EVALUATION OF FINDINGS IN CHILDREN WITH SICKLE CELL ANAEMIA
USING TRANSCRANIAL DOPPLER ULTRASOUND IN SICKLE-CELL
FOUNDATION CENTRE, LAGOS

BY:

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AWARD OF THE FELLOWSHIP OF THE NATIONAL POSTGRADUATE
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DECLARATION
I hereby declare that this project was carried out by Dr. USORO Uyi Uyai Oghomwan during the course of my residency training in the Department of Radiology, Lagos State University Teaching Hospital, Ikeja, Lagos. It is an original project and has neither been published nor submitted to any other college for fellowship.

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ii

ATTESTATION

This is to attest that the dissertation titled “EVALUATION OF FINDINGS IN CHILDREN WITH SICKLE CELL ANAEMIA USING TRANSCRANIAL DOPPLER ULTRASOUND
IN SICKLE-CELL FOUNDATION CENTRE, LAGOS ” undertaken by Dr Uyi Oghomwan Uyai Usoro, during her residency program at (L.A.S.U.T.H.) was supervised by us.

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iii

CERTIFICATION

I hereby certify that this project was carried out by Dr. USORO Uyi Uyai Oghomwan during the course of her residency training in the Department of Radiology, Lagos State University Teaching Hospital, Ikeja, Lagos.
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DEDICATION

To God Almighty the Father, Son and the Holy Spirit for your goodness, mercies, kindness, grace, favour and everlasting love. You who have revived, kept, restored and protected me always.

To my beloved husband Anthony Thompson Udofia Mfon Usoro, my pillar,

My wonderful children Inemesit, Idara-esit, Mfon-Abasi and Utibe-Abasi,
My father, Amen Osayimwen of blessed memory, my beloved mother Emwin Osayimwen, and my siblings.

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My other consultants: Dr Jinadu, Dr Adegboyega for their constant advice to get the job done and finish well. I am indeed grateful to our dear Professor G.O.G. Awosanya for his caring and unstoppable encouragement.

To my Head of Department (Dr. Babajide O. Balogun) who constantly steered me in the right path and to my great colleagues at Lagos State University Teaching Hospital. Thank you all.

vi

**LIST OF ABBREVIATIONS**

**ACA** - Anterior cerebral artery

**BDNF** - Plasma Brain Derived Neutropic Factor

**CBFv** - Cerebral blood flow velocity

**CR** – Conditional risk

**dICA** - Distal internal carotid artery

**EDV** - End diastolic velocity

**Hb** - Hemoglobin

**HCT** - Hematocrit

**HR** – High risk
ICA- Internal carotid artery
MCA- Middle cerebral artery
PSV - Peak systolic velocity
PDGF-AA and AB/BB - Platelet Derived Growth Factor
RBC- Red blood cell
SCA- Sickle cell anemia
SCD- Sickle cell disease
SpO2- Peripheral Hb O2 saturation
SR- Standard risk
STOP – Stroke Prevention Trial in children with SCA
TAMM- Time Averaged Maximum Mean Velocity
TCD- Transcranial Doppler ultrasonography
TCDI- Transcranial Color Doppler Imaging
TIA- Transient Ischemic Attack
WBC – White blood cell

vii

TABLE OF CONTENTS

TITLE PAGE......................................................................................... i
DECLARATION...................................................................................... ii
ATTESTATION.................................................................................... iii
CERTIFICATION.................................................................................. iv
DEDICATION....................................................................................... v
ACKNOWLEDGEMENTS................................................................. vi
LIST OF ABBREVIATIONS..................................................................... vii
TABLE OF CONTENTS......................................................................... viii
SUMMARY........................................................................................... 1
INTRODUCTION................................................................................... 2
SUMMARY

**Background:** Sickle Cell Disease (SCD) is the most common genetic cause of illness and death in the world, with Africa bearing the highest burden. Trans-cranial Doppler ultrasound (TCD) which is different from transfontanelle ultrasound, was used to measure mean flow velocities in the large intra-cranial arteries. It is a readily available, economical, reliable, non invasive method of imaging and has been shown to predict risk of stroke when cerebral blood flow velocity ≥ 200cm/s.

**Aim & Objectives:** The aim of this study was to evaluate the common findings in TCD in children with Sickle Cell Anemia (SCA) in this environment, the associated various risk factors and to identify the high risk patients who are likely to have primary stroke.

**Materials and Methods:** This prospective study was conducted on 200 children with SCA, without a known history of stroke, at the Sickle Cell Foundation Nigeria, Lagos over a period of 6 months. A TCD machine - DWL Doppler box (Scan Med) s/n DB-0563, p/n 301748 ® manufactured in Germany and equipped with a 2MHz transducer probe was used to measure the cerebral blood flow (CBFv) in internal carotid artery (ICA), middle cerebral artery (MCA) and
anterior cerebral artery (ACA). Measurements were entered into the data sheet and analyzed using Statistical Package for Social Science Software (SPSS) version 20.

**Results** showed that the 5-8 years age group constituted 43.5% of those screened, 25% was under 4 years of age, 24% were 9-12 years and 7.5% were 13-16 years. Females were 56.5% while 43.5% were males. They were grouped according to CBFv in the analyzed vessels. The standard risk (CBFv <170cm/seconds) was 60.5%, conditional risk (170-200cm/s) was 36% and high risk group (>200cm/s) was 3.5%.

**Conclusion:** Significant correlation was noted between haematocrit and Time Averaged Mean of the Maximum Velocity (TAMMV), with a p-value of 0.045, white blood cell and TAMMV (p-value of 0.032) and dactylitis and TAMMV (p-value of 0.007). Also a significant negative correlation was shown between children below 4 years and dactylitis (p-value 0.026).

**Keywords:** Transcranial Doppler Ultrasound, SCA children, TAMMV

**INTRODUCTION**

SCD is a major cause of loss of potential leaders in the world, with Africa bearing the highest burden\(^1,2\). It is estimated that 20-25% of the Nigerian population carries sickle cell gene with about 2-3% (150,000) of children born annually with SCD\(^2\). There is need to explore other preventive measures apart from periodic blood transfusion to ameliorate the burden of stroke associated with SCD in a resource poor country like Nigeria. Its socioeconomic burden is enormous, as a lot of resources are allotted to its diagnosis and management.

Sickle cell hemoglobinopathy was first described in 1910 by Dr James Herrick of Chicago, who hypothesized that his patient’s symptoms came from the sickle shaped red blood cell he observed through the microscope\(^1\). HbSS is SCA while HbAS is Sickle cell trait and all combinations with HbS are referred to as SCD\(^1,3\).

SCD is a genetically transmitted autosomal recessive disorder, inherited in a Mendelian fashion with amino acid substitution of valine for glutamic acid at the sixth position on the beta chain of
the hemoglobin molecule in the red blood cell (RBC)\(^3\). The instability of the hemoglobin molecule in the deoxygenated state results in HbS polymerization and causes RBC to change from the usual biconcave disc shaped structure to an irregular sickled shape\(^3\). The abnormal shape of these RBC and their propensity to adhere to the walls of blood vessels can occlude the vessels, preventing normal blood flow and decreasing the delivery of oxygen to organs and tissues resulting in infarction of tissues and organs distal to the obstruction, a condition known as sickle cell crisis\(^3\). The sickled cells are also susceptible to hemolysis. Stroke or acute neurological syndrome is caused by vascular occlusion or hemorrhage in the brain with resultant ischemia and focal neurological symptoms or signs lasting greater than 24 hours\(^4\), while Transient Ischemic Attack (TIA) occurs when the above stroke symptoms last less than 24 hours. The higher stroke incidence in SCA patients in Africa of 1.3/100 patient years\(^5\) compared to 0.6/100 patient years in USA, is probably due to high prevalence of key risk factors such as low hemoglobin, increased white blood cell and in Bantu haplotype\(^6, 7\).

Stroke is a major cause of preventable death in children with SCD. About 11% of SCD patients would have stroke by age 20 years\(^4, 8, 9\) the risk depending on the genotype. Stroke occurs in 7-13% of children with SCA (HbSS) and can lead to motor disability, neuropsychological impairment and death\(^10\). The risk of developing stroke which is worse in HbSS than other sickle cell traits increases from ages 2–10 years\(^11, 12\).

HbSS patients are affected more than HbS-thalassemia O, HbS beta thalassemia + and HbSC in decreasing order\(^4\).

The risk factor for stroke occurs when the TCD velocities are >200cm/s on two consecutive examinations\(^4\). Other risk factors include low baseline hemoglobin, high leucocyte (white blood cell (WBC) count), prior TIA, frequent and recent acute chest syndrome, elevated blood
pressure, history of stroke in a sibling (due to any cause), dactilytis in the first 2 years of life and absence of alpha gene selection.

Stroke is a complication of SCD and its prediction by TCD offers primary prevention. Increased ICA, MCA or ACA velocities are associated with greater risk of ischemic stroke.

The prediction of stroke is also possible using Peripheral HbO2 saturation (SpO2), plasma Brain Derived Neutropic Factor (BDNF) and Platelet Derived Growth Factors (PDGF-AA and AB/BB). TAMMV, Peak Systolic Velocity (PSV) and Transcranial Color Doppler Imaging (TCDI) are also predictors of stroke but they are not as reliable as TCD.

SpO2 is a predictor of overt stroke and may also predict death since it causes pulmonary hypertension.

Elevated BDNF and PDGF-AA are good predictors of risk for stroke development. TAMMV is a better stroke predictor than End Diastolic Velocity (EDV), but equivalent to PSV in prediction of stroke.

PSV cut-points define two relevant Stroke Prevention trial in SCA (STOP) risk categories using TCDI and STOP protocol. These are:-

1) “Conditional” of 200cm/s is recommended as threshold for increased TCD surveillance, (comparable to a TCD TAMMV of 170cm/s in STOP).

2) “Abnormal” PSV cut-off points of 250cm/s on repeat second examination should result in treatment with blood transfusion. PSV is equivalent to TAMMV in STOP protocol to select children with SCD for therapy or increased surveillance to prevent a first stroke.

TCD is a simple, non invasive predictor of stroke. It predicts 40% risk of stroke in abnormal CBFv of greater than 200cm/s and 7% in those having 170-199cm/s over 3 years while CBFv greater than 150cm/s indicate intracranial vessel stenosis.
This study is therefore aimed at evaluating the various findings on TCD in SCA children, highlighting the risk factors for prediction of stroke in such patients and identifying the high risk patients likely to have primary stroke.

AIM & OBJECTIVES

BROAD

To evaluate Transcranial Doppler ultrasound (TCD) findings in sickle cell anaemia (SCA) patients.

SPECIFIC

1. To identify children with sickle cell anaemia who are at greater risk of having primary stroke.

2. To identify the risk factors associated with primary stroke in children with SCA.

HYPOTHESIS: SCA children with low haematocrit levels will have high TCD values.

SUB HYPOTHESIS: SCA children with high total white blood cell count levels will have high TCD values.
JUSTIFICATION

SCD is common in blacks worldwide, especially in Nigeria where the awareness of risks associated with SCD is low especially among rural dwellers of limited education and literacy. About 11% of patients with SCD will have a stroke by age 20 years leading to motor disability, neuropsychological impairment and death. The risk is worse in the 2-10 years age group with SCA (HbSS)⁴⁻¹². Discovering the stroke risk of these children with SCA would help avert stroke and make the children live a better life.

Stroke, a sequel of SCA can be predicted and therefore prevented using TCD. To the best of the researcher’s knowledge, such studies have not been carried out in Lagos State University Teaching Hospital.

It measures the flow velocity in the large intracranial arteries and is used for screening and identifying children at greater risk for primary stroke, in order to initiate preventive therapy. It is a cheap, non invasive, non-ionizing, readily available imaging modality which can be conducted by the bedside.
The findings of this study would therefore serve as a benchmark for future reference on this subject in and around Lagos.

**GROSS ANATOMY**

The vascular anatomy of the brain involves branches of vertebro-basilar system anastomosing with branches of internal carotid artery to form the Circle of Willis.

The internal carotid artery is a terminal branch of the common carotid artery (CCA). It arises most frequently between C3 and C5 where the CCA bifurcates to form internal carotid artery (ICA) and external carotid artery (ECA)\(^\text{16}\). Asymmetry may exist between the left and right branches of the ICA origins\(^\text{17}\). The ICA has seven segments\(^\text{18}\) which include the Cervical (C1), Petrous(C2), Lacerum(C3), Carvenous(C4), Clinoid(C5), Ophthalmic (supraclinoid)C6 and Communicating (terminal)C7 segments. The cervical, lacerum and clinoid segments have no branches. The other segments have the following branches:

- **C2 - Petrous segment** has petrous caroticotympanic and vidian branches
- **C4 - Carvenous segment** has meningohypophyseal trunk and inferolateral trunk
- **C6 – Ophthalmic segment** has ophthalmic and superior hypophyseal arteries
C7 - Communicating segment has posterior communicating, anterior choroidal artery, ACA and MCA.

The branches of ACA are anterior communicating artery, recurrent artery of Heubner, medial frontobasal, polar frontal, callosomarginal and pericallosal arteries\textsuperscript{18, 19}.

The MCA branches include medial lenticulostriate arteries and lateral lenticulostriate arteries.

This study involves the distal ICA, MCA and ACA (figures 1 and 2).
Figure 1: Diagram showing the branches of the ICA in lateral view
Figure 2: Diagram showing the internal carotid artery and its branches in frontal view
RADIOLOGICAL ANATOMY

Ultrasonographic anatomy

Ultrasonographic anatomy of the internal carotid artery only illustrates its course in the neck by Carotid Doppler ultrasound. Its course in the brain can only be insonated and waveforms recorded with TCD machine (figures 3 - 5) when the fontanelles have closed.

The two methods for TCD are: firstly the “B-mode” imaging which displays a 2- dimensional image on the monitor once the desired vessel is identified. Blood flow velocities are measured with a pulsed Doppler transducer, which then traces graphs of spectral velocities over time in a waveform (figures 3-5). Duplex scanning implies simultaneous display of B-mode grey scale image and spectral velocity waveform on the monitor.

The second method uses only the second transducer’s spectral velocity waveform function and relies on the training and expertise of the sonologist in finding the correct vessels (TCD which was used in this study).

TCD is a non invasive, non-ionizing, inexpensive, portable and safe technique that insonates distal ICA (before its bifurcation), MCA and the ACA. TCD allows real-time evaluation of the intracranial cerebral circulation. There is no direct visualization like is seen in carotid Doppler. Rather, it is indirect evaluation by means of an ultrasonic beam of 2MHz frequency which is produced from piezoelectric crystals that have been stimulated electrically. This beam is reflected from the erythrocytes within the insonated artery.
Figure 3: The TCD tracing of MCA waveform which shows as a predominant yellow upward deflection
Figure 4: The TCD tracing of ACA waveform which shows as a predominant yellow downward deflection
Figure 5: The TCD tracing of the ICA waveform which shows as an upward yellow deflection and downward blue deflection.
The reflected signal is received by the transducer and converted to an electric signal. This information is subtracted from the transmitted signal and then processed to obtain a waveform which allows accurate determination of blood flow velocities and direction of flow and to evaluate other useful parameters (such as pulsatility index)\textsuperscript{21, 22}.

The waveforms for the MCA is predominantly an upward deflection, ACA is predominantly a downward deflection. However that of ICA is a combination of both upward yellow and downward blue deflections (figures 3-5).

TCD has been demonstrated to identify those at highest risk of stroke among children with sickle cell disease\textsuperscript{8, 9, 23, 24}. It offers the possibility of decreasing risk of first stroke\textsuperscript{8, 24}. High risk associated with distal intracranial ICA and proximal MCA stenosis can be detected by TCD\textsuperscript{8, 25, 26}.

Clinical routine TCD examination of the intracranial vessels was demonstrated by Aaslid et al\textsuperscript{27} in 1982, then in 1992. Value obtained for a particular artery is the velocity of blood flowing through the vessel. TCD measures relative changes in the blood flow. It predicts stroke in children with SCA as well as assess patients with intracranial stenosis, collaterals, cerebral circulatory arrest, arterio-venous (AV) malformations, peri-operational, subarachnoid hemorrhage and meningeal infection\textsuperscript{27}.

Blood flow velocity is recorded when a high pitched sound wave is emitted from the ultrasound scanner and represents an echo\textsuperscript{27}. Multiples of 2MHz, speed of blood in relation to the transducer cause a phase shift whereby frequency is increased or decreased. A range of depths and angles are measured to ascertain the correct velocities. Angulated reading may however give artificial low velocity\textsuperscript{27}. Bones of the skull block transmission of ultrasound hence regions of thinner bone walls called– insonation windows are used for analyzing. The insonation windows include: petrous temporal window (above the zygomatic arch), orbital, sub-mandibular or occipital.
window. The skull bone wall (especially the petrous-temporal insonation window) is thin in children of age 2-16 years4 hence this age group is selected for TCD. Patient’s age, gender and race may affect the bone thickness and make access more difficult.

Apart from TCD and Transcranial Colour Doppler (TCCD), other predictors include implantable TCD which is connected to a drug delivery system with an oximeter and administers the drugs during a stroke (since the latter impairs oxygen that triggers the release of the drug)27. There is also functional TCD (fTCD) which measures cerebral blood flow velocity as it relates to neural activation. Functional TCD spectroscopy (fTCDS) is another application of TCD. Transcranial Color Doppler Imaging (TCDI), though easier to use and learn with a few adjustments, gives lower velocities than TCD for the same segment of the vessel27, hence TCD is currently the only recommended method for treatment-selection for primary stroke prevention9.

**Angiographic anatomy** Angiographic imaging could be Conventional, Magnetic Resonance or Computed Tomography and illustrates the anatomy of the internal carotid artery, middle cerebral artery and anterior cerebral artery16.
LITERATURE REVIEW

Stroke is defined as a focal neurological deficit lasting more than 24 hours and has a vascular basis.

Predisposing factors to stroke in children include sleep disorders, congenital heart diseases, sickle cell disease, Down’s syndrome and William’s syndrome. The risk of stroke increases significantly with increasing velocity of blood flow in the ICA and MCA. This formed the basis of primary STOP and its age occurrence.

Pathophysiology of stroke could be sequel to inflammation, reduced nitric oxide and plasma free hemoglobin. Chronic intravascular hemolysis occurs in SCD leading to excessive free heme, oxidative stress and inflammation by induction of pro-inflammatory adhesion molecules which interact with the endothelium to cause vasculopathy. Free heme is scavenged by haptoglobin and nitric oxide resulting in reduction in nitric oxide (NO) bioavailability which causes vascular spasm and intimal thickening.

Molecular pathological abnormality of SCD leads to microvascular occlusion and intravascular hemolytic anemia. Microvascular occlusions are related to painful episodes and probably cause circulatory problems in the brain. The most commonly recognized stroke syndrome in children with SCD is large artery infarction.

According to Ryan et al, there are different types of stroke which include:

- **Overt Stroke** or acute neurological syndrome caused by vascular occlusion or hemorrhage with resultant ischemia and focal neurological symptoms and signs lasting for over 24 hours.

- **Silent stroke** in which there is MRI evidence of cerebral ischemic injury in the absence of focal neurological deficits or history of overt stroke.
**Transient Ischemic Attack** gives neurological symptoms lasting for less than 24 hours.4

“**Reversible ischemic neurological deficit**” refers to deficit lasting for over 24 hours but with complete recovery.3

“**Stroke-like episode**” occurs in 10-20% of children and is a focal neurological deficit lasting greater than 24 hours without obvious vascular abnormality.3 Other diagnoses for stroke-like episode are hemiplegic migraine and hypertensive encephalopathy. Tumor, trauma, causing extra-dural or sub-dural haematoma, infections such as focal encephalitis and abscesses, demyelinating disease e.g. acute disseminated encephalitis, Todd’s paralysis and migraine could mimic stroke-like episode.

Patients with silent stroke have increased incidence of subsequent infarctive stroke.4 Seventeen to twenty-three percent of patients with SCD have silent stroke, twice the number of those who have overt stroke.4

The higher stroke incidence in SCA patients in Africa is 1.3/100 patient years compared to 0.6/100 patient years in USA.5 This is possibly due to the high prevalence of key risk factors such as low hemoglobin or hematocrit, increased white blood cell (WBC) and in Bantu haplotype.6,7

Stroke is a major cause of preventable death in children with SCD. About 11% of SCD patients would have stroke by age 20 years.4,8 The risk depends on the genotype. Stroke occurs in 7-13% of children with SCA (HbSS) and can lead to motor disability, neuropsychological impairment and death.10 The risk of developing stroke which is worse in HbSS than other sickle cell traits increasing from ages 2–10 years. HbSS is affected more than HbS-thalassemia O, HbS beta thalassemia + and HbSC in decreasing order.4

TCD has been demonstrated to identify those at highest risk of stroke among children with sickle cell disease.8,9,23-25 High risk associated with distal intracranial ICA and proximal MCA stenosis can be detected by TCD.8,26
Clinical routine TCD examination of the intracranial vessels was demonstrated by Aaslid et al\textsuperscript{27} in 1982, then in 1992. The value obtained for a particular artery is the velocity of blood flowing through that vessel. TCD measures relative changes in the blood flow and predicts stroke in children with SCA as well as assesses patients with intracranial stenosis, collaterals, cerebral circulatory arrest, arterio-venous malformations, peri-operative, subarachnoid hemorrhage and meningeal infection\textsuperscript{27}.

Blood flow velocity is recorded when a high pitched sound wave is emitted from the ultrasound scanner and represents an echo\textsuperscript{27}.

Elevated BDNF and PDGF-AA are good predictors of risk for stroke development. TAMMV is a better stroke predictor than EDV, but equivalent to PSV in prediction of stroke\textsuperscript{8}.

PSV cut-points define two relevant STOP risk categories using TCDI and STOP protocol. These are:

1) “Conditional” of 200cm/s is recommended as threshold for increased TCD surveillance, and this is comparable to a TCD TAMMV of 170cm/s in STOP.

2) “Abnormal” PSV cut-points of 250cm/s (which is comparable to a TCD TAMMV of 200cm/s) on repeat examination should result in treatment with blood transfusion. PSV is equivalent to TAMMV in STOP protocol to select children with SCD for therapy or increased surveillance to prevent a first stroke\textsuperscript{8}.

Hyacinth discovered that stroke incidence and increased TCD velocities were equally associated with increased BDNF and PDGF-AA and AB/BB. This suggested the role of the latter in pathophysiology of cerebrovascular accident in SCA. These ‘big strokes’ as a result of a vascular event in the large arteries of Circle of Willis lead to tentorial infarctions from perfusion failure or artery to artery embolism\textsuperscript{7, 30, 31, 33}. However, infarction is more prevalent than hemorrhagic stroke in the pediatric population\textsuperscript{4}. The median age for stroke is 5 years\textsuperscript{34} and those who survive it show disturbed learning profiles, psycho-emotional problems and perform poorly in school.
relative to their peers. Stroke impairs intellectual development. Kassab et al. noted that neovascularisation occurs in areas not perfused as a result of the stroke, leading to moyamoya formation (network of small delicate vessels which appear as cloud-like puff on arteriogram). This name was derived from a Japanese disorder. Moyamoya tends to rupture causing hemorrhage leading to more neurological deficit. A late complication is an aneurysm in the contra-lateral circulation. Aneurysmal bleeds are catastrophic and fatal. These lesions can be detected by TCD because flow velocity is inversely related to arterial diameter. High flow velocity has been correlated with stenosis on angiography also with increased cerebral blood flow and subsequent stroke in children with SCA.

An optimal stroke prevention strategy was projected to involve annual TCD screening until age 10 years, with transfusion for children at high risk until age 18. Muzumdar et al. predicted prevention of 32% of future strokes which would otherwise have occurred in children without intervention. This led to benefits similar to more intensive screening and transfusion strategies resulting in fewer adverse events. Overall, there was reduction in life expectancy due to serum iron overload post blood transfusion, which outweighed the projected mortality averted by stroke prevention. However with the advent of iron chelation therapy, results were sensitive to its adherence rates. With better adherence to chelation, there was improved life expectancy in all intervention strategies.

Stroke risk in all children with SCD is approximately 0.5-1%/year. Young children with SCD are at very high stroke risk with incidence of strokes being highest between ages 2-9yrs. Forty to seventy-five percent of children who suffer a first stroke would have recurrence in the absence of medical intervention like blood transfusion and 26% of those who survived the first stroke would have another stroke within one year. When left untreated, ninety percent of children with SCD who have stroke will have recurrent stroke. Adams et al. in 2001
discovered that overall age specific incidence of stroke in SCA (HbSS) is low (0.13\%) at ages less than 24 months, increasing to greater than 1\% at ages 2-5 years with only a slight decrease to 0.7\% at ages 6-9 years. There is a decreased risk of brain infarction until a second peak at age greater than 50 years when incidence increases to 1.3\%\textsuperscript{41}.

Raffaella et al\textsuperscript{43} noted that there is increased frequency of the S gene in Sicilian population and influx of African immigrants has increased the SCD population over the years in Sicily. Using TCD and TCCD, pulsatility index and depth values in the MCA and basilar artery (BA) were similar in three groups namely Italians, Africans and Caucasians. TAMMV, PSV and EDV in these vessels were higher in the patients’ group (Italians) on both TCD and TCCD evaluation. Healthy Africans and Caucasians controls had similar lower values\textsuperscript{43}. However it was concluded that ethnic background did not influence TCD velocities and internationally accepted reference values, though long prospective trials are needed to verify their efficacy in defining stroke risk in North East Italy\textsuperscript{43}. Raffaella and his team\textsuperscript{43} also noted that parental education preferably in native language, on stroke risk and prevention in SCD increases compliance of TCD screening. Fatunde et al\textsuperscript{41}, in a retrospective review, arrived at 5.4\% as estimated hospital stroke prevalence rate among Nigerian children with SCD while studying a clinic population of 500 children with mean age of 6.8 years ranging from 17 months to 11 years. Fatunde\textsuperscript{41} also concluded that SCD was responsible for 87\% of strokes in children in Ibadan, Nigeria. Despite this, incidence of stroke among African children appears not to be as high as that in North America\textsuperscript{41}. Adams\textsuperscript{24} in 2005 found out that using TCD, the prevention of stroke was possible and demonstrated it in a randomized clinical trial called STOP.
**Definition of disease:** TCD results were classified as Normal or standard risk (SR), when the velocity was less than 170cm/s; Conditional risk (CR), between 170 and 200cm/s and Abnormal or high risk (HR) when it is greater than 200cm/s\(^4,7,24\).

Adams\(^7,24\) studied MCA and ICA and carefully searched for them to find the highest velocity which was then used to stratify patients for stroke risk. Those with HR TCD were split into two groups and the first group received monthly transfusion while the other group received no transfusion (control). Those randomized to transfusion compared with the control, had better stroke outcomes (1 to 10) and fewer other medical problems when transfused\(^7,24\). Control group was not transfused in order to elicit the outcome of transfusion in preventing stroke and the outcome was less than in those transfused. The researcher then recommended that TCD screening should begin from 24 months and should be repeated every 6-12 months during early childhood. It is unknown if TCD velocities are predictive of stroke in patients with other sickle cell syndromes like HbSC and HbS beta thalassemia\(^4\).

Since TCD cannot predict all strokes, TCD and TCDI together offer an opportunity to determine the mode of treatment for patients in risk groups and eliminate many potential first time strokes. TCDI using an Acuson ultrasound scanner gives moderately lower velocities than those obtained with the dedicated Doppler using Nicolet scanner TCD for same segments of the blood vessels, with difference in values reduced from 15% to 10% by modifications to the TCDI protocol\(^9\).

MRI and Magnetic Resonance Angiography (MRA) provide cerebral vascular information. There is no definitive data on the role of MRI/MRA for screening of initial stroke prevention. However MRI is better than Computed tomography (CT) in diagnosing infarction of less than 24hours although it is comparable to CT in diagnosing hemorrhagic cases. Prolonged neurological deficit in sickle cell disease may result from infarction while short lasting deficits or no deficit at all may paradoxically have resulted from extensive infarction\(^2,4,7\). The latter can be
predicted by imaging with TCD\textsuperscript{2,4-7}. However, if TCD is abnormal, then both TCD and MRA/MRI are recommended a month later.

Ryan et al\textsuperscript{4} noted that education at clinic visits is needed for the family so that there will be compliance with screening using TCD, follow up and suggested proven chronic blood transfusion therapy for abnormal TCD. Informing the family of the results also encourages further compliance.

Ryan and his team\textsuperscript{4} also discovered hydroxyurea as an alternative therapy although its efficacy has not been proven\textsuperscript{4}. It boosts red cell count and improves clinical outcome of the SCA patient. However only few studies have shown its effect on TCD flow velocities.

Zimmerman et al\textsuperscript{44} in 2007, in a prospective study, indicated that hydroxyurea can significantly decrease elevated TCD flow velocities often into normal range at below toxic levels. Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) study was abruptly halted because seven stroke cases were recorded in hydroxyurea group while, none occurred in transfusion group. Therefore further multicentre trials are required to determine the efficacy of hydroxyurea for the management of increased TCD values and ultimately for primary stroke prevention in children with SCA\textsuperscript{4}.

Adams et al\textsuperscript{26} in 2004 used the STOP study to compare prophylactic blood transfusion with standard care in SCA children aged 2-16 years selected for high stroke risk by TCD. The authors described changes seen on repeated TCD and reported the outcome without transfusion in the STOP screened cohort. Increased risk of stroke was noted with abnormal TCD compared to normal or CR (p<0.001), or inadequate TCD (p=0.002). Also risk with CR was greater than normal TCD\textsuperscript{39}. Sustained differences in the probability of conversion to abnormal TCD were observed with younger children and those with higher velocity more likely to have abnormal TCD with rescreening\textsuperscript{26}.
Lagunju et al\textsuperscript{45} in 2012 found out that no previous report on TCD studies existed in Nigerian children with SCD. This necessitated their study which showed pattern of flow velocities in the major intracranial arteries as measured by TCD ultrasound in a cohort of Nigerian children with SCD and the clinical and hematological parameters that are associated with increased TAMMV in these arteries\textsuperscript{45}.

HCT is lower in HbSS than HbSC, while WBC is higher in HbSS than HbSC. TAMMV was found to be higher in HbSS than in HbSC. Abnormal TCD is also higher in HbSS. All categories of risk velocities (normal, conditional, high) added up to 127 patients in the HbSS group compared with only 18 patients having normal and low conditional risk in HbSC\textsuperscript{45}.

Significant correlation was noted between age and TAMMV p=0.001, hematocrit (HCT) and TAMMV p=0.002. For every month increase in age, there was associated reduction in TAMMV of about 0.22cm/sec, while TAMMV reduced by about 2.5cm/sec for every unit increase in HCT\textsuperscript{44}. This is probably explained by the excellent cooperation and positive results in children with SCD and their caregivers\textsuperscript{44}.

Adams\textsuperscript{7} report also showed significant correlation by CBFv and stroke with age, hemoglobin concentration and white blood cell count. Significant negative correlation between age, HCT and TAMMV are consistent with stroke\textsuperscript{29}. Progressive decline in flow velocity with increasing age after 4-5years is a pointer to stroke. Glucose-6-Phosphate Deficiency (G6PD), anemia and hemolysis are associated with abnormal high velocity.

The mean TAMMV of 152+27cm/sec recorded in the Nigerian HbSS cohort is higher than the mean TAMMV 141+35cm/s in the African-American cohort\textsuperscript{45} and the Creteil newborn cohort\textsuperscript{29}. Also 140-145cm/s noted between 4 and 5 years of age and 130cm/s at age 9years\textsuperscript{29}.

Presence of TAMMV of $\geq$170cm/s which is CR is 24.4\% in HbSS cohort and higher than the prevalence of 17.5\% reported by Adams et al\textsuperscript{46} in a cohort of 315 African-American children, about twenty percent of these patients are in the CR category of the HbSS cohort as opposed to
9% reported in African-American cohort. The prevalence of CR in this study is lower than the 27% reported in the prospective Creteil study\textsuperscript{29}. Despite stroke prevalence in African children, only 4.7% of HbSS had abnormal velocity compared to 8% in African-American cohort\textsuperscript{45}.

Reasons for this disparity were unclear leaving two possibilities, one suggesting that Nigerian children with SCD develop stroke at relatively lower velocity than previously reported. The other suggested that those with abnormal velocity had suffered a stroke prior to availability of routine TCD screening\textsuperscript{45}.

Despite education and counseling, the abnormal velocity found in 4.7% of children with HbSS was due to unwilling caregivers consenting to periodic blood transfusion which confers 90% reduction in stroke risk in high risk children\textsuperscript{22}. This attitude is probably as a result of difficulties in the treatment plan such as its being intensive, rigorous, time consuming and costly with tremendous impact on the meager resources of the families, who practice mainly out of pocket payment for health care services with no government subsidy\textsuperscript{22}. The stroke risk among children with CR velocity is estimated to be 2-5%/year compared with 9%/year for children with abnormal velocity\textsuperscript{38, 46}. However despite lower relative risk of stroke in children with CR, more children have CR velocity, such that the absolute number of children with CR who will develop stroke without treatment is comparable to those with abnormal velocities\textsuperscript{38, 46}. Children with CR velocity have a potential risk of converting to abnormal velocity by a progressive increase in their flow velocity over time to high risk range\textsuperscript{21, 26}. This makes detection of CR velocity in one of five Nigerian children with HbSS a major concern and partly accounts for the relatively higher prevalence of stroke in Nigerian children with SCD\textsuperscript{44}. Younger aged patients and other patients with higher initial flow velocities were most likely to convert to abnormal TCD\textsuperscript{26}. CR velocities occur more frequently in Nigerian children with HbSS disease than their African-American counterparts.
Low hematocrit and young age are associated with higher TAMMV in children with SCD\textsuperscript{45}. Bantu haplotype is associated with low fetal hemoglobin (HbF) and severe manifestation of SCA which is predominant in Kenya compared with less severe Benin haplotype which predominates in Nigeria. Haplotype is an ordered list of alleles of multiple linked loci on a single chromosome. It is a way of denoting the collective genotype of a number of closely linked loci on a chromosome. Haplotypes are named according to areas where they were first discovered. Genotype is a single locus.

Lagunju and his team\textsuperscript{45} also noted that more males were available for recruitment for his TCD study with male: female ratio being 1.5:1 which he attributed to superstition and high value placed on the male child in the African setting.

Oniyangi et al\textsuperscript{47} studied stroke in children with SCD in National Hospital Abuja, Nigeria using CT and MRI and reported a risk of 0.85/100 patient for first stroke. George and Frank - Briggs\textsuperscript{48} in University of Port Harcourt Teaching Hospital, Nigeria correlated CT findings with HCT and found out that stable state HCT of patients with stroke showed that 72% of the patients had HCT levels below 20%, 18.2% of the patients had HCT levels between 20-30% and 9.1% of the patients had HCT levels above 30%. White blood cells were elevated in 81.8% of the patients studied. Blood transfusion effectively reduced the risk of recurrent stroke in SCA\textsuperscript{49, 50}.

Many ‘big strokes’ that occur in small persons (children with SCD) can be reduced by aggressively screening patients at young age and periodically throughout the childhood risk period, interrupting the process using regular blood transfusion\textsuperscript{7, 24, 30, 31}.

In 2011, Krejza et al\textsuperscript{51} discovered reference values of inter-hemispheric differences and ratios of blood flow Doppler parameters in the distal ICA, MCA and ACA in children with SCA. These may be helpful in identification of intracranial vessel narrowing in children with SCD undergoing TCD screening for stroke prevention.
If one or two indicators of abnormal risks are present, MRA is recommended. Positive findings of stroke on MRA such as stenosis or occlusions of the vessels necessitated therapy by transfusion or other methods for prevention of stroke.

Nichols et al\textsuperscript{52} in 2001 used STOP protocol and TCD to screen children with SCD with no history of stroke. It was noticed that among children randomized to transfusion and standard care according to their TCD velocities, over approximately 20 months follow up, 11 strokes occurred in standard care arm while there was only one stroke in the transfusion arm. This study generated great interest in using TCD to screen children with SCD and it sets guidelines.

Children with high flow velocity in ICA and MCA of 200cm/s have a 10%/year risk of first stroke\textsuperscript{8,9}. Irrespective of risk factors, the current SCD guidelines recommend the use of TCD as a screening tool for risk of stroke in all 2-16 years old children with SCD at least once a year\textsuperscript{22}. TCD detects developing cerebral vasculopathy and prompts intervention\textsuperscript{7}. It also measures blood flow velocity in large arteries of the Circle of Willis. General increased velocity is noted in severe anemia, while focal increased velocity is seen in stenosis\textsuperscript{7}. Children with SCD develop high stroke risk which can be detected months or years before the stroke using TCD\textsuperscript{7}.

It is important to note that blood flow velocity varies naturally with age. Blood flow in the MCA is low after birth but increases rapidly during the first few days of life\textsuperscript{21}. Velocities of 100cm/s are reached between ages 4 and 6 years, and after decreases throughout life\textsuperscript{21}. Healthy adults have MCA velocity of 60cm/s, children without anemia have approximately 90cm/s and in SCD mean is 130cm/s\textsuperscript{7}.

For normal TCD results (less than170cm/s), screening schedule is repeated every 6-12 months but for conditional TCD results (170 – 200 cm/s), screening is 3 months. For abnormal TCD (greater than 200 cm/s), TCD is repeated in 1 month. MRI and MRA with neuropsychological evaluation are also recommended for repeat in 1 month. Repeat screening is also based on other factors such as; new TIA in a previously treated patient for whom screening is one month after
resolution, or TCD showing significant change from previous examinations, such cases should have repeat in 3-6 months.

However if significant asymmetry in TCD is seen, repeat scan should be done in 3-6 months. Other indications for TCD evaluation for SCA include the presence of SCA with no prior stroke between ages of 2 and 16 years, abnormal previous TCD levels in distal ICA or MCA. TAMMV with velocities of greater than 170 cm/s or 200 cm/s will require further TCD evaluation.

TCD should NOT be performed in hypoxia, hypercapnia, fever, acute chest syndrome, pneumonia and hypoglycemia due to increased cerebral blood flow in children in these disease states. Also decreased cerebral blood flow and velocity seen in hypocapnia and recent transfusion makes TCD unreliable.

Increased carbon dioxide (CO₂) and increased velocity are noted in a sleeping child and this causes mis-diagnosis. Crying leads to hyperventilation which impacts velocity negatively. Restlessness, agitation and variations in positioning should be avoided by cajoling the child through distraction.
MATERIALS AND METHODS

This is a prospective descriptive study which was conducted at:

**Sample site:** the Sickle Cell Foundation Centre, Idi-Araba, Lagos, Nigeria (which is the only center with the TCD machine being used for all cases in Lagos and its environs).

**Duration of the study:** Six months (October 2014 – March 2015).

**Study population:** Two hundred children with sickle cell anaemia were recruited into the study.

The TCD findings and the images obtained were documented and analyzed.

**Sample size** was estimated using the formula below:

\[
N = \frac{(z)^2 pq}{d^2} = \frac{(z)^2 p(1-p)}{d^2}
\]

Where:

\( z \) = Standard normal variant = 1.96 at 95% confidence interval

\( p \) = Prevalence

\( d \) = Precision or tolerance error (0.05)

\( N \) = Sample size

Taking \( p \) to be 11%(0.11), this gives the sample size,

\[
N = \left(1.96\right)^2 \times 0.11(0.99) = 167.34
\]
This figure was rounded off to 200 to broaden the base of the study and reduce sampling error.

**INCLUSION CRITERIA**

1) Children referred to the centre with confirmed Sickle Cell Anemia - HbSS disease between two and sixteen years old with no previous stroke were recruited.

**EXCLUSION CRITERIA**

1) Children with Sickle Cell Disease- HbSC disease, HbS thalassemia +
2) Children already on chronic blood transfusion program (more than three pints of blood done serially to achieve a stable state)
3) Children with hypoxia, hypercapnia, fever, acute chest syndrome, pneumonia and hypoglycemia.
METHODOLOGY

All children with sickle cell anemia referred to the centre were screened according to the inclusion and exclusion criteria. Written informed consent (Appendix III) and assent (Appendix IV) were obtained from the parents/guardians and their children while only informed consent was obtained from parents/guardians whose children could not comprehend or sign assent.

Assent is an agreement by an individual not competent to give legally valid informed consent to participate in a research e.g. a child (below age 18) or cognitively impaired persons. Age 7-12 use a child assent while age 13-17 use the youth assent format.

Informed consent is the voluntary agreement of an individual who has the legal capacity to give consent and who exercises free power of choice, without undue inducement or any other form of constraint or coercion to participate in research.

Here a general assent was used in conjunction with informed consent signed by parents/guardians.

After written consents (assent and informed consent) were obtained, history was taken from participants/parents or guardians.

Data was collected using protocol that consisted of:

Questionnaire: an English structured interview which was translated into local languages for those who do not understand English. The questionnaire which comprised of three parts namely demographic, social history and past medical history were included as data.

The following information was retrieved from the request cards and history given by parents at the time of initial visit:
Age, Gender, History of prior TIA in the child, History of stroke in sibling, History of dactylitis in the first 2 years of life, Presence, frequency and recent history of acute chest syndrome and also History of blood transfusion.

1) Measurements of weight (kg), height (cm) using a weighing scale and standiometer, respectively.

2) Data: Hematocrit level and white blood cell count were done and reports were retrieved from the request cards of each child.

All studies were performed using DWL Doppler box (Scan Med) s/n DB-0563, p/n 301748 ® manufactured in Germany and equipped with a hand-held probe that has 2MHz transducer and computer monitor and printer. Examination couch and consumables such as ultrasonic gel, cotton wool, couch rolls and tissue paper were also provided.

**TECHNIQUE**

The patient was placed in supine position with head tilted to the opposite side and coupling gel was applied to a hand-held 2MHz transducer and placed in the temporal region of the scalp just above the ear. By manipulating transducer angulations, position and depth setting of the equipment, the internal carotid artery and its branches’ waveforms were identified. Adjusting the depth, gain, scale and volume, spectral waveform, TAMMV, reflecting the blood flow velocities of the distal ICA, MCA and ACA, the machine automatically generated the TCD values which were recorded. By increasing the depth by 2mm gradually, from 50 to 60mm for ICA and ACA, while decreasing the depth from 50 to 30mm for MCA depending on which vessel was located first, waveform measurements were taken. About 2-3 readings were recorded at each depth if a full waveform was observed (figures 6 - 11 series for each category: standard (3), conditional (2) and high risk).

The procedure was repeated on the contra-lateral side.
The highest automated recorded mean velocity for each artery was taken as the TAMMV as seen in figures 6-11. For ACA the right mean reading was taken while for ICA and MCA, the left mean reading was taken see figures 6-11. The highest mean reading was taken as the final reading for the series of ACA, ICA and MCA on the right temporal window. The same procedure was repeated on the left side.

The TAMMV was correlated with age, haematocrit, total white blood cell count and history from the questionnaire along with other risk factors.

In cases with elevated velocities of $\geq 170\text{cm/s}(\text{conditional})$, a repeat TCD scan was done after two weeks or repeated after one week if $\geq 200\text{cm/s}$ (abnormal or high risk). These repeat values determined the next appointment for the child, three months for HR, six months for CR and one year for SR.
Figure 6: Spectral Doppler tracing of right MCA showing standard stroke risk with TAMMV of 101 at depth 44
Figure 7: Spectral Doppler tracing of right ICA showing standard stroke risk with TAMMV of 120 at depth 50
Figure 8: Spectral Doppler tracing of the right ICA showing conditional risk with TAMMV of 190 at depth 52
Figure 9: Spectral Doppler tracing of the right ACA showing standard risk with TAMMV of 167 at depth 50.
Figure 10: Spectral Doppler tracing of the right ACA showing conditional risk with TAMMV of 181 at depth 56
Figure 11: Spectral Doppler tracings of right ACA showing high stroke risk with TAMMV of 208 at depth 52
ETHICAL CONSIDERATIONS

Approval was sought and obtained from the Health Research and Ethics Committee of the Lagos State University Teaching Hospital, Lagos. Informed consent also was obtained from the parents and or guardians of the participants and/or assent form was filled by the child.
DATA ANALYSIS

Data was entered in Excel Spread Sheet where it was exported into the Statistical Package for Social Sciences Software (SPSS) version 20.0. Chicago, Illinois, USA and results were documented using tables, bar and pie charts. Association between variables was explored using Chi square and Student’s t-test for comparison at 95% confidence interval and associations were considered significant if p values are <0.05.

LIMITATIONS OF THE STUDY

1) Some selected risk factors such as: SpO₂ and blood pressure could not be ascertained due to the fluctuating oximeter readings and non-availability of various sizes of pediatric cuffs respectively, hence these two parameters were discontinued.

2) Several children dropped out of the study, especially the ages 2 to 3years due to their restlessness, un-cooperating or crying state.

3) Other children who fell asleep on pacifying them had to be excluded as well.

4) Some guardians or parents accompanying the participants could not remember details of their past medical history (especially the older children).

5) There were some indeterminate studies, meaning readings were generated from some vessels and not ascertained from others (in the same patient) probably due to thick skull bones in the older children.
RESULTS

In the course of this study, 200 children were screened. The socio-demographic characteristics of participants illustrated that the mean age of the patients was 7.4 ± 3.3 years. The most common age group 5–8 years was 87 in numbers (43.5%) while the least occurring group 13-16 years was 15 in number (7.5%) as depicted in table 1. Most of the children were firstborn of their parents 85 (42.5%), while the sixth born were 2 (1%) as shown in table 2.

Majority of the screened children were Christians, 110 in number (55%), while the Muslims were 90 in number (45%) as shown in figure 12. Females 113 (56.5%) were more than males 87 (43.5%) with a ratio of 1.3/1 as shown in figure 13.

The number of children who had no blood transfusion was 126 (63.0%) and was a lot more than those who had blood transfusion 74 (37.0%) as shown in figure 14. Table 3 showed frequency of blood transfusion. Those who had blood transfused once were the majority 53 (26.5%) while those who had frequent blood transfusion (thrice) were only 4 (2%).

Very few 5 (2.5%) children with SCA had history of transient ischaemic attack while majority 195 (97.5%) had not experienced TIA as shown in table 4. Also fewer patients 75 (37.5%) had history of dactylitis while majority 125 (62.5%) had no history; table 5. Only 22 (11%) had history of acute chest syndrome among those screened; table 6, while table 7 shows that only one sibling of the participants had a history of stroke.

Figure 15 shows children with risk categories SR, CR and HR with a prevalence of children with SCA who are at risk of stroke being 3.5%, while those with low risk (SR and CR) were much higher.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group (Years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>50</td>
<td>25.0</td>
</tr>
<tr>
<td>5 – 8</td>
<td>87</td>
<td>43.5</td>
</tr>
<tr>
<td>9 – 12</td>
<td>48</td>
<td>24.0</td>
</tr>
<tr>
<td>13 – 16</td>
<td>15</td>
<td>7.5</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>100</td>
</tr>
</tbody>
</table>
### TABLE 2: POSITION OF PATIENTS AMONG SIBLINGS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Position in the family</strong></td>
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<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} child</td>
<td>85</td>
<td>42.5</td>
</tr>
<tr>
<td>2\textsuperscript{nd} child</td>
<td>48</td>
<td>24.0</td>
</tr>
<tr>
<td>3\textsuperscript{rd} child</td>
<td>32</td>
<td>16.0</td>
</tr>
<tr>
<td>4\textsuperscript{th} child</td>
<td>19</td>
<td>9.5</td>
</tr>
<tr>
<td>5\textsuperscript{th} child</td>
<td>11</td>
<td>5.5</td>
</tr>
<tr>
<td>6\textsuperscript{th} child</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>7\textsuperscript{th} child</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>200</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
Figure 12: Pie chart showing distribution of religion in all participants
Figure 13: Pie chart showing distribution of gender in all participants
Figure 14: Pie chart showing history of blood transfusion in the participants
TABLE 3: NUMBER OF BLOOD TRANSFUSIONS

<table>
<thead>
<tr>
<th>Number of blood transfusion</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>52</td>
<td>26.0</td>
</tr>
<tr>
<td>1</td>
<td>106</td>
<td>53.0</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>17.0</td>
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<tr>
<td>3</td>
<td>8</td>
<td>4.0</td>
</tr>
<tr>
<td>Total</td>
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<td>100</td>
</tr>
</tbody>
</table>
### TABLE 4: HISTORY OF TRANSIENT ISCHAEMIC ATTACK

<table>
<thead>
<tr>
<th>History of Transient Ischaemic Attack</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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</thead>
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<tr>
<td>No</td>
<td>195</td>
<td>97.5</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>History of Dactylitis</td>
<td>Frequency</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>No</td>
<td>125</td>
<td>62.5</td>
</tr>
<tr>
<td>Yes</td>
<td>75</td>
<td>37.5</td>
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<tr>
<td>Total</td>
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</table>
### TABLE 6: HISTORY OF ACUTE CHEST SYNDROME

<table>
<thead>
<tr>
<th>History of Acute Chest Syndrome</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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<tr>
<td>No</td>
<td>178</td>
<td>89.0</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>11.0</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>Stroke in siblings</td>
<td>Frequency</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>No</td>
<td>199</td>
<td>99.5</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>100</td>
</tr>
</tbody>
</table>
Figure 15: Bar chart showing stroke risk categories based on transcranial Doppler ultrasound measurements

*Prevalence of children with SCA who are at risk of stroke is 3.5%.
Table 8 shows the characteristics of the children with SCA found with HR of stroke. It is more common in 5-8 years age group and females with male: female ratio of 3:4. None of the children had history of acute chest syndrome or transient ischaemic attack. Only one child had no history of dactylitis while six of them had history of dactylitis. Three of the children have been transfused with blood. First born position was in majority. The mean height and weight for these set of children was 1.16± 0.1metre and 19.5 ± 3.9 kg respectively with a mean BMI of 14.5 ± 2.0. The mean HCT and WBC were 24.8 ± 4.4 % and 19.5 ± 21.6 cmm respectively.

Table 9 shows association between continuous variables and risk of primary stroke in children with Sickle Cell Anaemia (SCA). The mean BMI was lowest in the CR group being 13.6 ± 1.8 intermediate in the in SR group being14.3 ± 2.0 and highest in the HR group being 14.5 ± 2.0 . The mean weight was highest in the SR group being 20.2 ± 0.9 kg and lowest in the HR group 19.5 ± 3.9 kg. The mean height was highest in the SR and CR group being 1.2 m and lowest in the HR group 1.16± 0.1m. The mean HCT was highest in the SR group 27.3 ± 20.5% while the WBC was lowest in the SR group 19.3 ± 14.8 cmm reflecting the relationship between the risk of primary stroke in children with SCA and HCT and WBC as being significant (HCT p=0.032, WBC p= 0.045). The mean age however was same being 2± 0.9 years. The platelets count was highest in the HR group 514.42 ± 234.3 and lowest in the SR group being 392.48 ±159.6.

Table 10 shows association between categorical variables and risk of primary stroke in SCA children and significant negative relationship between dactylitis and stroke risk p=0.007.

Table 11 shows relationship between dactylitis and age group with significant negative relationship between age under 4years and dactylitis. However dactylitis occurred more in the 5-8 years group (38 ± 43.7) than the 13 -16 years group (1 ± 6.7).

Table 12 shows the relationship between HCT, WBC and stroke risk: with significant correlation HCT p value = 0.045, WBC p value = 0.032.
TABLE 8: CHARACTERISTICS OF THE CHILDREN FOUND WITH HIGH RISK OF STROKE

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency</th>
<th>Percentage (%)</th>
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<tr>
<td><strong>Age group</strong></td>
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<tr>
<td>5 – 8</td>
<td>5</td>
<td>71.4</td>
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<td>9 – 12</td>
<td>2</td>
<td>28.6</td>
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<tr>
<td><strong>Mean±SD</strong></td>
<td>6.86</td>
<td>1.78</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
<td>3</td>
<td>42.9</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>57.1</td>
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<tr>
<td><strong>History of Acute Chest</strong></td>
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<td></td>
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<tr>
<td>No</td>
<td>7</td>
<td>100.0</td>
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</tr>
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<td>85.7</td>
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<td><strong>Blood transfusion History</strong></td>
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<td>57.1</td>
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<td>42.9</td>
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<td>Yes</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Position of child in the family</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st child</td>
<td>3</td>
<td>42.9</td>
</tr>
<tr>
<td>2nd child</td>
<td>2</td>
<td>28.6</td>
</tr>
<tr>
<td>4th child</td>
<td>2</td>
<td>28.6</td>
</tr>
<tr>
<td><strong>Variables</strong></td>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
</tr>
<tr>
<td>Height</td>
<td>1.16</td>
<td>0.10</td>
</tr>
<tr>
<td>Weight</td>
<td>19.54</td>
<td>3.91</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>14.48</td>
<td>2.04</td>
</tr>
<tr>
<td>HCT</td>
<td>24.80</td>
<td>4.40</td>
</tr>
<tr>
<td>WBC</td>
<td>19.54</td>
<td>21.63</td>
</tr>
</tbody>
</table>
### TABLE 9: ASSOCIATION BETWEEN CONTINUOUS VARIABLES AND RISK OF PRIMARY STROKE IN CHILDREN WITH SCA

<table>
<thead>
<tr>
<th>Variables</th>
<th>SR Mean(SD)</th>
<th>CR Mean(SD)</th>
<th>HR Mean(SD)</th>
<th>Statistics</th>
<th>df1, df2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>14.30(2.02)</td>
<td>13.65(1.77)</td>
<td>14.48(2.04)</td>
<td>2.785</td>
<td>2, 197</td>
<td>0.054</td>
</tr>
<tr>
<td>Age</td>
<td>2.20(0.92)</td>
<td>2.03(0.84)</td>
<td>2.29(0.49)</td>
<td>0.947</td>
<td>2, 197</td>
<td>0.390</td>
</tr>
<tr>
<td>Weight</td>
<td>22.15(8.95)</td>
<td>20.29(8.00)</td>
<td>19.54(3.91)</td>
<td>1.116</td>
<td>2, 197</td>
<td>0.330</td>
</tr>
<tr>
<td>Height</td>
<td>1.21(0.20)</td>
<td>1.20(1.66)</td>
<td>1.16(0.10)</td>
<td>0.208</td>
<td>2, 197</td>
<td>0.812</td>
</tr>
<tr>
<td>HCT</td>
<td>27.64(20.46)</td>
<td>24.36(3.91)</td>
<td>24.80(4.40)</td>
<td>0.967</td>
<td>2, 197</td>
<td>0.032*</td>
</tr>
<tr>
<td>WBC</td>
<td>14.59(14.80)</td>
<td>15.60(2.07)</td>
<td>19.54(21.62)</td>
<td>0.370</td>
<td>2, 197</td>
<td>0.045*</td>
</tr>
<tr>
<td>Platelet</td>
<td>392.48(159.64)</td>
<td>434.21(169.79)</td>
<td>514.42(234.25)</td>
<td>2.810</td>
<td>2, 197</td>
<td>0.063</td>
</tr>
</tbody>
</table>
TABLE 10: ASSOCIATION BETWEEN CATEGORICAL VARIABLES AND RISK OF PRIMARY STROKE IN CHILDREN WITH SCA

<table>
<thead>
<tr>
<th>Variables</th>
<th>SR N(%)</th>
<th>CR N(%)</th>
<th>HR N(%)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N(%)</td>
<td>N(%)</td>
<td>N(%)</td>
<td>X2</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>29(58)</td>
<td>21(42)</td>
<td>0(0.0)</td>
<td>5.371</td>
</tr>
<tr>
<td>5 – 8</td>
<td>51(58.6)</td>
<td>31(35.6)</td>
<td>5(5.7)</td>
<td></td>
</tr>
<tr>
<td>9 – 12</td>
<td>29(60.4)</td>
<td>17(35.4)</td>
<td>2(4.2)</td>
<td></td>
</tr>
<tr>
<td>13 – 16</td>
<td>12(80.0)</td>
<td>3(20.0)</td>
<td>0(0.0)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51(58.6)</td>
<td>33(37.9)</td>
<td>3(3.4)</td>
<td>0.331</td>
</tr>
<tr>
<td>Female</td>
<td>70(61.9)</td>
<td>39(34.5)</td>
<td>4(3.5)</td>
<td></td>
</tr>
<tr>
<td>Acute Chest Syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>106(59.6)</td>
<td>65(36.5)</td>
<td>7(3.9)</td>
<td>0.551</td>
</tr>
<tr>
<td>Yes</td>
<td>15(68.2)</td>
<td>7(31.8)</td>
<td>0(0.0)</td>
<td></td>
</tr>
<tr>
<td>Dactylitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>78(62.4)</td>
<td>46(36.8)</td>
<td>1(0.8)</td>
<td>6.716</td>
</tr>
<tr>
<td>Yes</td>
<td>43(57.3)</td>
<td>26(34.7)</td>
<td>6(8.0)</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41(55.4)</td>
<td>30(40.5)</td>
<td>3(4.1)</td>
<td>1.407</td>
</tr>
<tr>
<td>No</td>
<td>80(63.5)</td>
<td>42(33.3)</td>
<td>4(3.2)</td>
<td></td>
</tr>
<tr>
<td>Number of blood transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32(60.4)</td>
<td>20(37.7)</td>
<td>1(1.9)</td>
<td>6.251</td>
</tr>
<tr>
<td>2</td>
<td>7(41.2)</td>
<td>9(52.9)</td>
<td>1(5.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2(50.0)</td>
<td>1(25.0)</td>
<td>1(25.0)</td>
<td></td>
</tr>
<tr>
<td>Transient Ischaemic Attack</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>117(60.0)</td>
<td>71(36.4)</td>
<td>7(3.6)</td>
<td>0.877</td>
</tr>
<tr>
<td>Yes</td>
<td>4(80.0)</td>
<td>1(20.0)</td>
<td>0(0.0)</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 11: RELATIONSHIP BETWEEN DACTYLITIS AND AGE GROUP

<table>
<thead>
<tr>
<th>Age group</th>
<th>No N(%)</th>
<th>Yes N(%)</th>
<th>X²</th>
<th>Df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
<td>33(66.0)</td>
<td>17(34.0)</td>
<td>8.405</td>
<td>3</td>
<td>0.026*</td>
</tr>
<tr>
<td>5 – 8</td>
<td>49(56.3)</td>
<td>38(43.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 – 12</td>
<td>29(60.4)</td>
<td>19(39.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 – 16</td>
<td>14(93.3)</td>
<td>1(6.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant negative relationship between age under 4 years and dactylitis
TABLE 12: RELATIONSHIP BETWEEN HCT, WBC AND HIGH STROKE RISK

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT</td>
<td>-0.092</td>
<td>0.045*</td>
</tr>
<tr>
<td>WBC</td>
<td>0.055</td>
<td>0.032*</td>
</tr>
</tbody>
</table>
DISCUSSION

This study evaluated the TCD findings in the children with SCA, categorized them into low and high risk, and identified children with SCA who were at greater risk of having primary stroke. In this study the prevalence of children with SCA who were at risk of stroke was 3.5%, more in the 5 – 8 years age group. This is similar to the findings of a prevalence of 4.7% by Lagunju et al\textsuperscript{42} in Ibadan and contrary to the African-American cohort by Adams of 8% prevalence. This shows that incidence of stroke among African children appears not to be as high as that in North America\textsuperscript{41}. In the study by Lagunju et al\textsuperscript{42}, in spite of educating and counseling them, the abnormal velocity found in 4.7% of children with HbSS was due to unwilling caregivers who did not consent to periodic blood transfusion which would have conferred 90% reduction in stroke risk in high risk children\textsuperscript{22}. This attitude is probably as a result of difficulties in the treatment plan, such as its being intensive, rigorous, time consuming and costly with tremendous impact on the meager resources of the families, who practice mainly out of pocket payment for health care services with no government subsidy\textsuperscript{22}. On the contrary, the index study involved compliant children and caregivers hence the prevalence was low.

Fatunde et al\textsuperscript{41} in a retrospective review arrived at 5.4% as estimated hospital stroke prevalence rate among Nigerian children with SCD while studying a clinic population of 500 children with mean age of 6.8 years ranging from 17 months to 11 years. The findings were similar to those in the present study though higher. The findings in this study could be explained by the increased awareness and care of the HbSS patients ultimately resulting in reduced stroke prevalence.

The median age for stroke is 5 years\textsuperscript{34} and those who survive it show disturbed learning profiles, psycho-emotional problems and perform poorly in school relative to their peers. Stroke impairs intellectual development\textsuperscript{35}. However the median age in this study was 7 years and none of the patients in this study developed stroke. This can also be explained by their compliant attitude.
With monthly increase in age, there was reduction in TAMMV of about 0.22cm/sec while TAMMV reduced by about 2.5cm/sec for every unit increase in HCT\textsuperscript{45}. The reduction of TAMMV as the age increased can be attributed to the excellent positive cooperation by children with SCD and their caregivers\textsuperscript{44}. The aforementioned was confirmed in the index study, as TAMMV reduced with increase in age from 8 years and TAMMV also reduced with increase in HCT.

The presence of $\text{TAMMV} \geq 170\text{cm/s}$ in 24.4% HbSS cohort is higher than the prevalence of 17.5% reported by Adams et al\textsuperscript{46} in a cohort of 315 African-American children with 19.7% being in the CR category of the HbSS cohort as opposed to 9% reported in African-American cohort. Reasons for this disparity was unclear, leaving two possibilities, one suggesting that Nigerian children with SCD develop stroke at relatively lower velocity than previously reported but this was contrary to the findings in this index study as none of the participants developed stroke. The other reason suggests that those with abnormal velocity had suffered a stroke prior to availability of routine TCD screening\textsuperscript{45}. This was different in this study as the sample size excluded participants with previous stroke. CR velocities occur more frequently in Nigerian children with HbSS disease than their African-American counterparts (9%)\textsuperscript{45}, as was corroborated in this study being (36%).

The prevalence of CR by Lagunju et al\textsuperscript{45} in Nigeria was less than 27%, which was obtained in the prospective Cretiel study\textsuperscript{29}. The researcher in the present study got a CR prevalence of 36%, a far cry from the findings in previous studies, illustrating the shift from high risk to conditional risk. This is also due to greater awareness and care by the society for HbSS children.

Children with CR velocity have a potential risk of converting to abnormal velocity (HR) by a progressive increase in their flow velocity over time\textsuperscript{21, 26}. This makes detection of CR velocity in one of five Nigerian children with HbSS a major concern and partly accounts for the relatively
higher prevalence of stroke in Nigerian children with SCD\textsuperscript{45}. This could not be confirmed in this study, as CR children repeating TCD after six months could no longer be accommodated because this study lasted only for six months. Adams et al had stated that younger aged patients and other patients with higher initial flow velocities were most likely to convert to (HR) abnormal TCD\textsuperscript{26}.

Younger children, ages 2-9 years are at high risk of stroke\textsuperscript{40} and this was confirmed in this study where high risk was more in ages 5-8 years and were advised for close follow up.

Lagunju et al\textsuperscript{45} also noted that more males were available for recruitment for his study with a male/ female ratio of 1.5:1, which he suggested was a reflection of superstition and the high value placed on the male child in the African setting. More females were recruited in the present study (with male/female ratio of 1.0:1.3), which is the opposite of Lagunju team’s study\textsuperscript{45}. This is probably due to the fact that nowadays both genders get almost equal care, education and spending, removing all gender discrimination.

Ryan et al\textsuperscript{4} noted that education at clinic visits is needed for the family so that there will be compliance with screening using TCD, follow up and suggested proven chronic blood transfusion therapy for abnormal TCD. Informing the family of the results also encourages further compliance\textsuperscript{4}. This was also proven in this study because patients, who fell into high risk group and were told to repeat TCD in a week, complied fully. Also the children in the conditional risk group, who were told to repeat in two weeks, did so judiciously. Some of these high risk children for repeat screening, remained high risk, while others fell into the conditional risk group probably having received treatment for undiagnosed prodromal illnesses in the waiting one-week period. The latter would also explain why the conditional risk children became standard risk after treatment in the two-week waiting period. Those who remained HR, probably had a severe underlying incubating infection which was not visible enough to exclude the child from the study.
The stroke risk factors studied here were low haematocrit (HCT), high leucocyte (white blood cell) count, prior transient ischemic attack, patients with frequent and recent acute chest syndrome, history of stroke in sibling and history of dactylytis in the first 2 years of life.

None of the children in this study had history of acute chest syndrome or transient ischaemic attack. However 85.7% had a history of dactylitis while 42.9% had history of blood transfusion. About three children were transfused out of the seven children who were found to be high risk.

An optimal stroke prevention strategy was projected to involve annual TCD screening until age 10 years with transfusion for children at high risk until age 18. Muzumdar et al predicted prevention of 32% of future strokes which would otherwise have occurred in these children without intervention. This led to benefits similar to more intensive screening and transfusion strategies resulting in fewer adverse events as observed in the index study over the six months period.

The advent of iron chelation therapy, and its better adherence improved life expectancy in all intervention strategies as noted in this study when the children came back for a repeat TCD after intervention therapy especially blood transfusion.

Adams et al in 2001 discovered that overall age specific incidence of stroke in SCA (HbSS) is low (0.13%) at ages less than 24 months, increasing to greater than 1% at ages 2-5 years, with only a slight decrease to 0.7% at ages 6-9 years. This was corroborated in this study as there were no high risk children below 4 years of age. However, HR stroke incidence increased in 5-8 years of age and later declined from age 9 years. No reason was attributed to this finding.

Dactylitis had significant negative correlation with high risk velocities (p value=0.007), which is a finding that was not confirmed in previous literature. Significant correlation between age under 4 years and dactylitis (p value = 0.26) was also noted, but could not be confirmed by previous studies.
The HCT values were higher in SR and CR children than in HR children with a HCT of 26.42% (SD of 16.43) in low risk children and 24.80% (SD of 4.40) in HR children) in the index study. The WBC values were higher in HR SCA children being 19.54cmm (SD of 21.62), than in low risk SCA children 14.99cmm (SD of 15.87). These HCT and WBC values are similar to findings by Lagunju et al\textsuperscript{45}. Significant correlation between HCT (p = 0.045), WBC (p=0.032) and TAMMV were found in the present study. Reasons were attributed to high HCT (good nutrition, better care, no anaemia) and low WBC (no infection) found in low SR and CR children, while low HCT(poor nutrition, poor care, anaemia, other co-existing pathology) and high WBC (infection, inflammation) are responsible for the HR children status.

Significant correlation between HCT and TAMMV in previous studies in literature\textsuperscript{45} was (p value = 0.002), as was confirmed in this study (p value = 0.045).

Low HCT and young age were associated with high TAMMV in children with SCD\textsuperscript{45} as was corroborated in this study also. Adams\textsuperscript{7} report also showed significant correlation of cerebral blood flow velocity (CBFv) and stroke with age, HCT and WBC\textsuperscript{7} and this was confirmed in the present study (p = 0.045, p = 0.032 respectively). The index study agrees with the findings by Bernuadin et al \textsuperscript{29} and Lagunju et al\textsuperscript{45} which stated that significant negative correlation between age, HCT and TAMMV are consistent with stroke risk\textsuperscript{29}. However no reason was suggested for this.

The present study also confirmed that progressive decline in flow velocity after 4-5 years is a pointer to stroke\textsuperscript{7}, thus increasing the number of children with HR.

Anemia and hemolysis were found to be associated with abnormal high velocity in the study by Adams\textsuperscript{7} but it was associated with anemia in this study.
CONCLUSION

1) The various risk factors were elicited and they include hematological parameters such as low HCT and high white blood cell count (WBC), history of dactylitis, history of acute chest syndrome, stroke in sibling and history of blood transfusion.

2) Dactylitis had significant negative relationship with high risk velocities (p value=0.007).

3) SCA children with low haematocrit HCT were found to have significant correlation with high TCD or TAMMV values (p value = 0.045).

4) Children with SCA having high total white blood cell count (WBC) had significant correlation with high TCD values (p value = 0.032).

5) Comparatively the researcher was able to identify children with SCA who are at greater risk of having primary stroke, the prevalence being 3.5%.

6) In addition a reversal of number of recruited children with male/female ratio was discovered being 1.0:1.3.

7) This study noted high velocities in anemic younger children with SCA.
1) Irrespective of risk factors, the current SCD guidelines recommend the use of TCD as a screening tool for risk of stroke in all 2-16 years old children with SCD at least once a year\textsuperscript{22}.

2) Transcranial Doppler ultrasound should be performed in all children with sickle cell anaemia to exclude anticipated development of stroke.

3) Follow up TCD checks should be encouraged; every six months – one year for standard risk, every six months for conditional risk group and every three months for high risk groups until they convert to a lesser risk group after therapy.
REFERENCES


PROJECT TITLE: EVALUATION OF FINDINGS IN CHILDREN WITH SICKLE CELL ANAEMIA USING TRANSCRANIAL DOPPLER ULTRASOUND IN SICKLE CELL FOUNDATION OF NIGERIA

REF. NO.: LREC/10/06/371

PRINCIPAL INVESTIGATOR: DR. USORO UYI

ADDRESS: DEPT. OF RADIOLOGY, LASUTH

DATE OF RECEIPT OF VALID APPLICATION: 10/1/14

DATE OF APPROVAL: 16/1/2014.

This is to inform you that the research described here in the submitted protocol, the consent forms, advertisements and other participant information materials have been reviewed and given full approval by the Health Research and Ethics Committee of LASUTH (LREC).

This approval dates from 16/01/2014 to 16/05/2014. If there is any delay in starting the Research, Please inform the HREC LASUTH so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. All informed consent forms used in this study must carry the HREC LASUTH assigned number and duration of HREC approval. In a multiyear research, endeavor to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

THE NATIONAL CODE FOR HEALTH RESEARCH AND ETHICS (www.nhrec.net) REQUIRES YOU TO COMPLY WITH ALL INSTITUTIONAL GUIDELINES, RULES AND REGULATIONS AND WITH THE TENETS OF THE CODE INCLUDING ENSURING THAT ALL ADVERSE EVENTS ARE REPORTED PROMPTLY TO THE HREC. NO CHANGES ARE PERMITTED IN THE RESEARCH WITHOUT PRIOR APPROVAL BY HREC LASUTH EXCEPT IN CIRCUMSTANCES OUTLINED IN THE CODE. THE HREC RESERVES THE RIGHT TO CONDUCT COMPLIANCE VISIT TO YOUR RESEARCH SITE WITHOUT PREVIOUS NOTIFICATION.

DR. (MED.) O. A. AJOSE
CHAIRMAN
HREC-LASUTH
Appendix II: QUESTIONNAIRE

EVALUATION OF FINDINGS IN CHILDREN WITH SICKLE CELL ANEMIA USING TRANSCRANIAL DOPPLER ULTRASOUND IN SICKLE-CELL FOUNDATION CENTRE, LAGOS

A Patient Bio-data: 1. Serial No:...........

2. Name or Initials.................. 3. Date of birth:............. 4. Sex:.............
5. Religion  a. Christianity: Yes__ No__  b. Muslim: Yes__ No__
c. Others: Yes__ No__
14. HCT: ............ 15. Wbc: ........

B Social history: 1. Patient’s position in family:.............

2. Relationship to patient :a. Parent Yes__ No__  b. Guardian Yes__ No__

C Past medical History:

1. Prior Transient Ischemic Attack (TIA) : Yes__ No__

2. Dactilytis in First 2 years of life: Yes__ No__

3. Frequency of acute chest syndrome: 1-3__ 4-7__ 8-10__

4. Recent acute chest syndrome: 1-2month ago__ >3months ago__

5. Stroke in sibling: Yes__ No__  6. Any previous blood transfusion: Yes__ No__
Appendix III: INFORMED CONSENT FORM

NAME OF PRINCIPAL INVESTIGATOR: DR. USORO UYI UYAI OGHOMWAN

DEPARTMENT: Radiology

E.MAIL: uyiusoro@yahoo.com

PHONE NUMBER: 08023069034

TITLE OF THE RESEARCH: EVALUATION OF FINDINGS IN CHILDREN WITH SICKLE CELL ANAEMIA USING TRANSCRANIAL DOPPLER ULTRASOUND IN SICKLE-CELL FOUNDATION CENTRE, LAGOS

NAMES AND AFFILIATIONS OF RESEARCHER: This study is being conducted by DR USORO of the Lagos State University Teaching Hospital, (LASUTH), Ikeja, Lagos State, Nigeria.

SPONSORS OF RESEARCH: This study is self-sponsored.

PURPOSE(S) OF RESEARCH: The purpose of this study is to elicit the findings on a TCD study of SCA children, find the risk factors and identify the high risk patients likely to have primary stroke.

PROCEDURE OF THE RESEARCH: The researcher intends to perform transcranial Doppler ultrasound (TCD) on children with sickle cell anaemia (ages 2-16 years) attending the Sickle Cell Foundation Nigeria (SCFN). The researcher will make the child lie on his or her back with head turned to one side. A small amount of ultrasound gel will be applied to the child’s temporal region and the ultrasound transducer will be moved over this area until the vessels of the brain
are located. Automated measurements will be taken while increasing or decreasing the depth of
the machine. The same will be done for the opposite side. Data will be collected.

Children with elevated velocities ≥ 170cm/s will have a repeat scan done on them a week later
and they will be identified as having conditional or abnormal risk. In total the researcher expects
to recruit a total of 200 participants.

**DURATION OF RESEARCH**: The research is expected to span about six months. Each
examination will last only 30 minutes.

**RISK**: There is no risk to the child.

**COST TO THE PARTICIPANTS**: This research is at no cost to the participants.

**BENEFITS**: The goal of this research is to elicit the findings on a TCD study of SCA Children,
highlight the risk factors and probably predict those of them that will result in stroke.

**CONFIDENTIALITY**: All information collected from this study will be given code numbers
and no name or residential address will be used. This cannot be linked to you in anyway and
your name or any identifier will not be used in any publication or reports from this study.

**VOLUNTARINESS**: Your participation in this research is entirely voluntary.

**ALTERNATIVES TO PARTICIPATION**: If you choose not to participate, this will not affect
your treatment in this hospital in any way.

**DUE INDUCEMENT**: No form of compensation or extra cost is to be received or borne by the
participant or the researcher.

**CONSEQUENCES OF PARTICIPANT’S DECISION TO WITHDRAW FROM
RESEARCH AND PROCEDURES FOR ORDERLY TERMINATION OF**
**PARTICIPATION**: The parents or guardians may decide to withdraw from the research at any time. Please note that the information that has been obtained about your child may have been modified or used in reports and publications. They cannot be removed anymore. However the researcher promises to make good faith effort to comply with your wishes as much as possible. The refusal of parent or guardian to participate will not in any way affect the researcher’s professional relationship with your child or affect your child’s treatment at the hospital.

**MODALITY OF PROVIDING TREATMENTS AND ACTION TO BE TAKEN IN CASE OF INJURY OR ADVERSE EFFECTS**: The procedure has no risk to your child.

**WHAT HAPPENS TO THE RESEARCH PARTICIPANTS AND COMMUNITIES WHEN THE RESEARCH IS OVER**: The findings of the study will be disclosed to the parents and those who are at high risk for stroke will be referred to paediatric hematologists for evaluation and follow up. The entire research and its findings will be published as a dissertation to be defended before a panel of examiners from the National Postgraduate Medical College of Nigeria. Thereafter the researcher will seek ways to disseminate the findings to health policy makers and clinicians for the benefit of the participants and the entire human race.

**CONFLICT OF INTEREST**: There is no conflict of interest and the researcher will work judiciously.
STATEMENT OF THE PERSON OBTAINING INFORMED CONSENT:

I have fully explained the research to__________________________________________

And I have given sufficient information, including about risks and benefits, to make an informed decision.

DATE: _______________                            SIGNATURE: _______________________

NAME: _________________________________

PLEASE KEEP A COPY OF THIS SIGNED INFORMED CONSENT.
STATEMENT OF PERSON GIVING CONSENT:

I, Parent/care giver, have read the description of the research or have had it translated into a language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my child’s participation is voluntary. I know enough about the purpose, method, risks and benefits of the research to judge that I want my child to take part in it. I understand that I may freely stop my child being part of this study at any time. I have received a copy of this consent form to keep for myself.

DATE:

SIGNATURE:

NAME:

DETAILED CONTACT INFORMATION OF RESEARCHER, INSTITUTIONAL HREC AND HEAD OF INSTITUTION: This research has been approved by the Health Research Ethics Committee of the Lagos State University Teaching Hospital (LASUTH) and the Chairman of this committee can be contacted at administration block in LASUTH, 1-5 Oba Akinjobi Way, GRA, Ikeja, Lagos. If you have any question about your participation in this research, you can contact the principal investigator, Dr Usoro at Radiology Department, BT Diagnostics, LASUTH, Ikeja, Lagos (08023069034, uyiusoro@yahoo.com).

You can also contact the Head of Department of Radiology at the Radiology Department, LASUTH, Ikeja, Lagos.

DATE: __________________ ______ SIGNATURE: ______________________
Appendix IV: EVALUATION OF FINDINGS IN CHILDREN WITH SICKLE CELL ANEMIA USING TRANSCRANIAL DOPPLER ULTRASOUND IN SICKLE-CELL FOUNDATION CENTRE, LAGOS

ASSENT FORM (7-11 YEARS)

I am Dr Usoro, a senior registrar in Department of Radiology, Lagos State University Teaching hospital, Ikeja, Lagos. I am conducting a study on children with sickle cell anemia using a machine called transcranial Doppler ultrasound (TCD) machine. I intend to evaluate the TCD findings, group you into various stroke risk categories and find the risk factors of stroke. Children with sickle cell anemia can remain healthy if they are well monitored and do not have complications such as stroke.

Transcranial Doppler ultrasound is a simple procedure that is neither painful nor harmful and is of short duration.

I will make you lie on your back with your head turned to one side. A small amount of ultrasound gel will be applied to your temple area and I will move the ultrasound probe over this area until the vessels of the brain are located. Readings will be taken and the same will be done for the opposite side. This procedure will take less than 30 minutes. I will explain the result to you and you will then go back to your doctor with the result for further management. This study will also help other children with sickle cell anemia by encouraging them to screen with TCD and prevent them from having stroke.

Your participation in this research is entirely voluntary. If you choose not to participate, this will not affect your treatment in this hospital in any way.

Initials…………….. Signature of patient: …….. Date……..

Name of researcher: Dr Uyi Usoro Signature: ……………..