pediatric stroke

Prevalence of Antiplatelet and Anticoagulation Therapy in Children with Sickle Cell Anemia and Stroke

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Running Title: Antithrombotic Therapy in Sickle Cell Anemia

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Pediatr Stroke. 2025;11: 111-140
www.pediatricstrokejournal.com

Abstract:

Sickle cell anemia (SCA) is a hemoglobinopathy resulting in both overt and silent strokes in the pediatric population. Multiple mechanisms including anemia, hypercoagulability, secondary moyamoya syndrome, paradoxical embolism, and platelet activation are implicated in the pathogenesis of stroke in SCA. Despite a paucity of literature on the safety or efficacy of antithrombotic therapies, these agents are used in patients with SCA for primary and secondary stroke prevention. This study examined the prevalence of antithrombotic usage in the SCA-Stroke arm of the Patent Foramen Ovale and Stroke (PFAST) study cohort. Approximately 46.5% (72/155) of patients report using antithrombotic medications. The frequency of antithrombotic medications increased with recurrent strokes: 39.6% (42/106) of patients were on antithrombotic medications after a single stroke, while 61.2% (30/49) of patients were on medications after a recurrent stroke. Within this population, 42.6% (66/155) were on antiplatelet medications, and only 4.5% (7/155) were on anticoagulants. Factors significantly associated with increased usage of antithrombotic therapy were the absence acute chest syndrome and higher baseline hemoglobin concentrations. While the majority of patients were taking antithrombotic therapies for secondary stroke prevention, a minority of patients were taking medications for other indications such as headache prophylaxis and prior venous sinus thrombosis. Given these current clinical practice patterns and prevalent use, further research is needed to define the role of antithrombotic agents in pediatric SCA. There appears to be clinical equipoise for the use of these agents in the SCA and pediatric stroke population.

Main Points:

1) This is the largest study of antiplatelet and anticoagulant usage for secondary prevention of stroke in pediatric SCA patients to date.
2) A total of 155 patients were identified between the ages of 2-19 years with pediatric overt cerebral infarction and sickle cell disease. Almost half (46.5%) of patients report the use of antithrombotic medications (antiplatelet/anticoagulant medications).
3) Factors that were significantly associated with the increased use of antithrombotic therapy were recurrent stroke or TIA, absence of acute chest syndrome, and higher hemoglobin concentrations.
4) There is clinical equipoise for the use of aspirin for secondary stroke prevention in pediatric SCA patients.

Introduction

Sickle cell anemia (SCA) is a blood disorder caused by the abnormal hemoglobin, sickle hemoglobin (Hb S), that affects millions globally [1]. The key pathophysiological processes in SCA are hemolysis and vaso-occlusion, resulting in chronic anemia, painful and other acute vaso-occlusive episodes (VOE), and progressive organ damage. In particular, SCA greatly increases the risk of stroke [2]. Cerebral infarction can be overt, with focal neurological deficits, or covert ("silent"), without motor or somatosensory correlates, and found only on screening MR imaging while still correlating with learning disabilities[3]. There are multiple mechanisms of stroke in SCA, including anemia, steno-occlusive vasculopathy, hypercoagulability due to SCA, paradoxical embolism due to intra- or extra-cardiac shunting, and others [4-6]. Due to the diversity of causes, the optimal strategy for stroke prevention— in addition to chronic transfusion therapy—is still not defined.

Platelets are implicated in the pathogenesis of SCA [4]. In the steady-state, the overtly quiescent period between VOE, platelets are abnormally activated [7,8] and express biologically active CD40 ligand, suggesting ongoing platelet-mediated inflammation. During VOE, the platelet count is increased along with other inflammatory procoagulant markers (thrombin-antithrombin complexes (TAT), prothrombin fragment 1.2, and D-dimer) [9]. Platelet activation is further increased during VOE. [10,11]. Thrombocytosis which be worsened post-splenectomy is a risk factor for VOE. The frequency of VOE also correlates with activation of coagulation, which has been associated with stroke [9,12].

Platelets can also be activated by red blood cell (RBC) transfusions, which are often used in the treatment of SCA, either episodically or chronically. Chronic transfusion therapy is a standard of care for primary and secondary stroke prevention. Although effective, strokes can still occur despite transfusion therapy. It is possible that transfusion-related platelet activation limits the neuroprotection provided by the transfusions in SCA. Even in the general population, RBC transfusion increases platelet activation and aggregation *in vitro* [13]. In adults, adverse outcomes from transfusion have been linked to transfusion-related changes in coagulation and platelet activation [14]. Such changes include nitric oxide (NO) depletion in stored RBCs, which promotes platelet aggregation and impairs blood rheology and flow in the microvasculature [15], and increased ADP levels, which activate platelets and, secondarily, inflammation and coagulation [7].

Aspirin is an irreversible cyclooxygenase-2 inhibitor that has been used for secondary prevention of strokes in the adult population [16,17]. Antiplatelet therapy with aspirin is widely used in children without SCA to prevent recurrent stroke although the supporting data are sparse in pediatrics [18]. Aspirin and other antiplatelet agents are infrequently used for patients with SCA, especially because trials have failed to demonstrate any reduction in VOE, [19] in addition to the increased risk of intracranial hemorrhage in SCA. However, increasingly, and with little supportive data on safety or efficacy, aspirin is prescribed for patients with SCA for primary and secondary stroke prevention, usually in combination with other SCA disease-modifying therapies [20-22]. For example, the addition of antiplatelet therapy to exchange transfusions may be associated with a lower risk of recurrent stroke compared to transfusion therapy alone [23].

Given the uncertainty about the use of antiplatelet therapy in SCA, we analyzed the PFAST [Patent Foramen Ovale and Stroke] study cohort to determine the prevalence of antithrombotic therapy (antiplatelets and anticoagulation) across major medical centers in the US and UK for secondary prevention of overt ischemic stroke.

Methods

Patient Selection

All patients analyzed in this study were in the SCA - Stroke arm of the PFAST cross-sectional study (2010-2015), as described previously [6]. All patients had a diagnosis of SCA (defined to include HbSS and sickle-β^0 thalassemia) and overt stroke. Patients were 2-19 years of age and recruited from 14 various centers across the US and UK. Overt stroke was defined as an episode of acute onset of focal neurological deficits with a corresponding anatomical lesion on CT or MRI. Children with only silent stroke were excluded. Age-appropriate assent and parental consent was obtained from all patients or parents. This study was approved by the local ethics and Institutional Review Boards (IRBs) of participating institutions.

Statistical Testing

Demographic, clinical history and laboratory data were obtained by questionnaires and medical record review. All data were validated by dual entry techniques, and outliers were verified by querying local centers. Student's T Test and Mann-Whitney U test were used for continuous variables, and the Pearson Chi-Square test and Fisher Exact test were use for categorical variables. A p-value of <0.05 was considered statistically significant; no correction

for multiple hypothesis testing was used in this descriptive and exploratory study. Statistical analysis was performed using SPSS Version 29.0 (IBM Corp., Armonk, N.Y., USA).

Results

We identified 155 children, ages 2-19y, with SCA and overt stroke. Approximately half (72/155, 46.5%) had reported use of antithrombotic medications. Most received antiplatelet therapy (66/155, 42.6%); only a few received anticoagulants (7/155, 4.5%). The most common antiplatelet therapy was aspirin monotherapy. Clopidogrel monotherapy and dual therapy aspirin and clopidogrel were reported in one patient each. The most common indication was prevention of stroke (59/155). An uncommon indication was headache prophylaxis (7/155); either daily aspirin (N=2) or aspirin-containing formulations (e.g. Excedrin) (N=5). The dose of aspirin ranged from 20.3 mg to 325 mg daily (0.91 mg/kg/day to 5.44 mg/kg/day). The most common anticoagulant was warfarin (N=5). Low molecular weight heparin and an unspecified agent were reported in 1 patient each. Direct oral anticoagulants were not reported, likely due to the PFAST study period (2010-2015). The indications for anticoagulation varied: venous sinus thrombosis (N=4), systemic lupus erythematosus (N=1), or unspecified (N=2). Most study sites (13/14) reported use of antithrombotic medications. Antiplatelet agents and anticoagulants were reported by 12 and 3 centers, respectively. The distribution of aspirin use by clinical site is shown (Fig. 1). There was no apparent geographic bias in the use of antithrombotic medications.

Characteristics of PFAST participants are shown by antithrombotic medications use or not (Table 1). The subgroups were similar across most variables. Higher antithrombotic

medications use was seen in those with recurrent stroke or TIA (P=0.012), even though the clinical outcomes of stroke were similar. Approximately 40% (42/106) with a single (first) stroke received antithrombotic medications, while approximately 60% (30/49) with recurrent stroke received antithrombotic medications (Fig 1). Recurrence likely influenced the decision to initiate antithrombotic medications, rather than the medications increasing the risk of recurrence. In the antithrombotic group, the hemoglobin concentration was higher at the time of stroke and the most recent measurement. Patients with recurrent stroke were likely to be receiving transfusion therapy at the time of recurrence resulting in higher hemoglobin concentrations. The prevalence of antithrombotic medications was lower in patients with a history of acute chest syndrome, which is likely also related to the higher likelihood of transfusion therapy. Previous analysis of the PFAST cohort showed higher proportion of shunting in children with sickle cell disease and stroke [6]. The presence of a shunting did not influence antithrombotic usage, because the echocardiogram was obtained for the PFAST study years after the clinical stroke. The prevalence of additional therapies (hydroxyurea, transfusion therapy, and bone marrow transplant) is similar across both groups, although there was a nonsignificant trend of transfusion therapy in antithrombotic group. This illustrates that combination therapy with antithrombotic medications in these patients may be a practicable option.

Discussion

SCA is among the commonest causes of stroke in children, at least historically in high-resource settings before effective stroke prevention programs, resulting in overt stroke, silent stroke, and transient ischemic attacks (TIA) (Table 2) [24-39]. There are multiple

mechanisms of stroke in SCA [40], including activation of platelets as well as the coagulation and inflammation pathways. So, antiplatelet therapy could theoretically decrease the risk of stroke in SCA. Although we found antiplatelet therapy to be highly prevalent among children with SCA and overt stroke, its effectiveness is unknown. Because anemia, hypoxemia, vaso-occlusion, pathologic shunting, and limitation of blood supply by vasculopathy also cause stroke in SCA, antiplatelet therapy should best be considered as additive therapy to standard of care, which is chronic transfusions. RBC transfusions are well-established to reduce the risk of primary and secondary stroke [4,7,9,41-43]. However, transfusion itself can activate platelets (donor and recipient), potentially limiting its full neuroprotective potential. As such, we speculate that the addition of antiplatelet to transfusion therapy might have additive benefit.

Given the evidence of the involvement of platelets in the pathophysiology of SCA, antiplatelet therapy has been studied in SCA for decades (Table 3) [44-51]. No clear overall benefit for the disease has been demonstrated. Rates of VOE are not different in randomized trials, including different antiplatelet agents. A role in stroke prophylaxis, specifically, has not been definitively studied. Antiplatelet agents are commonly used in the adult, general population for secondary stroke prevention [16,17], but strong evidence for benefit in SCA has not been reported despite its increasing use in SCA [19,22,52,53].

This secondary, cross-sectional analysis has several limitations. Inferences cannot be made about effectiveness or toxicity (especially bleeding) of antithrombotic medications for secondary stroke prevention. We can only describe the prevalence and correlates of use in

children with SCA and overt stroke. Further, a few patients received antithrombotic medications for headache prophylaxis or treatment of venous thrombosis rather than overt stroke. Direct oral anticoagulants (DOACs) have become available for use in children since the publication of the primary PFAST manuscript, so this study provides no data about these newer agents. Finally, the PFAST study protocol did not include MR angiography, so the association of antithrombotic medications use with steno-occlusive vasculopathy is not known. In the general population with moyamoya, for example, antiplatelet therapy is widely prescribed [54]. This is a major limitation as the presence of a vasculopathy significantly increases the risk of stroke and therefore likely plays a key role in decision use anti-thrombotic therapy [55]. Future efforts are needed to delineate the role of aspirin in this population and the presence of a vasculopathy in the decision for initiation of antithrombotic agents. Nevertheless, to the authors' knowledge, this is the largest study of antithrombotic medications use in children with SCA and overt stroke.

Conclusion

Antiplatelet therapy was highly prevalent among children with SCA and overt stroke. Despite this, there are no high-quality data or expert consensus guidelines to inform its use in this population. Randomized trials are needed to determine the risks and benefits of the addition of antiplatelet therapy to standard care for stroke prevention in SCA.

Acknowledgements

We would like to thank George Buchanan, MD, Zora Rogers, MD, Milton Packer, MD and Marie Virginia Moretti for their contributions to this project.

Financial Disclosures

There are no other financial disclosures from the remaining authors.

Funding/Support

This study was funded by an 'Innovations in Clinical Research Award' and a supplemental research grant from the Doris Duke Charitable Foundation (MMD) with additional support from the Children's Clinical Research Advisory Committee and the Women's Auxiliary to Children's Medical Center. Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR000003. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author contributions

MMD designed the study, obtained funding, and conducted the analysis. AP prepared the manuscript. CTQ participated in study design, participated as study committee member, and enrolled patients. PP was overall study coordinator. CR was the main study cardiologist who participated in study design and reviewed all study echocardiograms and participated in data analysis. FK served as study consultant and participated in study design, obtained ethics approval for the UK and participated in study design and analysis. LSH performed the biostatistics and study analysis. All other authors participated in study design at investigator meetings, enrolled patients, contributed to the analysis of the data, and critically reviewed the manuscript.

Pediatr Stroke. 2025;11: 111-140
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Table 1: Factors Associated with Use of Antiplatelet or Anticoagulant in Children with SCA and Stroke

Factor	Antithrombotic Use # (%)	None # (%)	P value*
Patient Characteristics			
Age at Stroke Onset (years, mean±SD)	6.7 ± 4.2	5.8 ± 3.6	0.190•
Age at Echocardiogram (years, mean±SD)	13.0 ± 4.6	12.4 ± 5.0	0.412•
Gender (% male)	36/72 (50.0%)	46/83 (55.4%)	0.500*
Acute Illness at Onset or 2w prior to stroke	43/71 (60.6%)	38/77 (49.4%)	0.171*
TIA prior to onset	2/72 (2.8%)	1/83 (1.2%)	0.597†
Headache at stroke presentation	18/56 (32.1%)	26/62 (41.9%)	0.272*
Ongoing Headache or Migraine	24/71 (33.8%)	31/83 (37.3%)	0.647*
Seizures (at presentation or subsequently)	22/72 (30.6%)	16/83 (19.3%)	0.104*
Stroke Outcome, PSOM median (range)	1.0 (0-8)	0.5 (0-8)	0.163‡
Recurrent Stroke or TIA	30/72 (41.7%)	19/83 (22.9%)	**0.012***
Any Cardiac or Pulmonary Shunting detected	34/69 (49.3%)	33/78 (42.3%)	0.397*
Patient Medical History			
Hx of Acute Chest Syndrome	24/62 (38.7%)	43/77 (55.8%)	**0.044***
Hx of Priapism (for males)	3/31 (9.7%)	7/43 (16.3%)	0.505†
Hx of Splenic Sequestration	13/61 (21.3%)	18/75 (24.0%)	0.710*
Hx of frequent pain crises (> 5)	14/59 (23.7%)	27/75 (36.0%)	0.126*
Hx of Gallstones	14/58 (24.1%)	13/74 (17.6%)	0.353*
Hx of Asthma	22/71 (31.0%)	23/82 (28.0%)	0.691*
Hx of Aplastic Crisis	6/58 (10.3%)	7/70 (10.0%)	0.949*
Hx of Aseptic Necrosis	1/62 (1.6%)	3/75 (4.0%)	0.626†
Hx of Pulmonary Hypertension	2/63 (3.2%)	2/69 (2.9%)	>0.999 †
Family Hx of Hypercoagulable State	37/70 (52.9%)	37/81 (45.7%)	0.379*
Report of Snoring or Diagnosis of OSA	18/71 (25.4%)	27/82 (32.9%)	0.305*
Laboratory Characteristics			
Hgb Oxygen Saturation median (range)	100 (96-100)	99 (93-100)	0.159‡
Hgb Conc at/prior to stroke median (range)	8.55 (5.0-13.9)	7.65 (2.4-13.7)	**<0.001 ‡**

Hgb Conc recent (median, range)	9.60 (7.5-13.6)	9.10 (6.1-14.1)	**0.011‡**
WBC at/prior to stroke (x10^3) median (range)	14.00 (4.4-42.4)	16.05 (4.7-41.3)	0.076‡
WBC recent (x10^3) median (range)	11.95 (4.3-22.6)	12.70 (5.0-39.2)	0.258‡
Plt at/prior to stroke (x10^3) median (range)	395.0 (114-763)	351.5 (92-1091)	0.475‡
Plt recent (x10^3) median (range)	378.0 (34-718)	371.0 (69-813)	0.733‡
HgbS% at/prior to stroke median (range)	44.0 (6-92)	65.0 (5-100)	0.073‡
HgbS% recent median (range)	29.2 (3-81)	27.0 (4-88)	0.955‡
Treatment Characteristics			
Hydroxyurea	6/57 (10.5%)	9/88 (10.2%)	0.954*
Transfusion Therapy	55/60 (91.6%)	71/88 (80.7%)	0.065*
Bone Marrow Transplant	2/60 (3.3%)	2/87 (2.3%)	0.704*

Laboratory values shown were obtained at the most recent stroke (at/prior to stroke) and echocardiogram visit (recent). •Student's independent samples t-test, ‡Mann-Whitney U test, *Chi-square test, or †Fisher's exact where indicated. Abbreviations: TIA= transient ischemic attack, WBC=white blood cell, Plt=Platelet, OSA= obstructive sleep apnea. Hgb= hemoglobin. PSOM= Pedi Stroke Outcome Measure (0= no deficit, 10= severe deficit)

Table 2: Reports of Risk of Stroke in Sickle Cell Patient Cohorts

Reference	Number of patients	Stroke risk	Notes
Russell 1984 [24]	N=30 w/ Simple transfusion	10% recurrent overt stroke	Decreased risk of recurrent stroke in patients with transfusion therapy.
Pegelow 1995 [25]	N = 60	13% recurrent overt stroke 22% TIA	Hemoglobin S level of less than 30% decreases risk of recurrent stroke.
Ohene-Frempong 1998 [26]	N = 2675	4.1% overt stroke 14% recurrence	Risk of stroke increased in prior TIA, lower hemoglobin concentration, episode of acute chest syndrome, and elevated systolic blood pressure.
Dobson 2002 [27]	N = 44 overall N = 19 w/ Moyamoya N = 25 w/o Moyamoya	41% overt stroke 58% overt stroke 28% overt stroke	Higher risk of recurrent stroke in those with moyamoya
Scothorn 2002 [28]	N = 137 N = 26 w/ medical event N = 111 w/o medical event	22% overt stroke 12% overt stroke 25% overt stroke	Lower incidence of recurrent stroke in those w associated medical event with none after 2 yrs.
Ganesan 2006 [29]	N = 35 N = 14 w/ Simple transfusion	51% TIA or overt stroke	Moyamoya and low birth weight were associated with recurrent stroke.
Niamnshi 2006 [30]	N = 120	6.7% overt stroke	Ischemic stroke thrice as common as hemorrhage
Hulbert 2006 [31]	N = 14 w/ Simple transfusion N = 38 w/ Exchange fusion	57% overt stroke 21% overt stroke	Exchange transfusion was superior to similar transfusion in reduction of recurrence.
Inusa 2007 [32]	N = 96	23% overt stroke 24% TIA	Moyamoya and absence of prodrome are independent risk factors for recurrence
Brousse 2009 [33]	N = 9	11% overt stroke 67% silent stroke	Transfusion therapy does not prevent moyamoya vasculopathy.
Ali 2011 [34]	N = 43 N = 10 w/ Hydroxyurea N = 33 w/o medication	49% overt stroke 10% overt stroke 61% overt stroke	Hydroxyurea decreases risk of stroke.
Hulbert 2011 [35]	N = 40	18% overt stroke 28% silent stroke	Stroke risk higher in those with progressive vasculopathy

Ware 2012 [36]	N = 66 w/ transfusion N = 67 w/phlebotomy	0% overt stroke 14% with TIA	Decreased risk of stroke with transfusion and chelation
Lagunju 2013 [37]	N = 32 N = 13 w/ Hydroxyurea N = 18 w/o med	19% overt stroke 7% overt stroke 28% overt stroke	Hydroxyurea is an alternative to prevent recurrent stroke in the absence of transfusions.
Dlamini 2017 [38]	N = 39	10.2% overt stroke 15.4% TIA	Low nocturnal hemoglobin oxygen saturation and reticulocytosis is associated with arteriopathy.
Abdullahi 2023 [39]	N = 101 N= 49 Hydroxyurea 10 mg/kg N = 52 Hydroxyurea 20 mg/kg	11% recurrent overt stroke 6 (12%) recurred 5 (10%) recurred	Low and moderate doses of hydroxyurea are efficacious for secondary stroke prevention

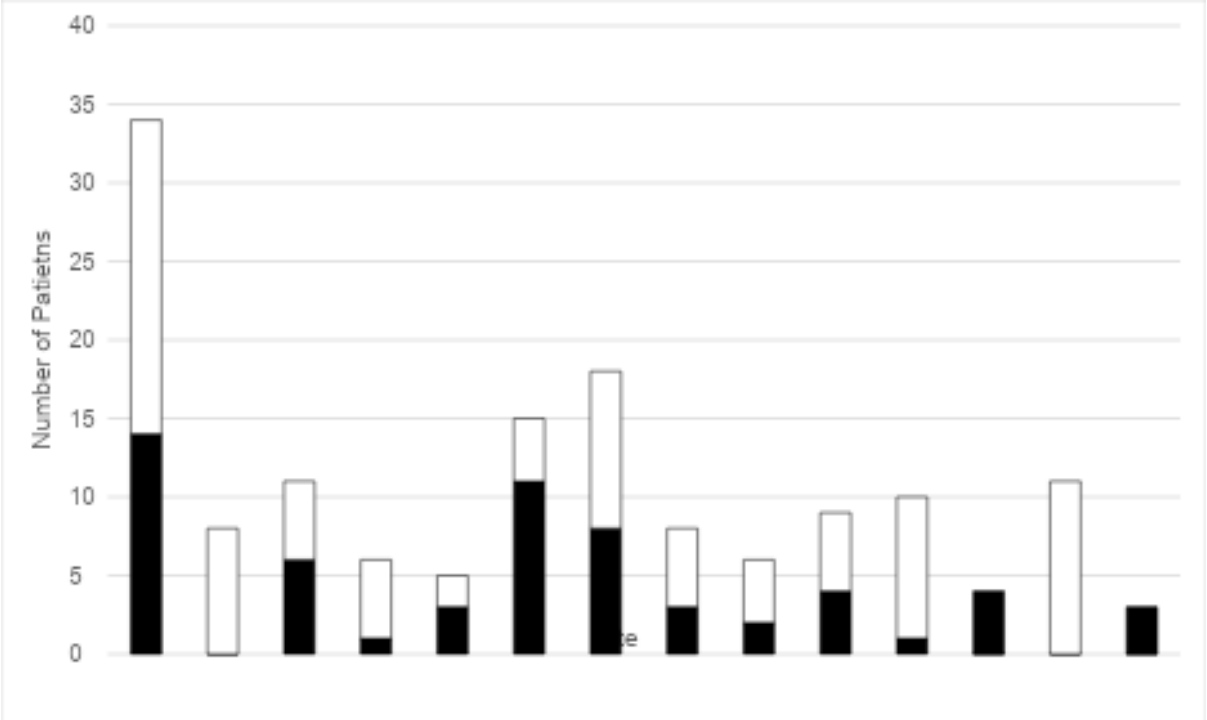
Incidence of overt stroke, silent stroke, and TIA in various sickle cell patient cohorts. Pertinent medication treatment and transfusion therapy is listed. The risk of overt and silent stroke is presented. Abbreviations: TIA = Transient Ischemic Attack

Table 3: Studies of Aspirin/Antiplatelet Agents in Sickle Cell Anemia

Reference	Number of Pts	Therapy	Duration	Outcome	Side effects
Chaplan 1980 [44]	3	Aspirin-Dipyridamole	104 weeks	Slight decrease in freq of pain, plt count and fibrinogen	None
Osamo 1981 [45]	100	Aspirin	6 weeks	Incr O2 affinity, hgb, RBC lifespan	None
Greenberg 1983 [46]	49	Aspirin vs. placebo	21 months	No change in pain episodes	One withdrew for epistaxis
Zago 1984 [47]	29	Aspirin vs. placebo	5 months	No change in pain, Hgb, retic count, irreversibly sickled cells, fetal Hgb	None
Semple 1984 [48]	9	Ticlopidine vs. placebo	4 weeks	No change in pain episodes, plt survival but incr platelet survival	VOE in one pt, nausea & abdominal discomfort
Cabannes 1984 [49]	140	Ticlopidine vs. placebo	6 months	Decreased frequency and duration of pain	None
Desai 2013 [50]	13	Eptifibatide vs. placebo	24 hours	No difference in length of pain crises	One minor bleeding episode in Eptifibatide arm
Heeney 2015 [51]	341	Prasugrel vs. placebo	9-24 months	No difference in VOE	None

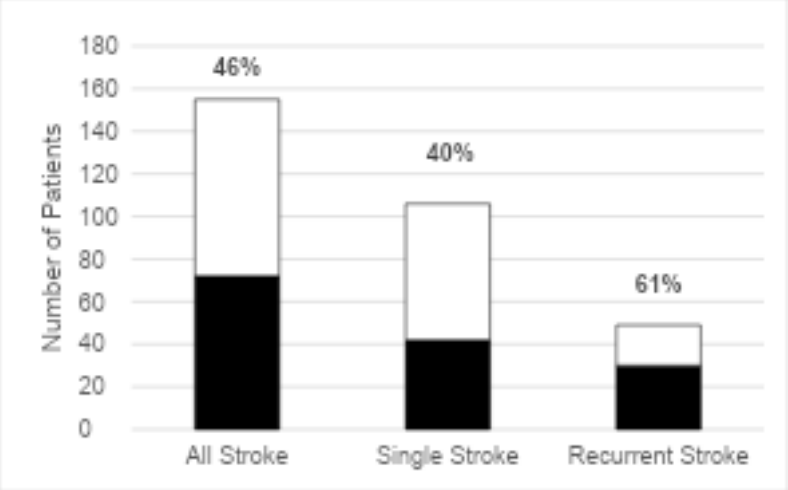
Various cohort studies and clinical trials of antiplatelet use in SCA. The number of patients, treatment arms, and duration of treatment are shown. The primary outcome and complications are presented. Abbreviations VOE = Vaso-occlusive event

Figure 1: Aspirin Use Among Clinical Sites



The frequency of aspirin use in patients by clinical site is shown. Black represents the number of patients that are prescribed aspirin. White represents the number of patients not on aspirin. The frequency is shown above the respective column.

Figure 2: Usage of Antithrombotic Agents with Recurrent Stroke or TIA



The prevalence of antithrombotic medications usage in patients with single stroke, recurrent stroke, all stroke is shown. Antithrombotic medications are inclusive of antiplatelet and anticoagulation medications. The frequency is shown above the respective column. Black represents patients on antithrombotic medications and white represents patients without medications.

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