total strokes and 91% of deaths in adults with SCD. This disparity may become even more pronounced with the widespread adoption of screening with transcranial Doppler ultrasound and regularly scheduled transfusion to maintain sickle hemoglobin less than 30% for the primary prevention of stroke in children with SCD (6,22). Primary hemorrhagic stroke continues to account for most of the mortality from stroke, and the role of emergency or scheduled transfusion or other treatments for this complication in children and adults is poorly defined (23). Likewise, the recommendations for the treatment of ischemic stroke in adults with SCD are based almost entirely on expert opinion and extrapolation from children with SCD and the general population (34), since there have been few reports of treatment of stroke (40,41) and no studies of prevention of stroke in adults with SCD (36). Prospective studies of both treatment (acute transfusion, aspirin or other platelet antagonists, or thrombolytics) and secondary prevention (hydroxyurea, platelet antagonists, or regularly scheduled transfusion) of stroke are warranted and should be feasible, given the ease of identifying those at increased risk (known SCD) and the frequency of events in adults with SCD.

## Methods

We obtained the public dataset of California Patient Discharge Databases (1998–2007) from the California Office of Statewide Planning and Development. This dataset includes up to 25 discharge diagnoses and up to 21 procedure codes per patient, and other variables that include age, sex, ethnicity, length of stay, hospital charges, source of admission, type of insurance, and disposition for over three million discharges (and deaths) per year from non-federal hospitals in California. To protect patient confidentiality, individual records with a unique combination of selected demographic variables have one of more of these variables masked to prevent identification. We extracted discharges related to SCD by International Classification of Disease, 9<sup>th</sup> revision (ICD-9) code (16). Use of this administrative dataset without personal identifiers was exempt from IRB review.

### Inclusion/Exclusion Criteria

We included discharges and deaths from acute care hospitals with any diagnostic code for SCD [sickle-thalassemia (282.41-2), SCD, unspecified (282.60), HbSS (282.61-2), sickle-hemoglobin C disease (282.63-4), and other SCD (282.68-9)] but excluded sickle cell trait (282.5) and screening for SCD (V78.2). We identified patients with acute stroke by the ICD-9 codes for primary hemorrhagic [subarachnoid hemorrhage (SAH, 430) or intracerebral hemorrhage (ICH, 431) or ischemic stroke [(occlusion of cerebral arteries, (434) or acute, but ill defined cerebrovascular disease, (436)] in the first three discharge diagnoses (16). ICD-9 codes more commonly associated with prior stroke or cerebrovascular disease without acute stroke were not included [occlusion and stenosis of precerebral arteries (433), transient cerebral ischemia (435), other and ill-defined cerebrovascular disease (437), or late effects of cerebrovascular disease (438)]. We also excluded ICD-9 codes for cerebral sinus thrombosis (325) and other and unspecified intracranial hemorrhage. This approach has a high sensitivity and specificity for the identification and classification of acute stroke from administrative databases (17,18) and permits the inclusion of recurrent acute strokes.

### Population at Risk

We estimated the number of persons at risk by using the prevalence of SCD by race identified by the California newborn screening program from 1990 to 1996 (19), and the population of California by race and 5 year age groups from the 2000 United States Census (20). To estimate the number of people with SCD by 5 year age group, we multiplied the birth prevalence of SCD for each racial group by the number of people in each age group (assuming no increase in mortality for SCD). Adjustment for early mortality was based on proportion of deaths among patients with SCD from the California Discharge Databases by age group divided by the survival reported for African- Americans in the United States for 2000 for the midpoint of each 5 year age group (21). We assumed that the prevalence of SCD at birth remained constant for each group (22) and that survival was constant for both those with SCD and African-Americans for the period of the study.

### Validation

We compared the performance of this ICD-9 based strategy to identify strokes in patients with SCD to those included in an existing research database of strokes in patients with SCD at Johns Hopkins Hospital from 1994–2008 with confirmation by review of medical records (23). We identified 31 of 42 acute strokes using ICD-9 codes and 8 false positives. The ICD-9 based strategy had a sensitivity of 74% (95% CI 58–86) and a specificity of 99.9% (95% CI 99.8–99.96) for the identification of discharges related to acute stroke in patients with SCD.

## Incidence and Case Fatality Rates

We estimated the incidence rates of all acute strokes, as well as hemorrhagic and ischemic strokes, as the number of events divided by the number of person-years at risk for each age group. We calculated person-years at risk as the population for each age group multiplied by the 10 years of observation. We calculated case fatality rates as the number of hospital deaths divided by the number of events for each stroke subtype.

## Comorbid Conditions and Treatments

To examine the association between comorbid conditions, treatments, and stroke, we identified patients with ICD-9 codes for hypertension, obesity, tobacco use, diabetes mellitus, hyperlipidemia, renal disease, history of myocardial infarction, atrial fibrillation, coagulopathy, asthma, sickle cell crisis, and procedure codes for transfusion.

## Statistical Analysis

We calculated 95% confidence intervals for incidence rates and odd ratios using exact methods and compared incidence rates between and among age groups and years by Poisson regression. We compared charges and length of stay among groups with the Wilcoxon rank sum test and the Kruskal-Wallis test for equality of populations, since these variables were not normally distributed. We compared case fatality rates by Fisher's exact test and used Intercooled Stata 10.1 (Stata Corporation, College Station, TX) for all analyses.

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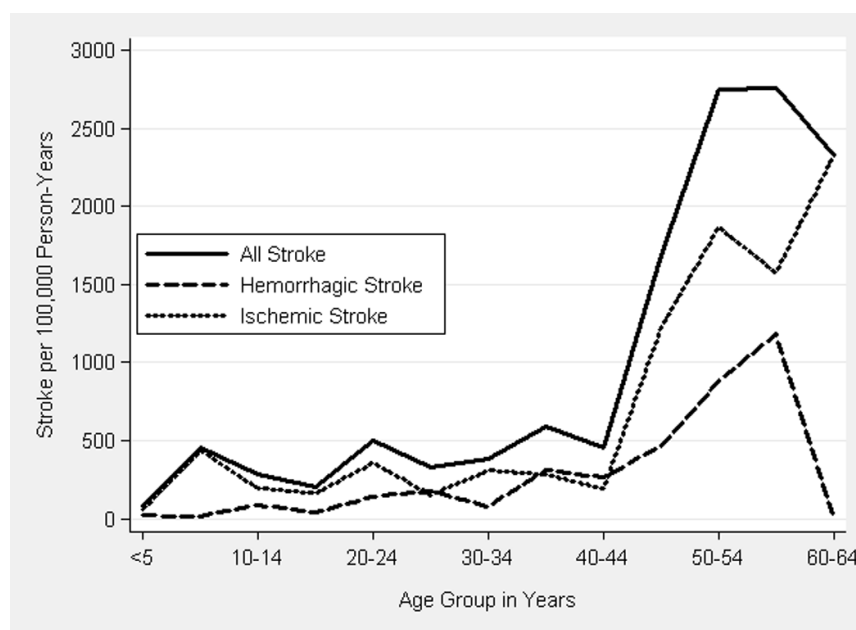
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**Figure 1.**  
Rates of Acute Hemorrhagic and Ischemic Stroke by 5 Year Age Group

**Table 1**

Stroke Type and Mortality by Age Group in Sickle Cell Disease

Age Group	Hemorrhagic	Case Fatality	Ischemic	Case Fatality
Children <18 years	8	13%	52	4%
Young Adults 18 to 34 years	16	31%	35	9%
Older Adults 35 to 64 years	40	38%	71	7%
Elderly Adults ≥65 years	4	0%	12	8%
Unknown	2	0%	15	13%
<b>Total</b>	<b>70</b>	<b>30%</b>	<b>185</b>	<b>7%</b>

**Table 2**

Rate of Acute Stroke and Person-Years of Observation by Age Group (online publication only)

Age group	Stroke per 100,000 person-years (95% CI)	Person-Years of Observation
<5 years	78 (21 – 201)	5101
5 – 9 years	454 (299 – 660)	5950
10 – 14 years	283(162 – 460)	5650
15 – 19 years	205 (98 – 377)	4875
20 – 24 years	499 (309 – 762)	4211
25 – 29 years	329 (175 – 563)	3951
30 – 34 years	387 (217 – 638)	3875
35 – 39 years	594 (368 – 908)	3534
40 – 44 years	456 (236 – 797)	2631
45 – 49 years	1680 (1130 – 2430)	1717
50 – 54 years	2750 (1780 – 4060)	910
55 – 59 years	2760 (1510-4630)	507
60 – 64 years	2330 (936 – 4800)	301

**Table 3**

Odds Ratio (and 95% CI) of Stroke Compared to No Stroke for Co-morbid Diagnoses and Procedures

Diagnosis	Prevalence	Ischemic	P-Value	Hemorrhagic	P-Value
<b>Hypertension</b>	9.5%	4.1 (2.9 – 5.7)	<0.0001	7.7 (4.7 – 12.7)	<0.0001
<b>Obesity</b>	1.7%	1.0 (0.2 – 3.0)	NS	0 (0 – 3.3)	NS
<b>Tobacco use</b>	7.6%	1.2 (0.7 – 2.0)	NS	1.2 (0.4 – 2.7)	NS
<b>Diabetes mellitus</b>	3.4%	2.2 (1.2 – 3.9)	<0.05	0.9 (0.1 – 3.2)	NS
<b>Hyperlipidemia</b>	0.7%	6.9 (2.9 – 14)	<0.0001	0 (0 – 8.4)	NS
<b>Renal disease</b>	2.6%	4.2 (2.4 – 6.8)	<0.0001	7.2 (3.4 – 13.9)	<0.0001
<b>Myocardial Infarction (old)</b>	0.7%	3.1 (0.8 – 8.1)	<0.05	0 (0 – 7)	NS
<b>Atrial Fibrillation</b>	1.1%	4.9 (2.2 – 9.5)	<0.0005	4.3 (0.9 – 13)	<0.05
<b>Coagulopathy</b>	0.8%	1.9 (0.4 – 5.8)	NS	9.1 (2.8 – 22.4)	<0.0005
<b>Asthma</b>	10.0%	0.9 (0.5 – 1.4)	NS	0.3 (0.03 – 0.99)	<0.05
<b>Crisis</b>	70.6%	0.3 (0.2 – 0.34)	<0.0001	0.2 (0.1 – 0.3)	<0.0001
<b>Transfusion</b>	27.5%	2.4 (1.8 – 3.2)	<0.0001	0.9 (0.5 – 1.6)	NS

NS indicated not statistically significant at P<0.05.