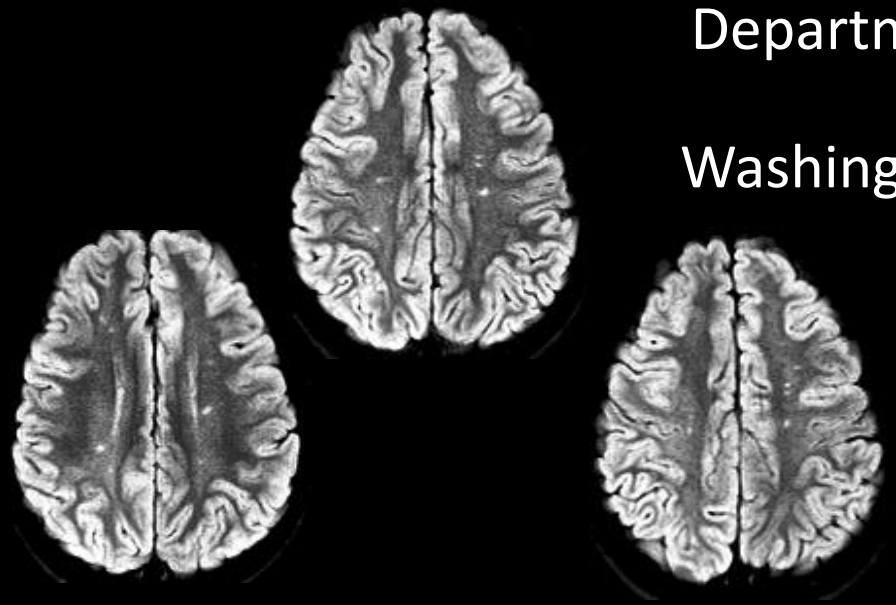
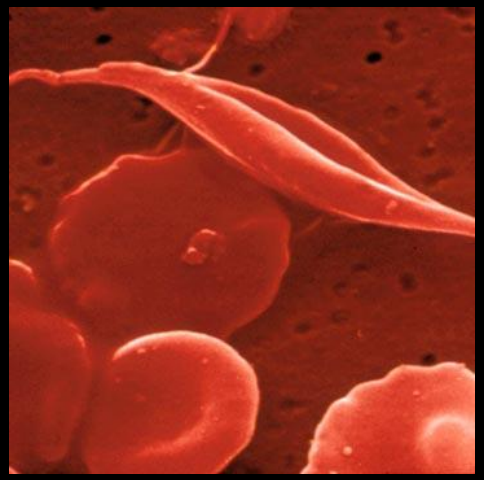
Sickle Cell Disease and Stroke: Mechanisms and Management

Andria L. Ford, MD
Departments of Neurology and Radiology
Director, Stroke Section
Washington University School of Medicine





Disclosures

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Clayco Foundation

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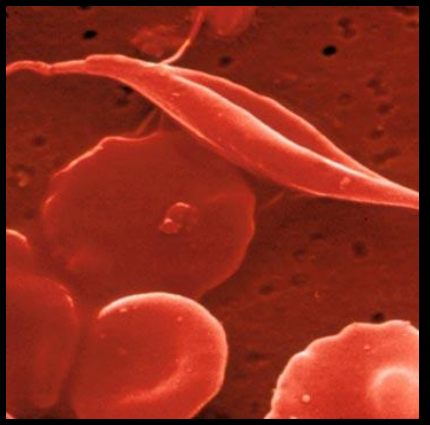
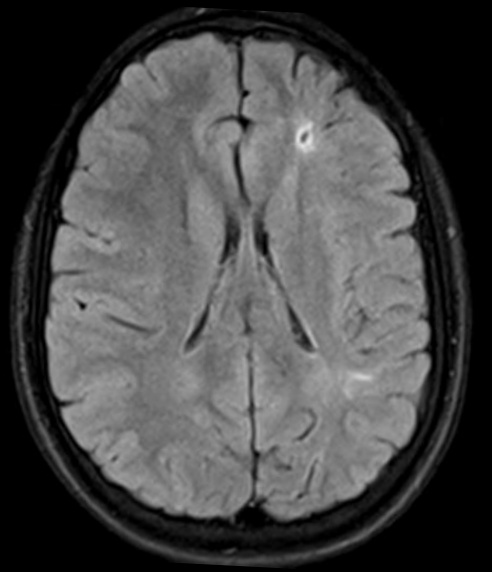
Sickle cell disease gives us a greater understanding of stroke pathophysiology

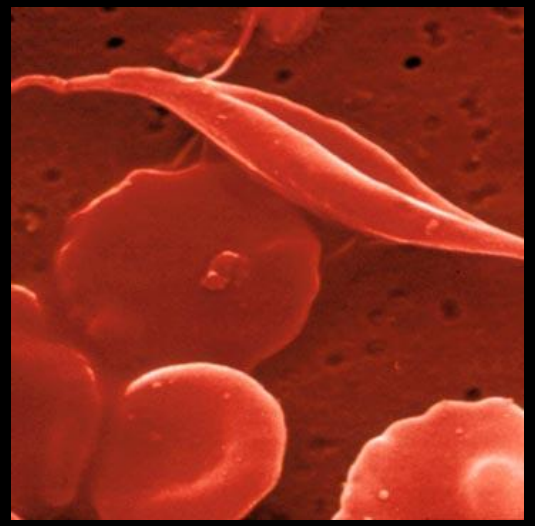
Objectives

- SCD and the Brain
- Relationship between cerebral oxygen metabolism and stroke
  - How a surrogate biomarker can revolutionize clinical care
  - Innate compensatory mechanisms brain leverages to prevent stroke
- Cerebral ischemic vulnerability in SVDs.
- Novel therapeutic approaches aimed at stroke prevention.
- Influence of race and disparities on cerebral ischemia and cognition.

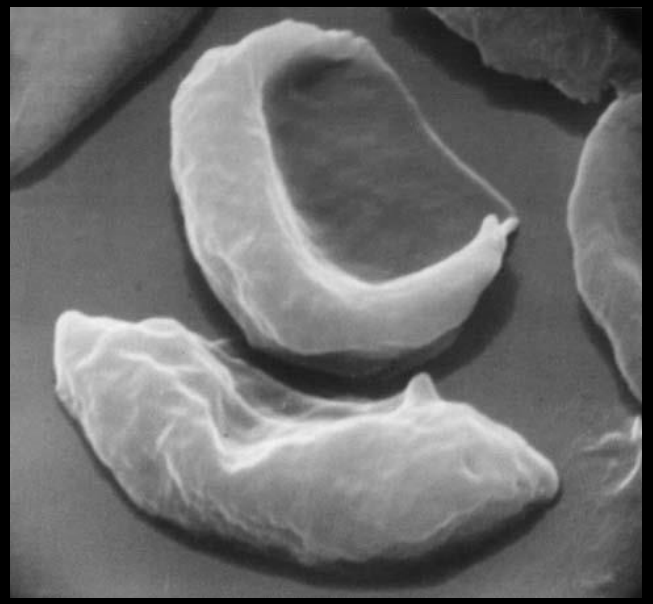




Sickle Cell Disease



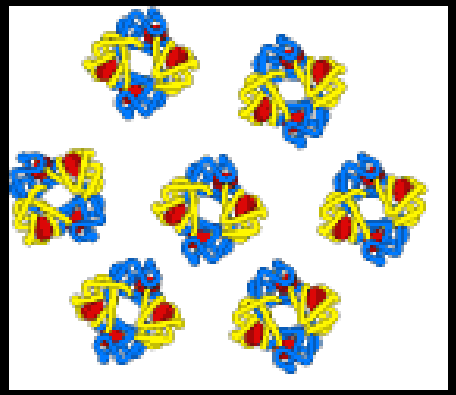
- Most common genetic disorder identified on newborn screening
- One in 400 African-Americans
- ~100,000 affected in the U.S.
- Median life expectancy 40 years
- Stroke as the 5th leading immediate cause of death
- Sickle cell trait - ~8% of Black Americans



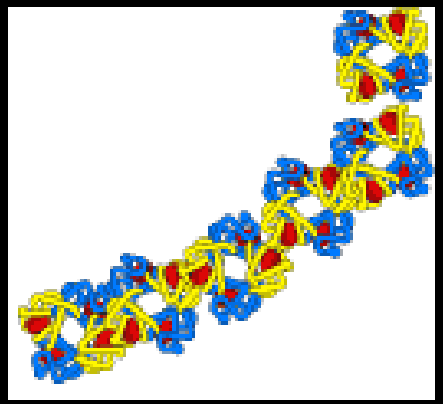
Lanzkron et al. Public Health Reports 2013. 128:110-6; Verduzco et al. Blood. 2009.

Hb A vs. HbSS

- A point mutation in the β-globin gene converts normal HbA into HbS, which pathologically polymerizes into chains under hypoxic conditions, distorting RBC shape.
- Sickled cells obstruct the microcirculation and hemolyze, leading to intravascular clotting, endothelial activation, inflammation affecting all organs, and chronic anemia



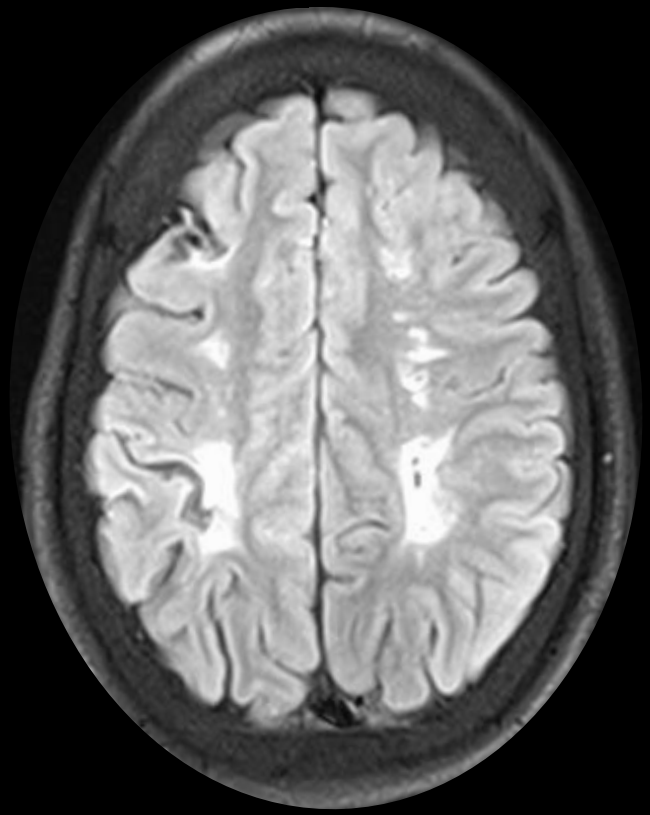
HbA



HbS

Rothman et al. Ann Neurol. 1986. Pavlakis et al. Ann Neurol. 1988.
http://evolution.berkeley.edu/evolibrary/article/mutations_06

Overt Stroke in Sickle Cell Disease



- ~10% of SCD patients have a a stroke by age 20 and ~25% have strokes by age 45
- Of these, 66% will have recurrent stroke
- Many of the recurrent strokes occur in the setting of Large vessel vasculopathy
- About 1/3 of strokes occur in the setting of acute illness or Sickle Cell Crisis

Dobson et al. Blood 2002; 99(9): 3144-50.
Hulbert et al. Blood 2011; 117(3): 772-9.

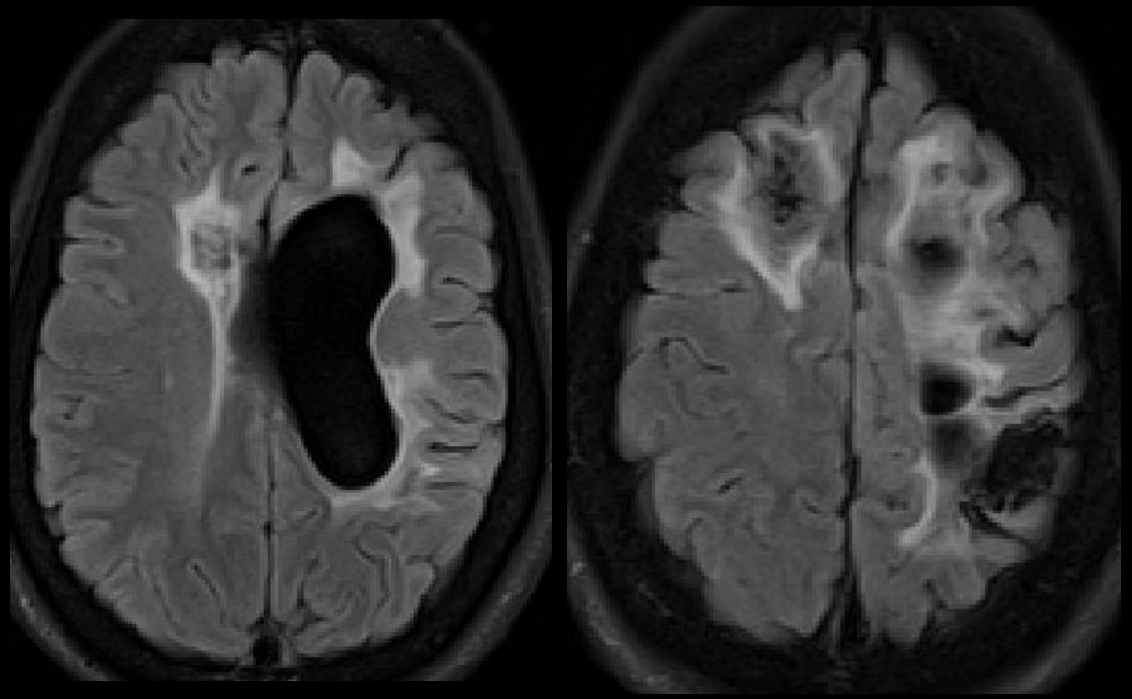
A Patient: LJ in Clinic

- 38 yo AA woman with HbSS disease.
- History: taken from predominantly from mom.
  - Ischemic stroke age 2.5 years
  - L hemorrhagic stroke age 14 years
  - Placed on exchange transfusions as a child, stopped for unclear reasons, placed on hydroxyurea
  - She has stable, chronic headaches and intermittent generalized tonic-clonic seizures for many years
- Exam: shy, paucity of speech, but intact naming/ comprehension; memory 1/3 at 5 min, right visual field cut, hemiparesis, walks without assistance
- *Mom is concerned about progressive decline in memory.*

A Patient: LJ in Clinic

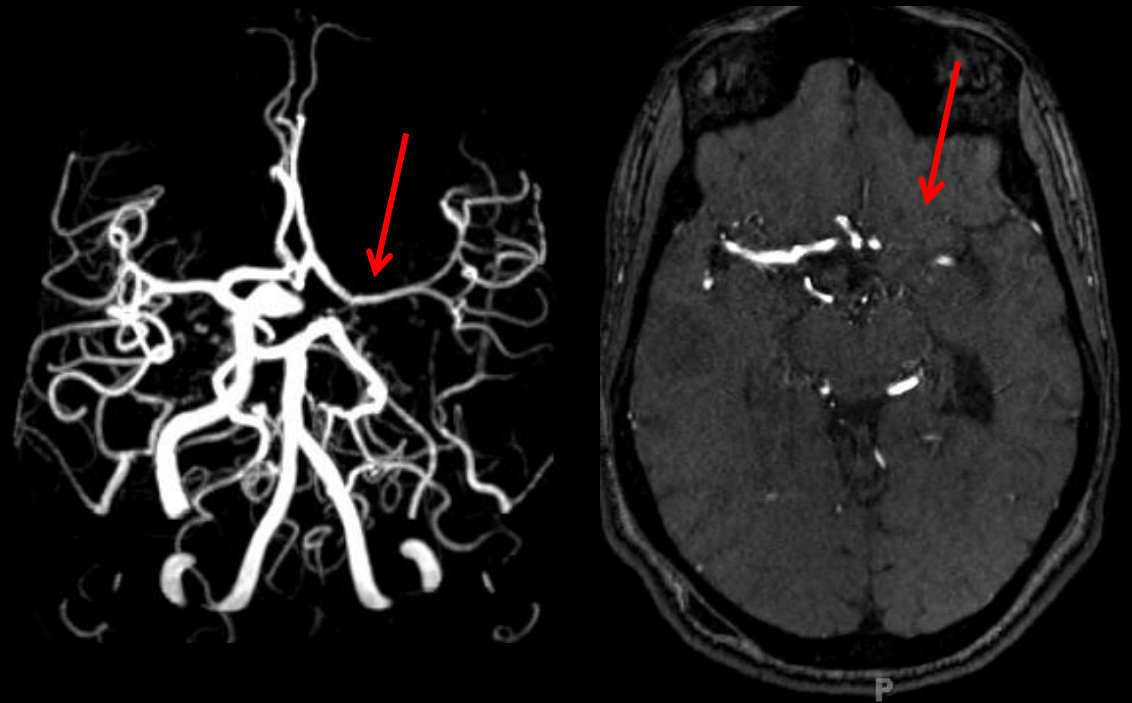
Brain MRI

Bilateral ischemic and hemorrhagic strokes, Left > Right; stable since 6 years prior



Brain MRA

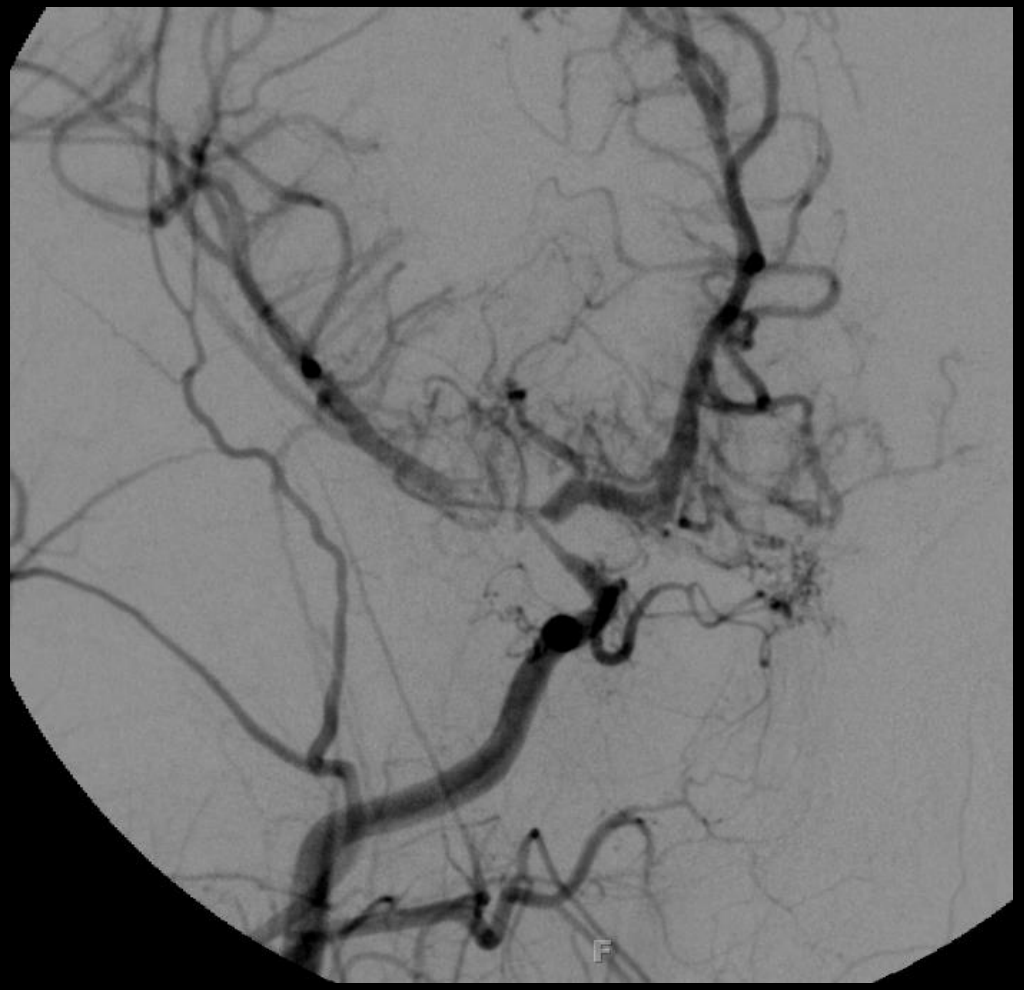
Left ICA occlusion and left Middle Cerebral Artery with Markedly Decreased Flow; Cavernous ICA and basilar tip aneurysms



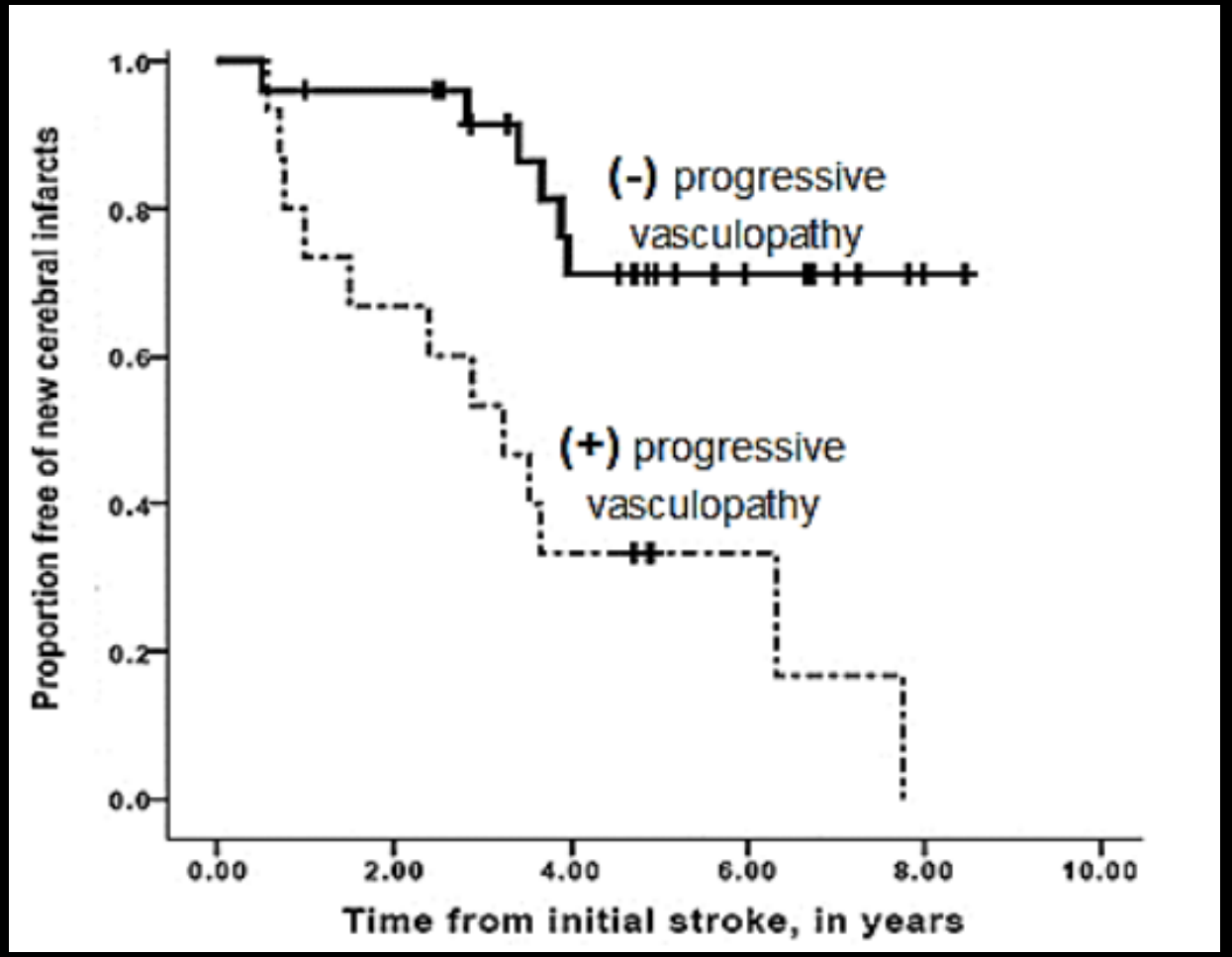
A Patient: LJ in Clinic
Neuropsychological Testing

- “In sum, Ms. LJ shows a pattern of s*ignificant cognitive impairment* primarily in”:
  - short-term memory
  - receptive language
  - auditory attention
  - Executive abilities, reasoning abilities moderately impaired.
  - Visual-spatial and expressive language relatively intact
  - Referral to Occupational Performance Center / Vocational Rehab to maximize independence in the home environment and potential for Volunteer Work
- Cannot drive, completed high school, could not finish any college; tried working, but unable to perform job duties, stays at home with Mom, likes art / drawing

Progressive Vasculopathy Decreases Event Free Survival

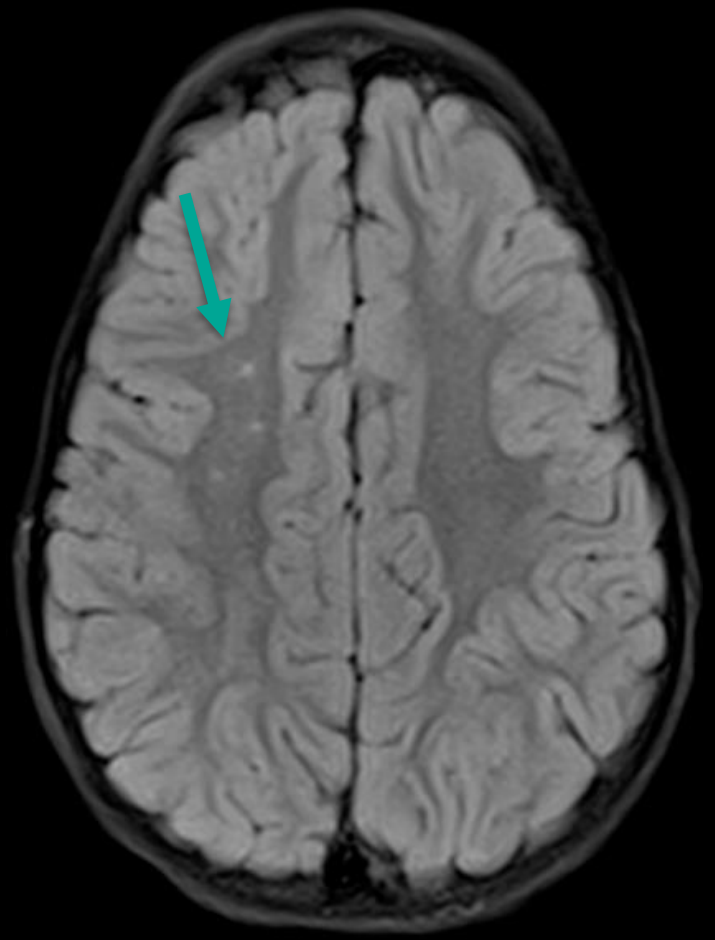


Moyamoya Vasculopathy in a 7 yo girl with HbSS



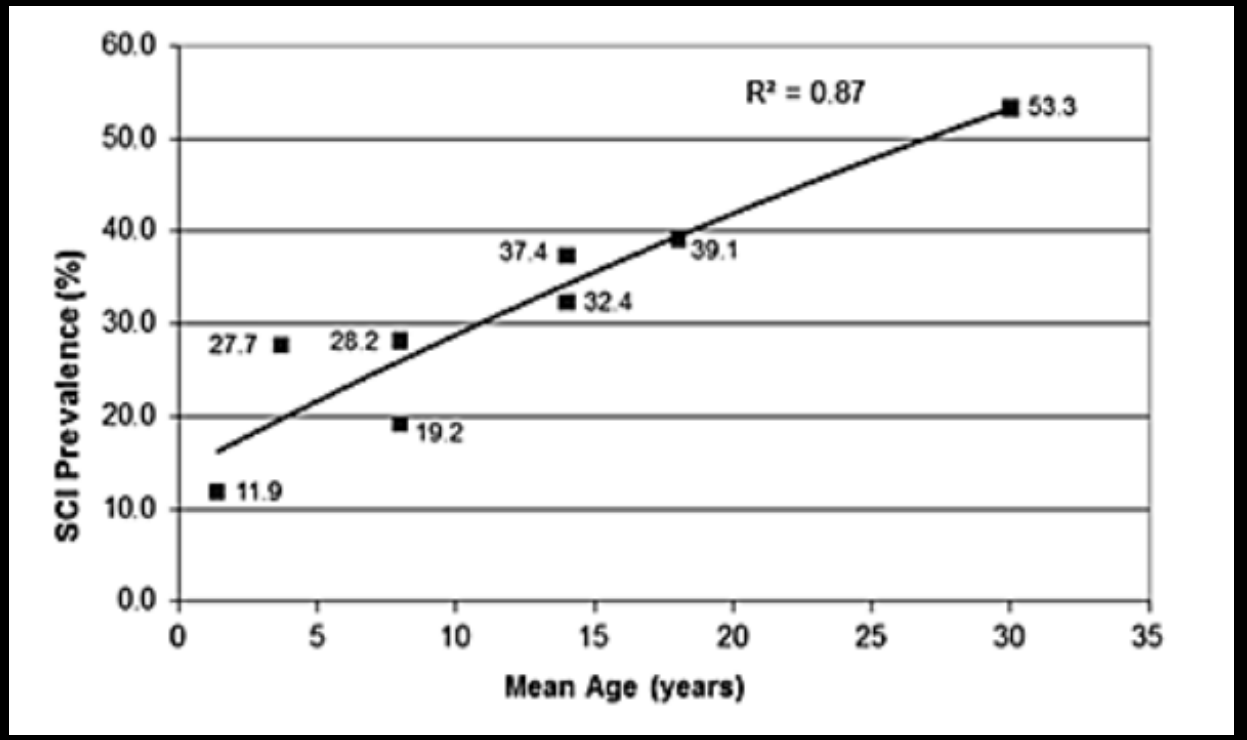
Hulbert et al. Blood. 2012.

Silent Strokes “SCIs” in Sickle Cell Disease



- 27% have SCIs by age 6
- 37% have SCIs by age 14

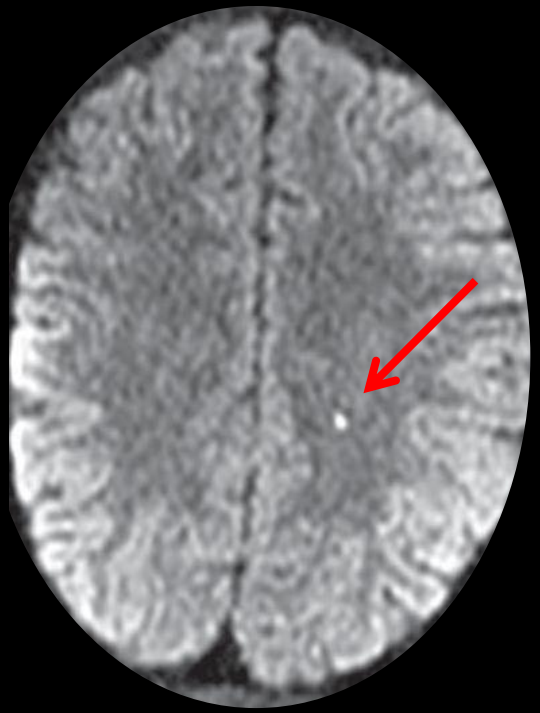
Bernaudin et al. Blood. 2011;117(4):1130-40.



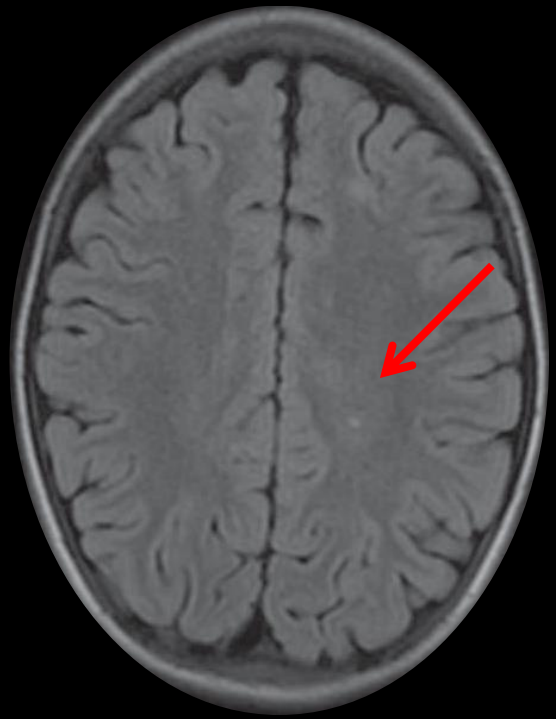
Kassim AA, et al. *Blood*. 2016;127(16):2038-2040.
Bernaudin et al. Blood. 2015;125(10):1653-61.

A State of Ongoing Ischemia:
Acute Silent Cerebral Ischemic Events

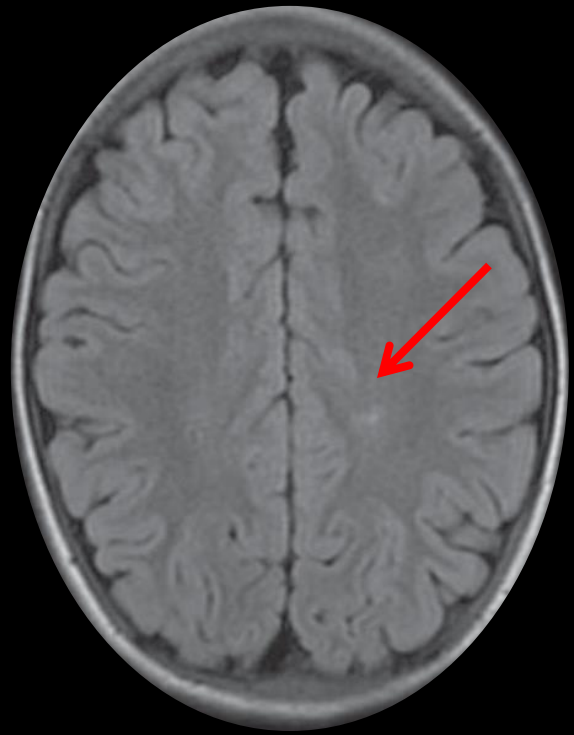
Acute DWI



Acute FLAIR

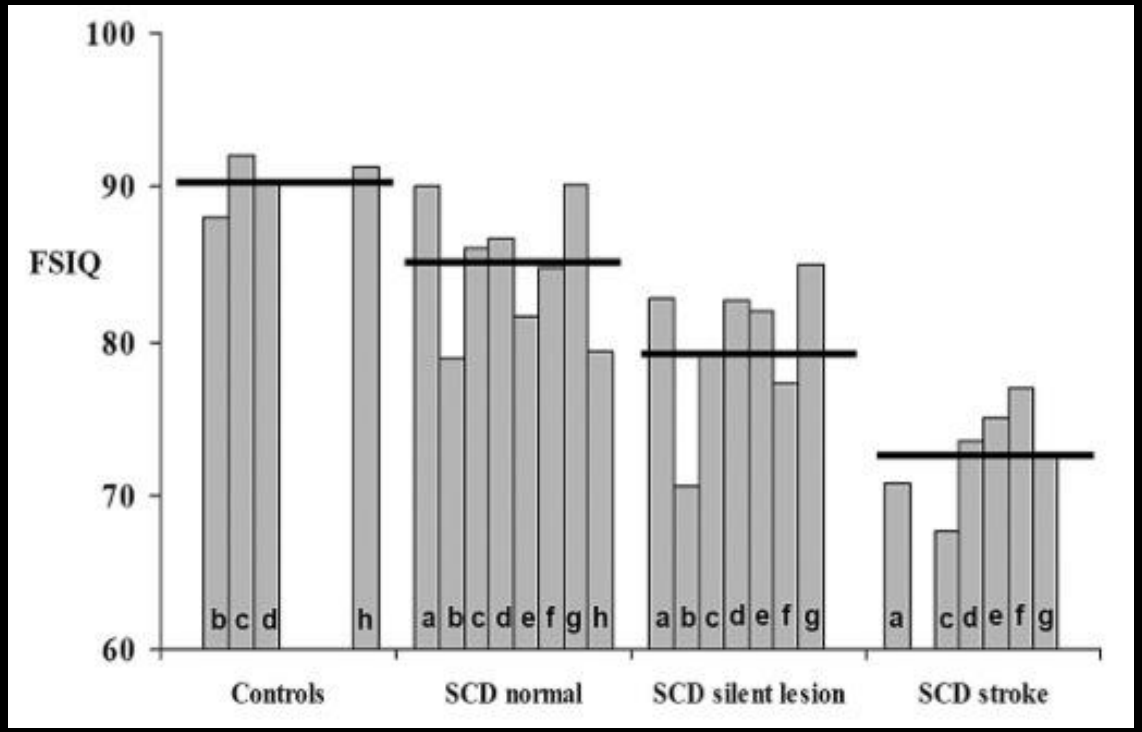


4 mos FLAIR



Quinn et al. JAMA Neurol. 2013;70(1):58-65.

Interaction between Silent Strokes and Cognitive Impairment



- Silent Strokes are associated with:
  - loss of IQ points
  - increased school grade retention
  - academic difficulties

Debaun et al. Blood. 2012;119(20):4587-96.

Multivariate Linear Regression Model for Full Scale IQ

Covariate	B	SE B	95% Confidence Interval	p
Age	-0.96	0.42	-1.79, -0.13	0.023
Baseline pulse oximetry	0.75	0.34	0.07, 1.42	0.030
Head of household completed some college	6.22	2.19	1.9, 10.55	0.005
Silent infarct	-5.21	2.16	-9.48, -0.93	0.017

King et al, AJH 89:162-167,2014

* This work by King et al. Highlights another learning objective stemming from sickle cell disease: How disparities in society and healthcare impact disease vulnerability and cognition.

Sickle cell disease gives us a greater understanding of stroke pathophysiology

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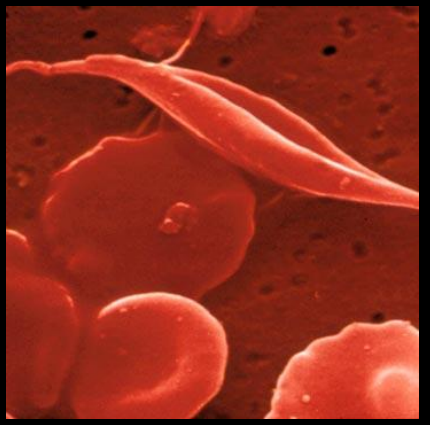
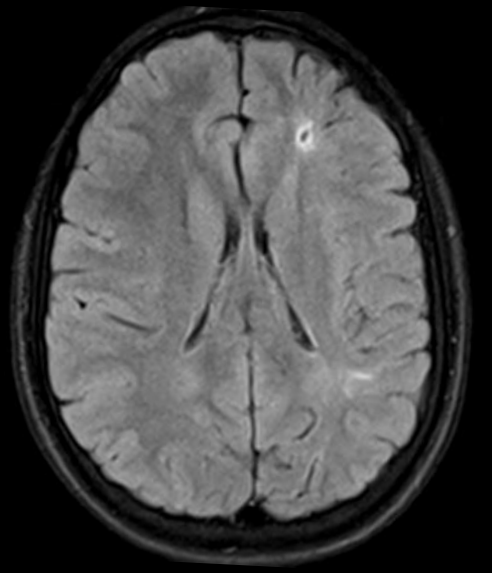


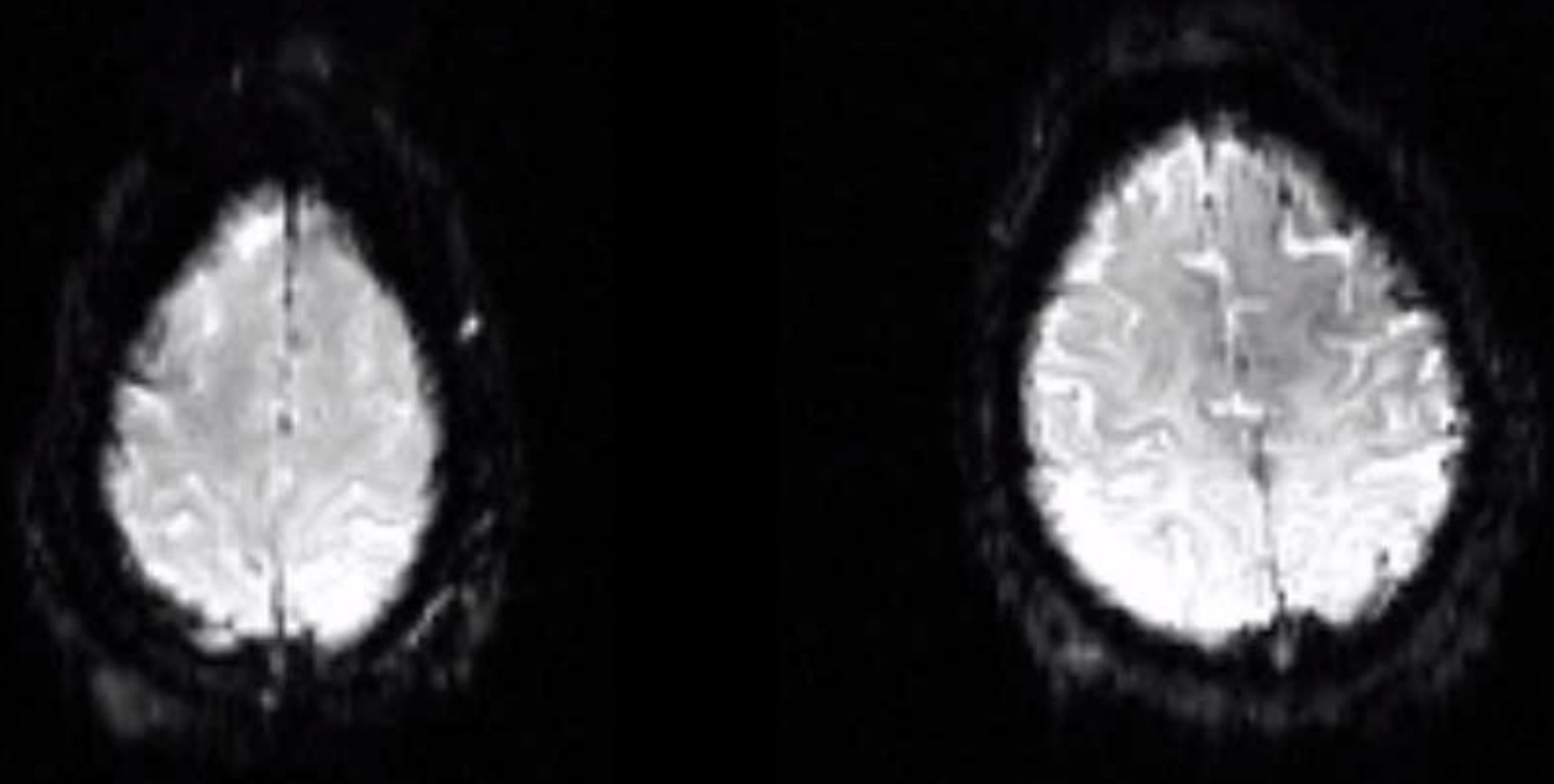


Cerebral Blood Flow (CBF) Measurement

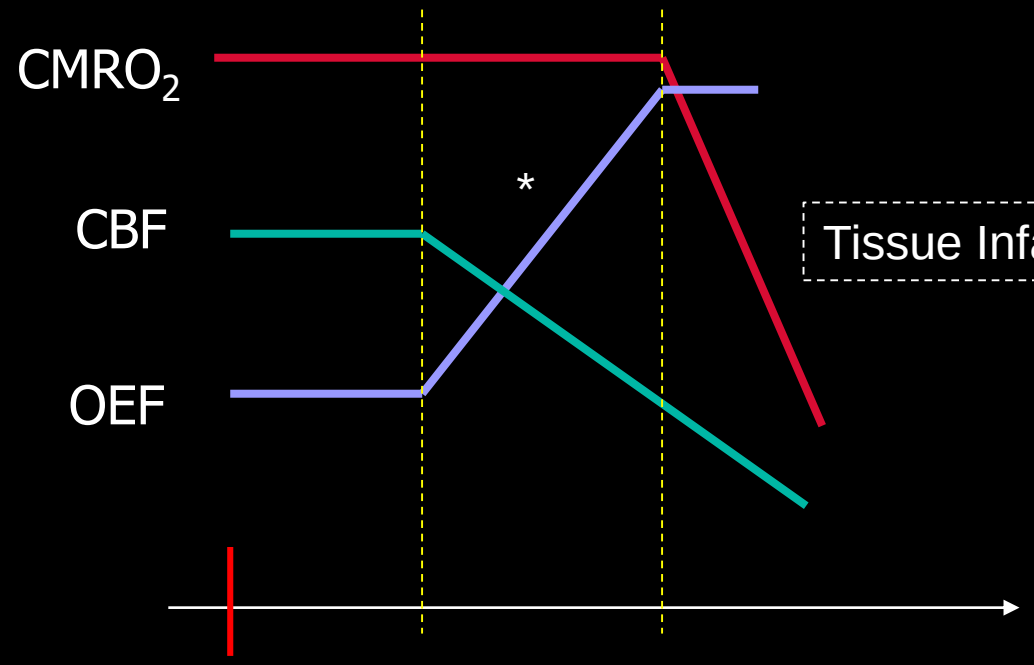
Dynamic Susceptibility Contrast

Normal Perfusion

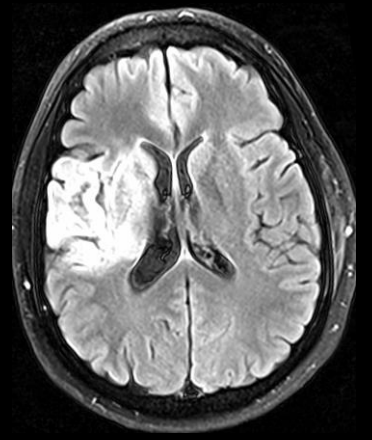
L MCA Ischemic Stroke



Cerebral Oxygen Metabolism during Adult Focal Ischemia



Tissue Infarction



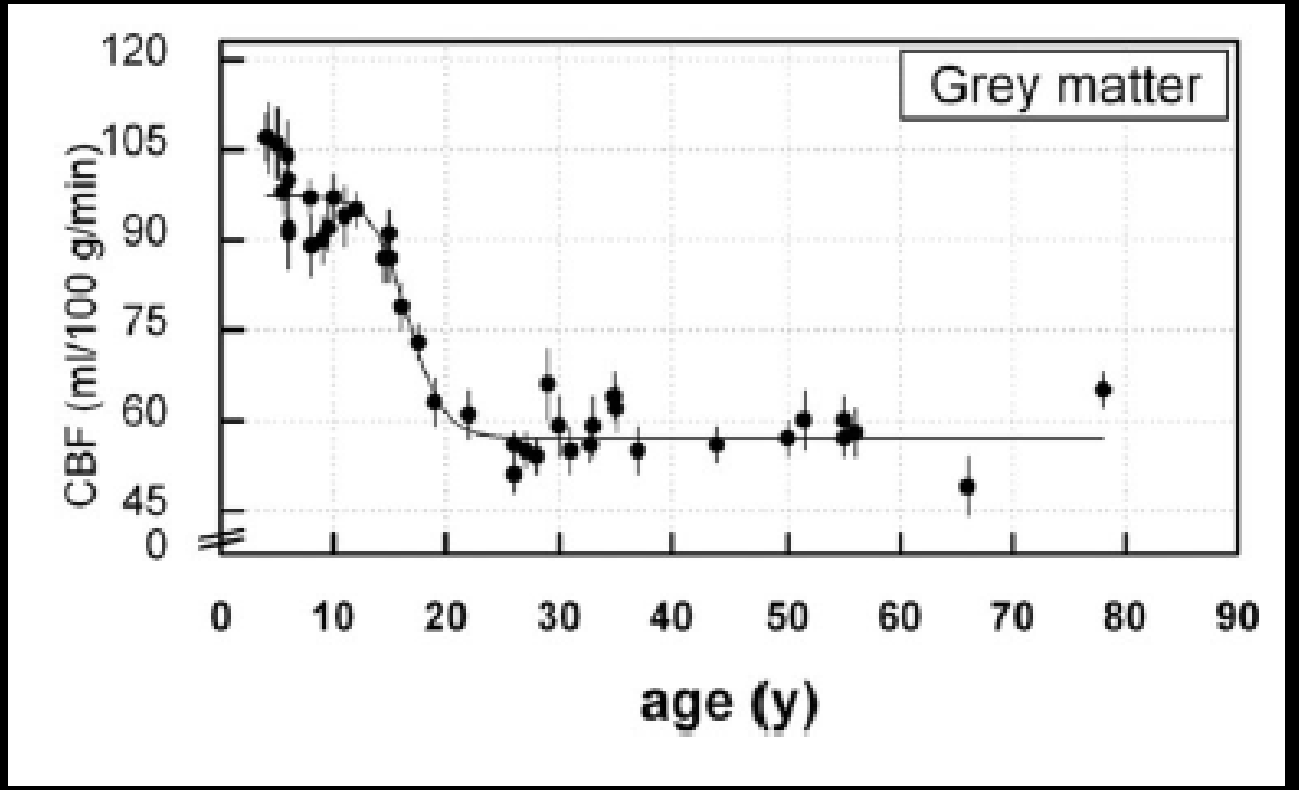
* Predictor of Increased Stroke Risk in Adult Ischemic Stroke, Carotid Occlusion

OEF = Oxygen Extraction Fraction
CMRO2 = Cerebral Metabolic Rate of Oxygen Utilization

Grubb et al. JAMA 1998.
Gupta et al. AJNR 2013.

Cerebral Blood Flow (CBF) in Children

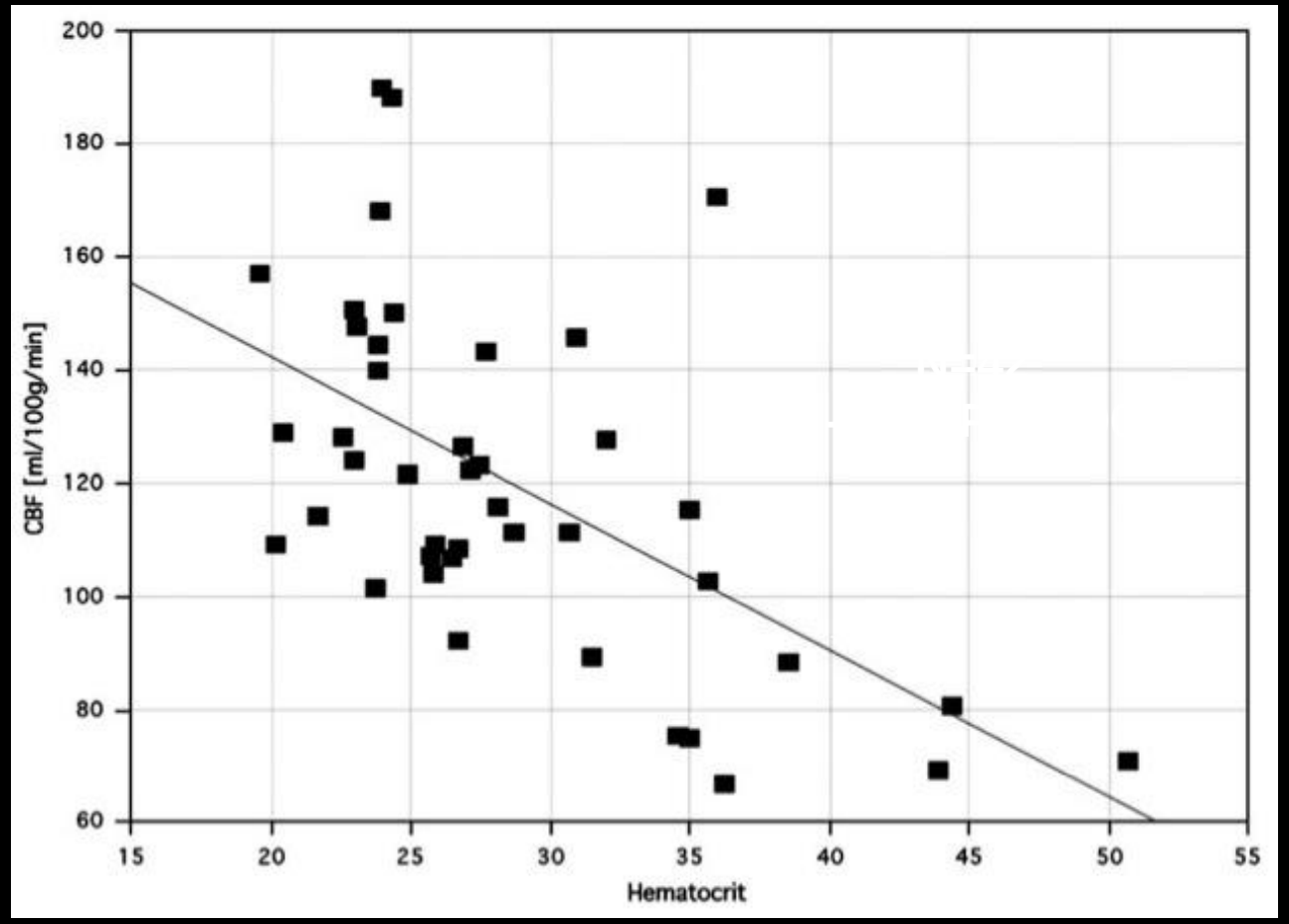
- CBF is elevated in children, likely due to increased metabolic demand during brain development



Biagi et al. JMRI. 2007. 25;696-702.

Cerebral Blood Flow (CBF) in Anemia

CBF



Hematocrit

Prohovnik et al., JCBFM, 2009; 29(4): 803-10.

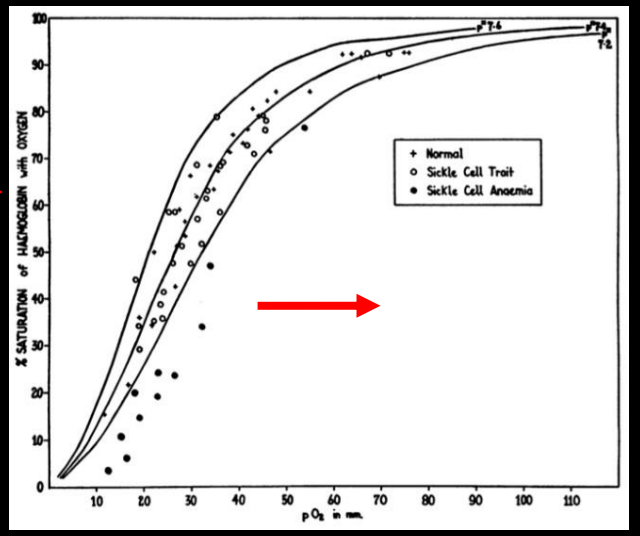
Cerebral Oxygen Delivery and Metabolism in Sickle Cell Disease

Oxygen Delivery

$CMRO_2 = CaO_2 \times CBF \times OEF$

BLOOD BRAIN

$CaO_2 = 1.35 \times [Hb] \times [SaO_2]$

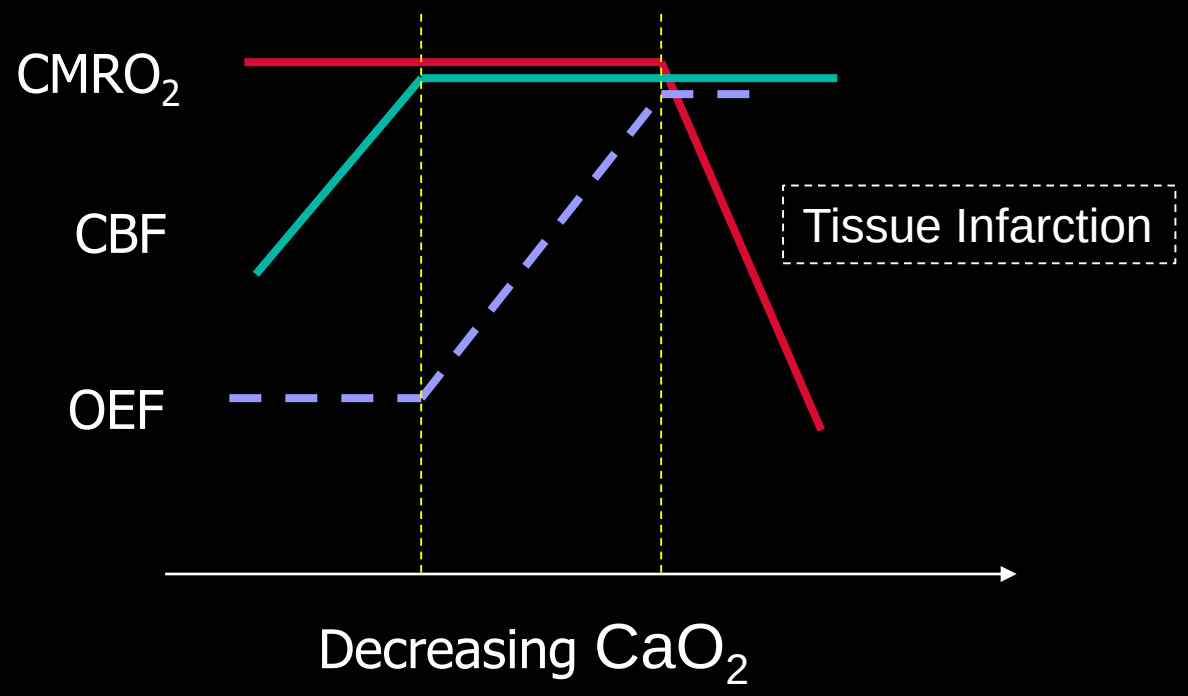


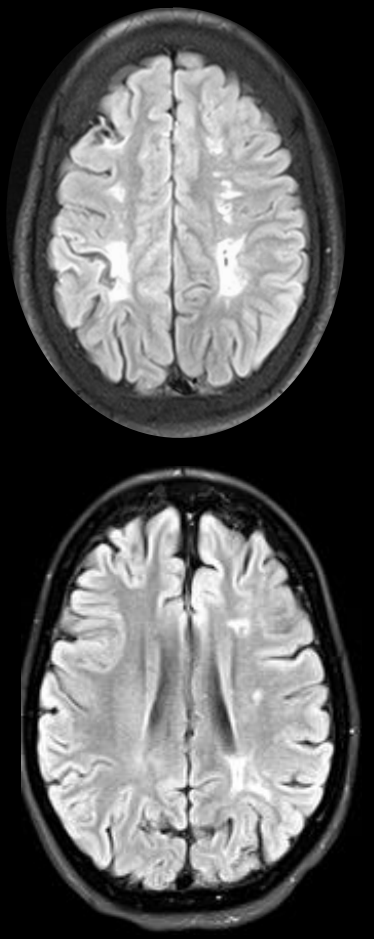
$[SaO_2]$

$[PO_2]$

Becklake et al. JCI. 1954. 751-5.

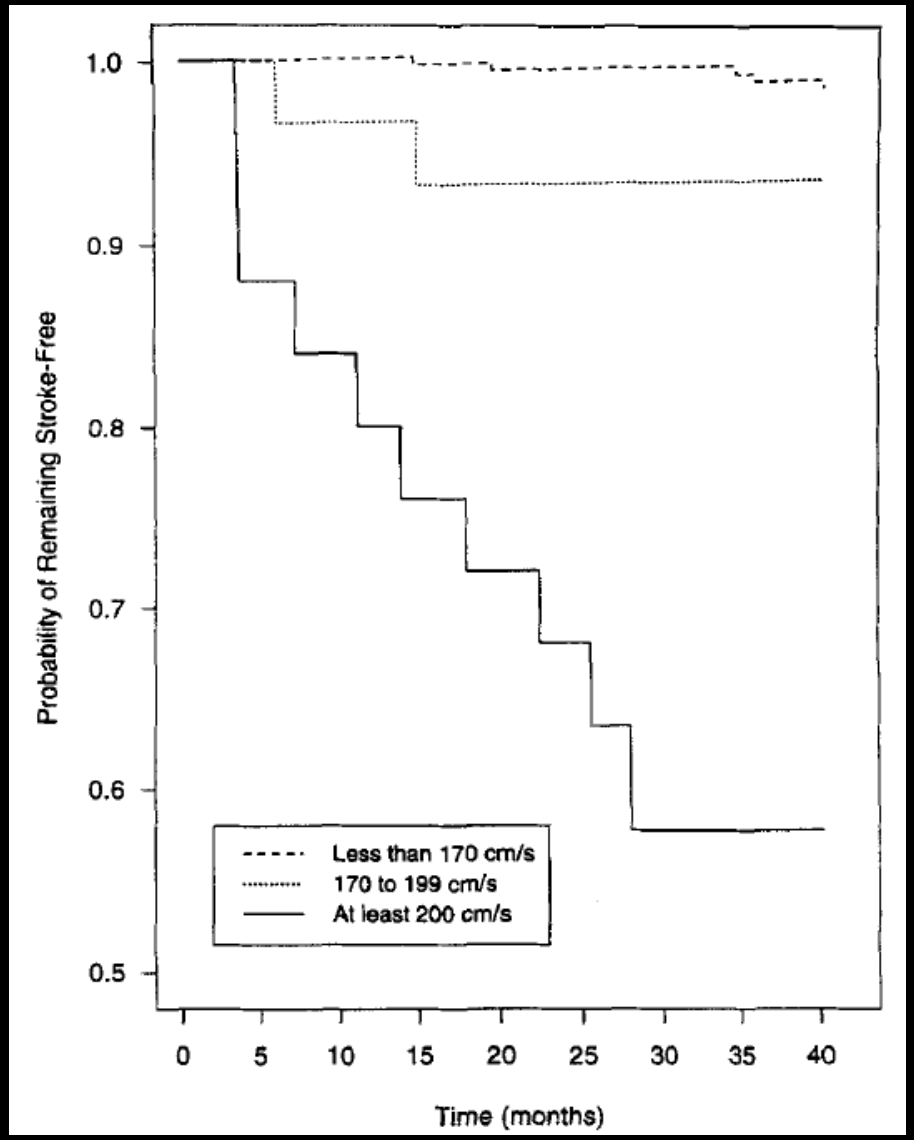
Hypothetical Cerebral Oxygen Metabolism in Sickle Cell Disease





Hulbert, Ford. Blood. 2015.

Physiological Studies in Sickle Cell Disease



- Transcranial Doppler (TCD) Velocities – a noninvasive imaging biomarker of stroke risk

Table 3. Predictors of Stroke Multivariate Cox Regression

Covariate	Parameter Estimate	SD	*p*
V_{max} (MCA/ICA)	0.0395	0.0075	<0.0001
Hematocrit	−0.1484	0.0839	0.0798

V_{max} = time average mean maximum; MCA = middle cerebral artery; ICA = internal carotid artery.

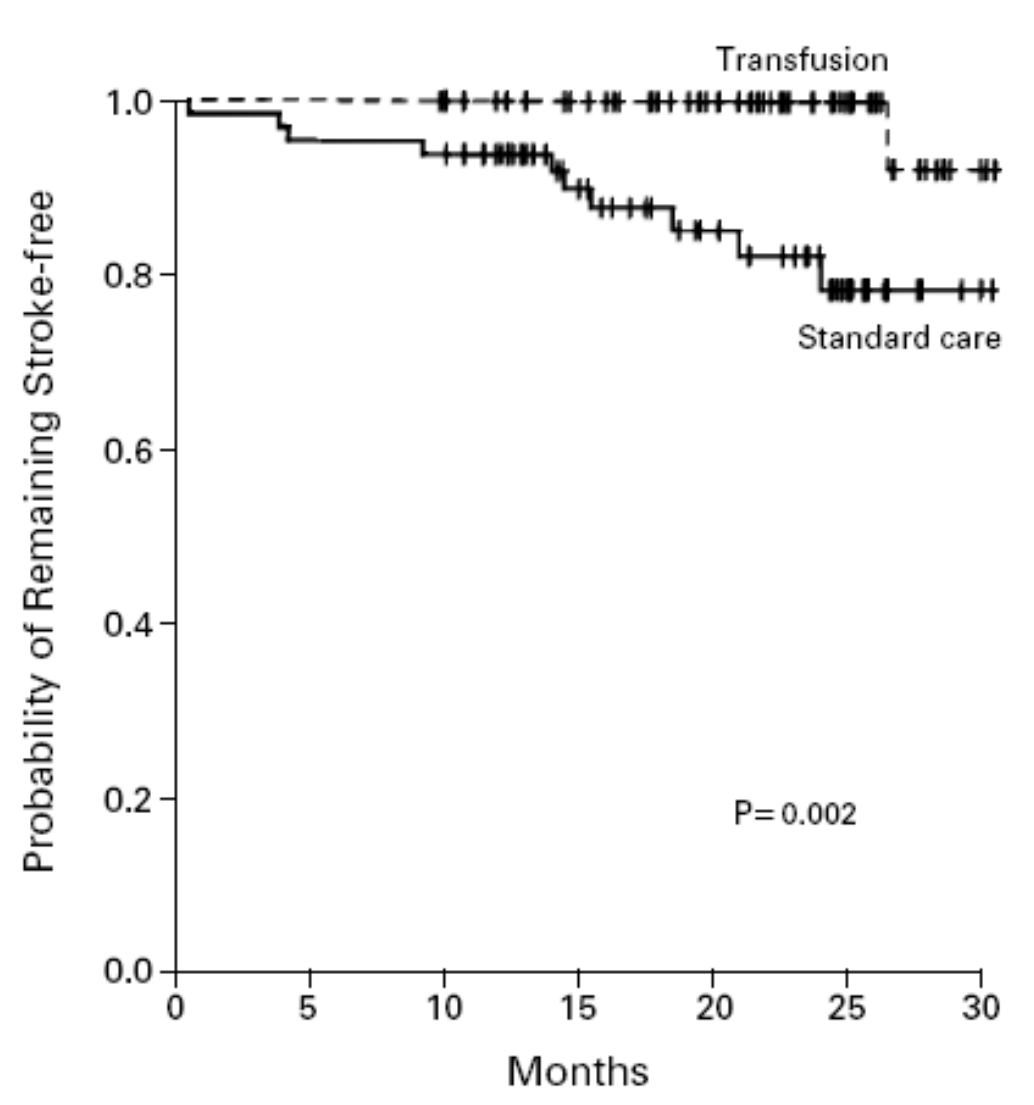
Adams et al. Ann Neurol 1997;42:699-704.

Transfusion for Stroke Prevention in Children with Elevated TCD Velocities STOP 1 and 2 Trials

- Design: Prospective, randomized, multi-center clinical trials
- Eligibility: Age 2 – 16, HgSS or HgS-βthal; Abnormal TCD velocity (> 200 cm/sec on 2 studies)
- Treatment: chronic transfusion vs. standard care
- Primary endpoint: clinical stroke (or reversion to elevated TCDs for STOP-2)
- Interim analysis → premature closure of both studies due to overwhelming benefit

Adams et al. N Engl J Med 1998;339:5-11.
Adams et al. N Engl J Med 2005;353:2769-78.

STOP I - Stroke Free survival



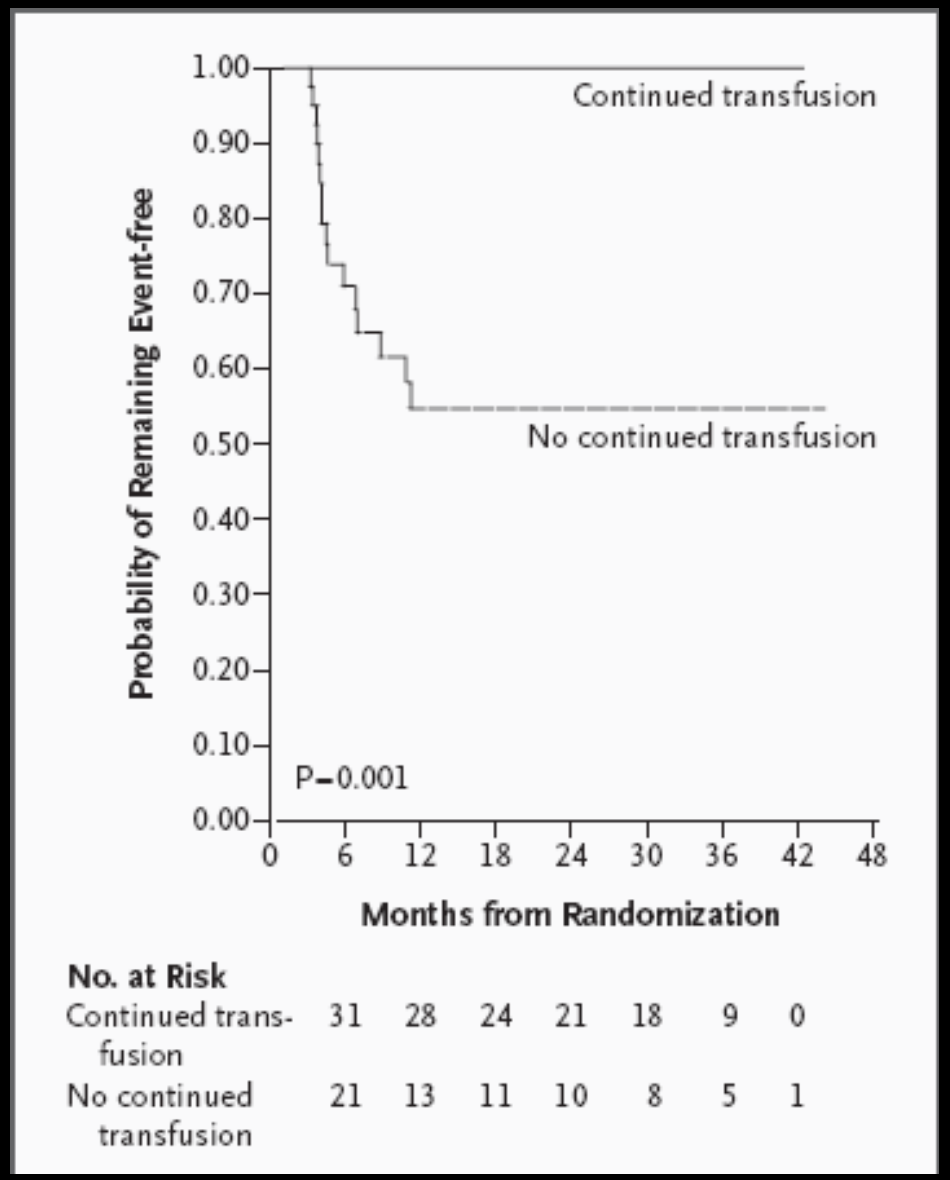
Transfusion:
N = 63 → 1 stroke
Standard:
N = 67 → 11 strokes

P < 0.002

ARR 15%

Adams et al. N Engl J Med 1998;339:5-11.

STOP 2 - Event Free survival

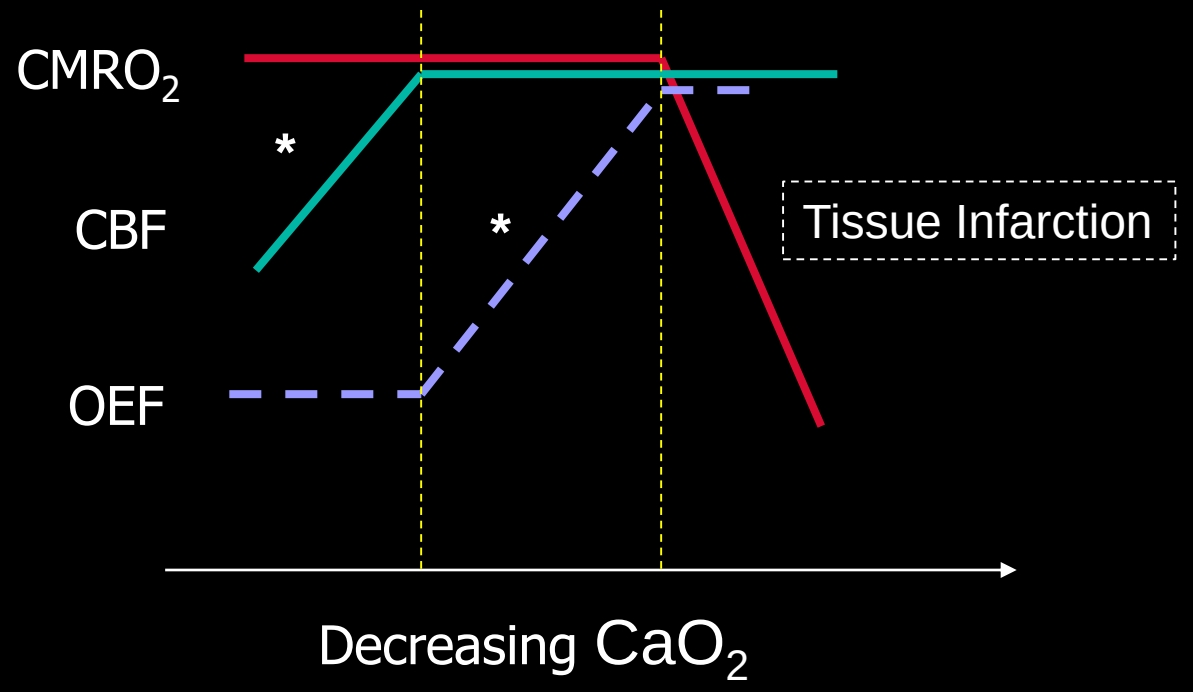


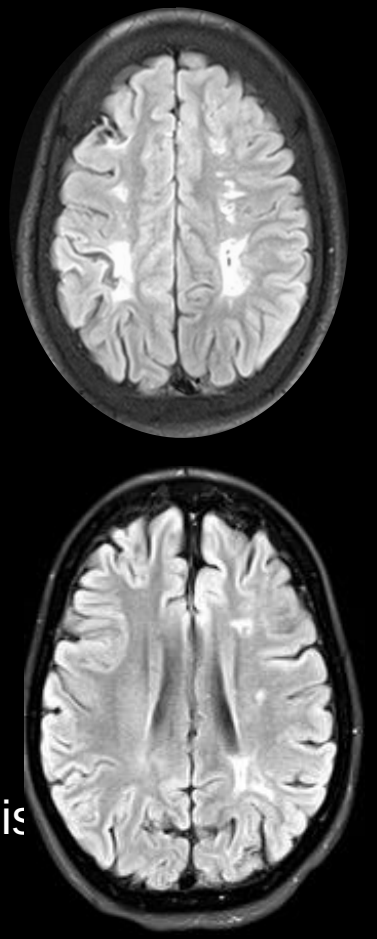
Cont. Transfusion:
N = 31 → 0 events
No transfusion:
N = 21 → 14 events (2 were strokes)

P = 0.001

Adams et al. N Engl J Med 2005;353:2769-78.

Hypothetical Oxygen Metabolism in Children with Sickle Cell Disease





* Hypothesized Predictors of Increased Stroke Risk in Sickle Cell Dis

Hulbert, Ford. Blood. 2015.

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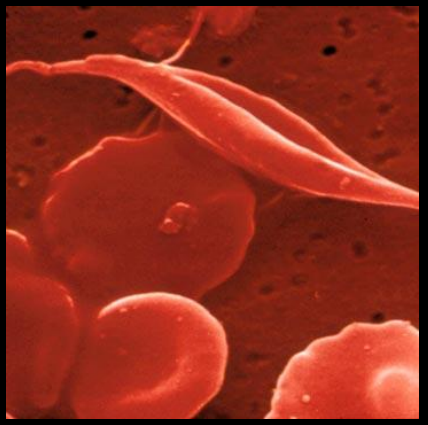
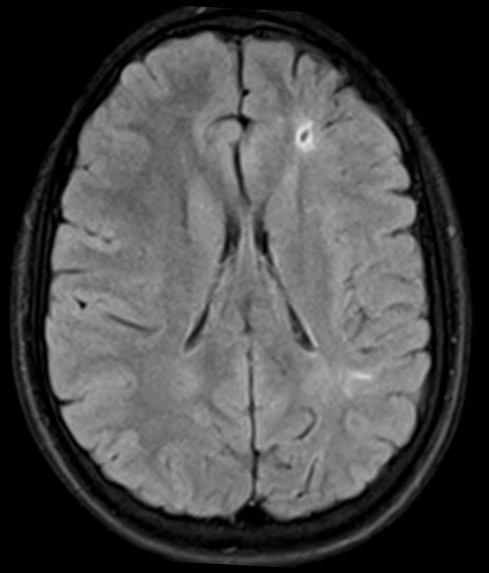
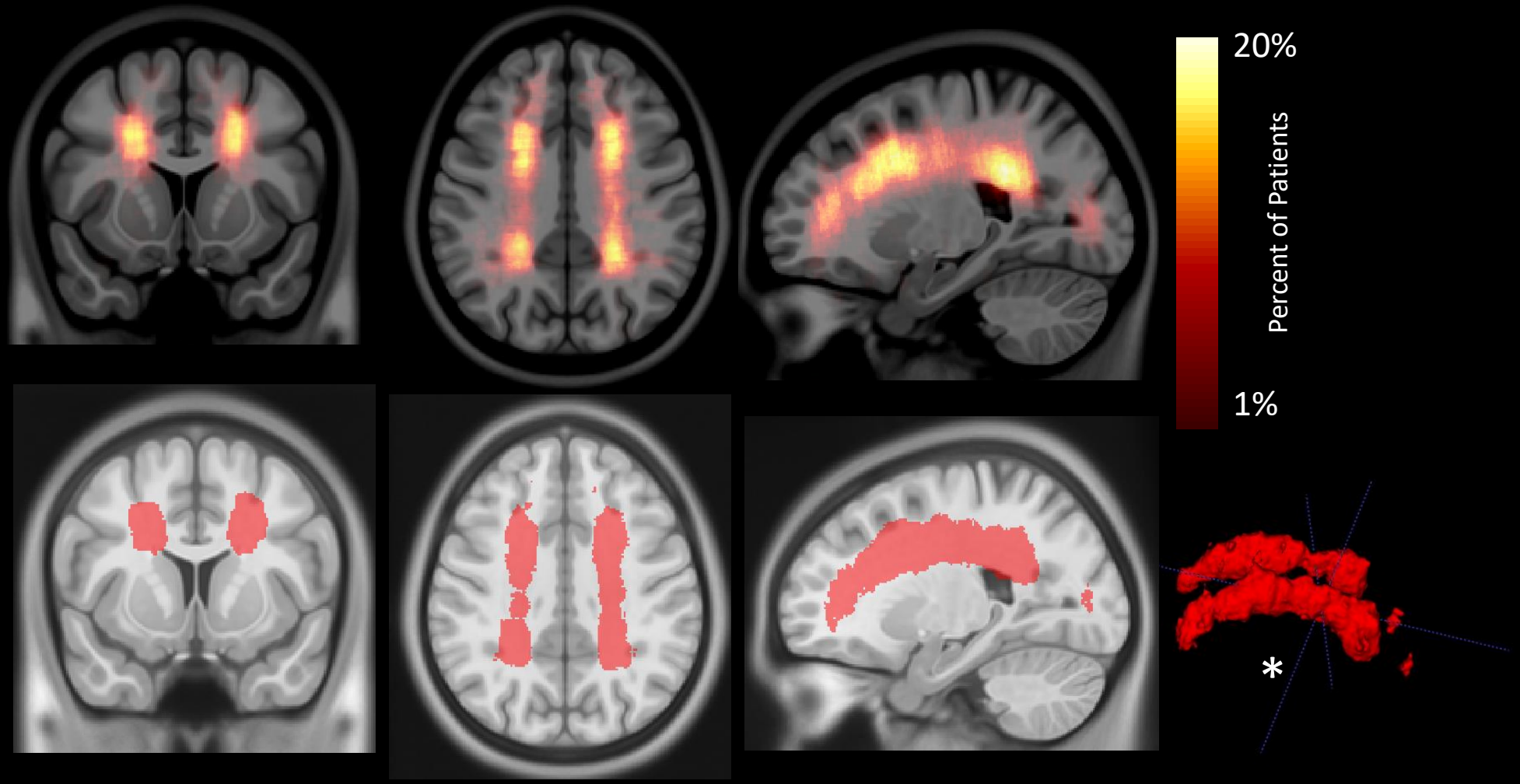




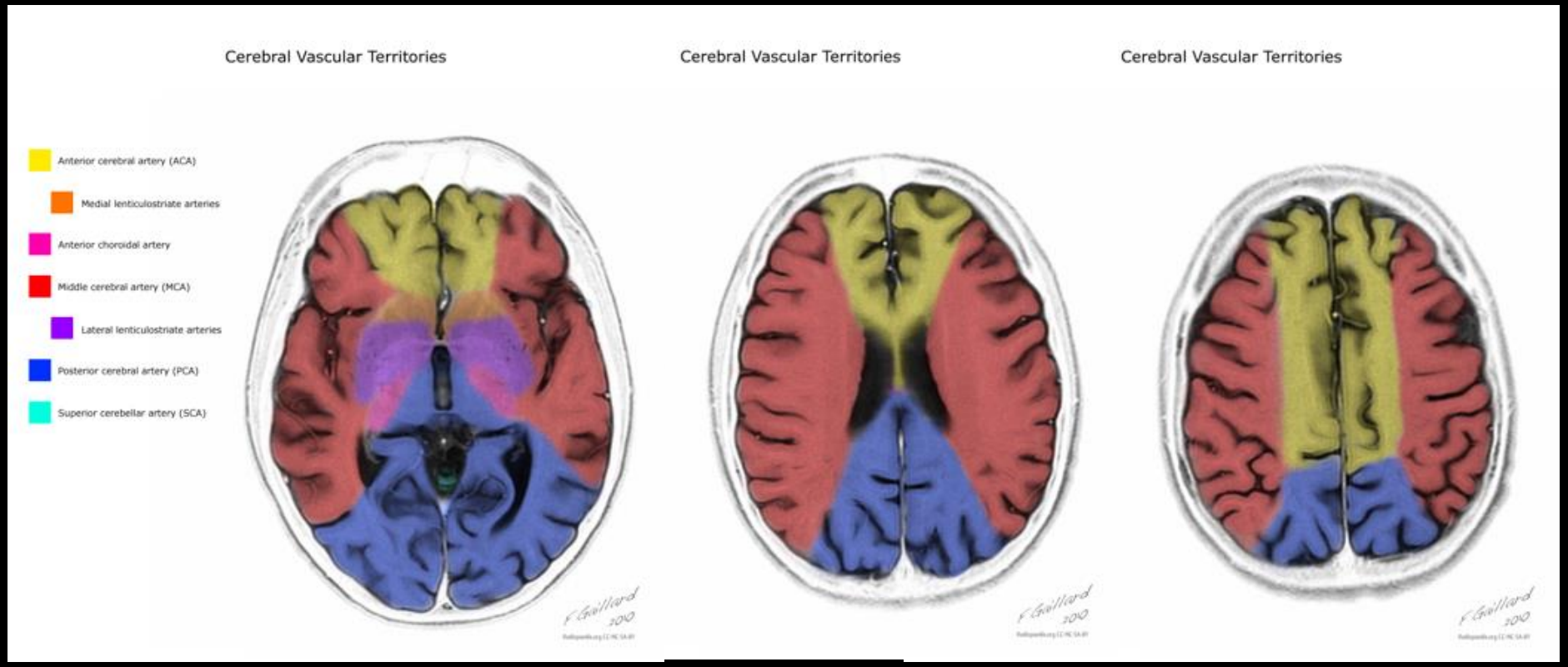
Majority of silent cerebral infarcts are located in the deep WM (N=286, Silent Infarct Transfusion Trial)



* SCIs for 90% of children are located within a confined region (~5.6% of total brain volume)

Ford et al., *Blood*, 2018

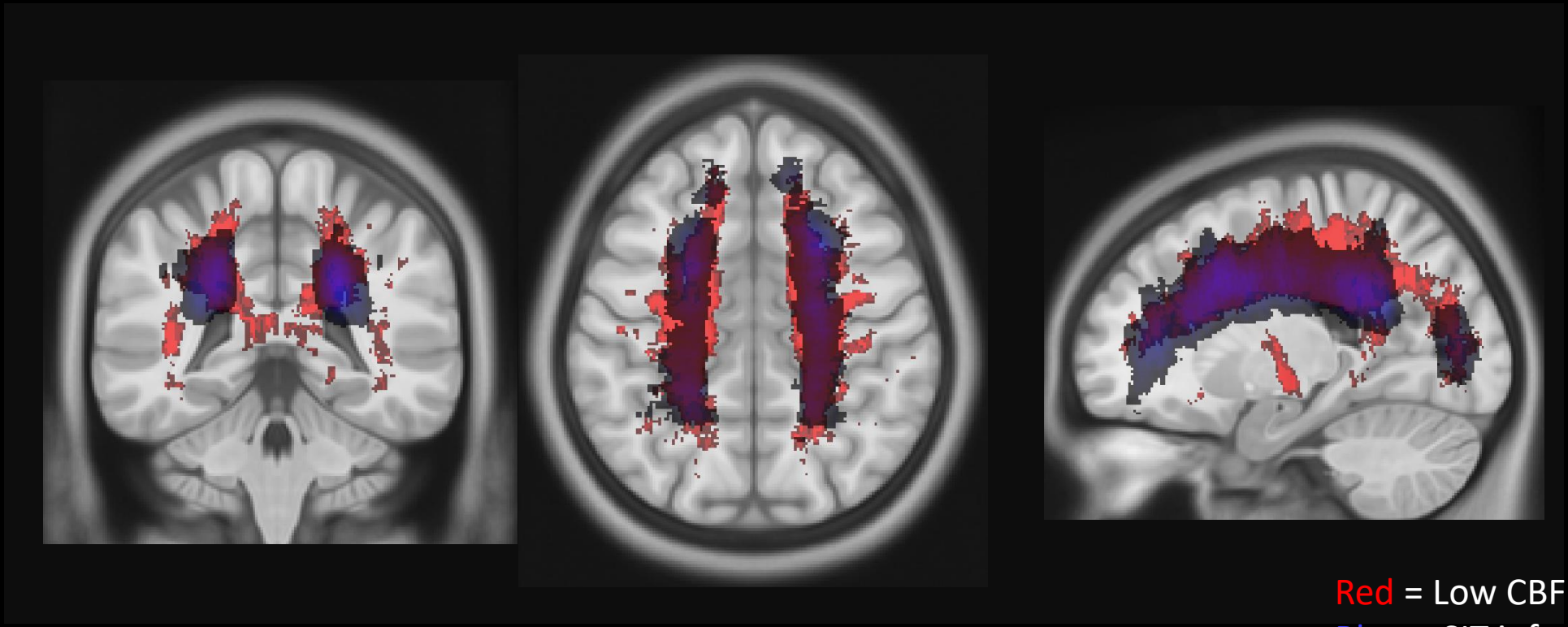
Regions of vulnerability appear to fall in the “watershed” or “borderzone” where arterial distributions are minimally or non-overlapping



Ford et al. Blood 2018

RadioGraphics 2011; 31:1201–1214

Regional vulnerability in SCD and in other CSVDs?

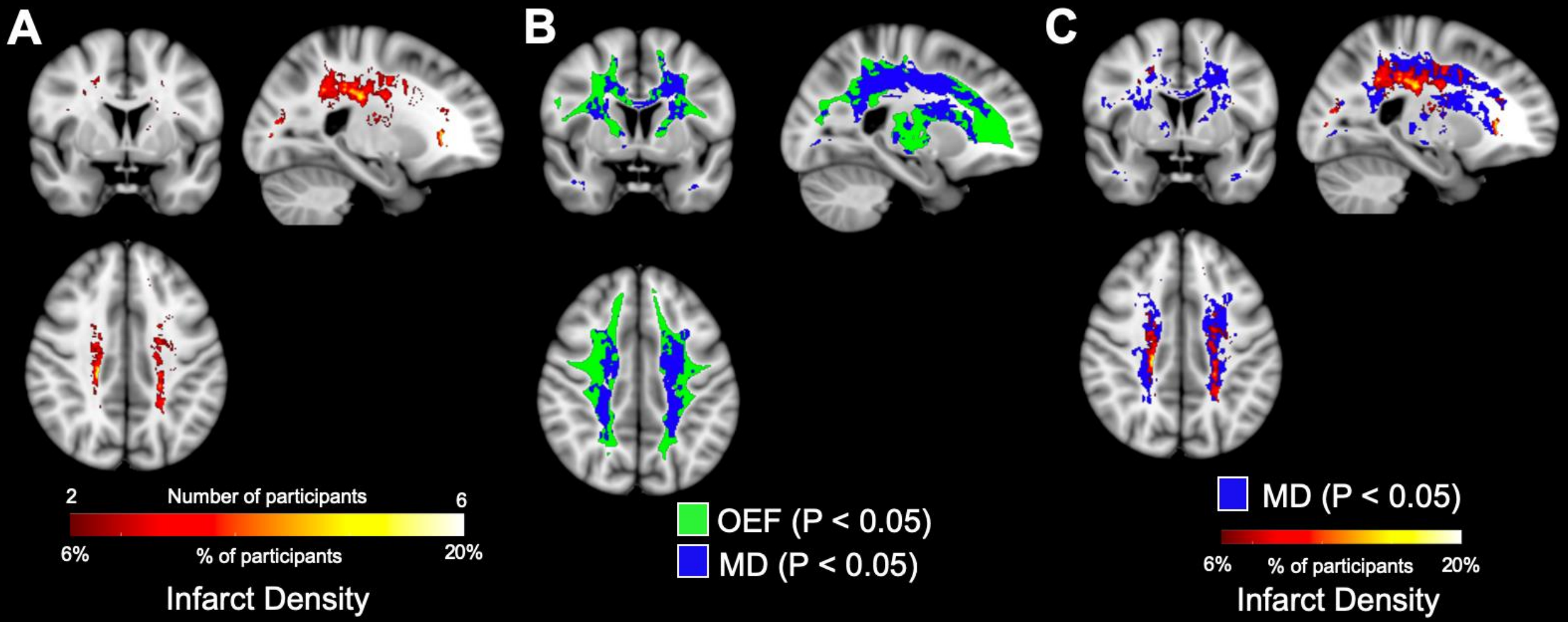


Red = Low CBF
Blue = SIT infarct heatmap

Overlap between nadir CBF and high infarct density

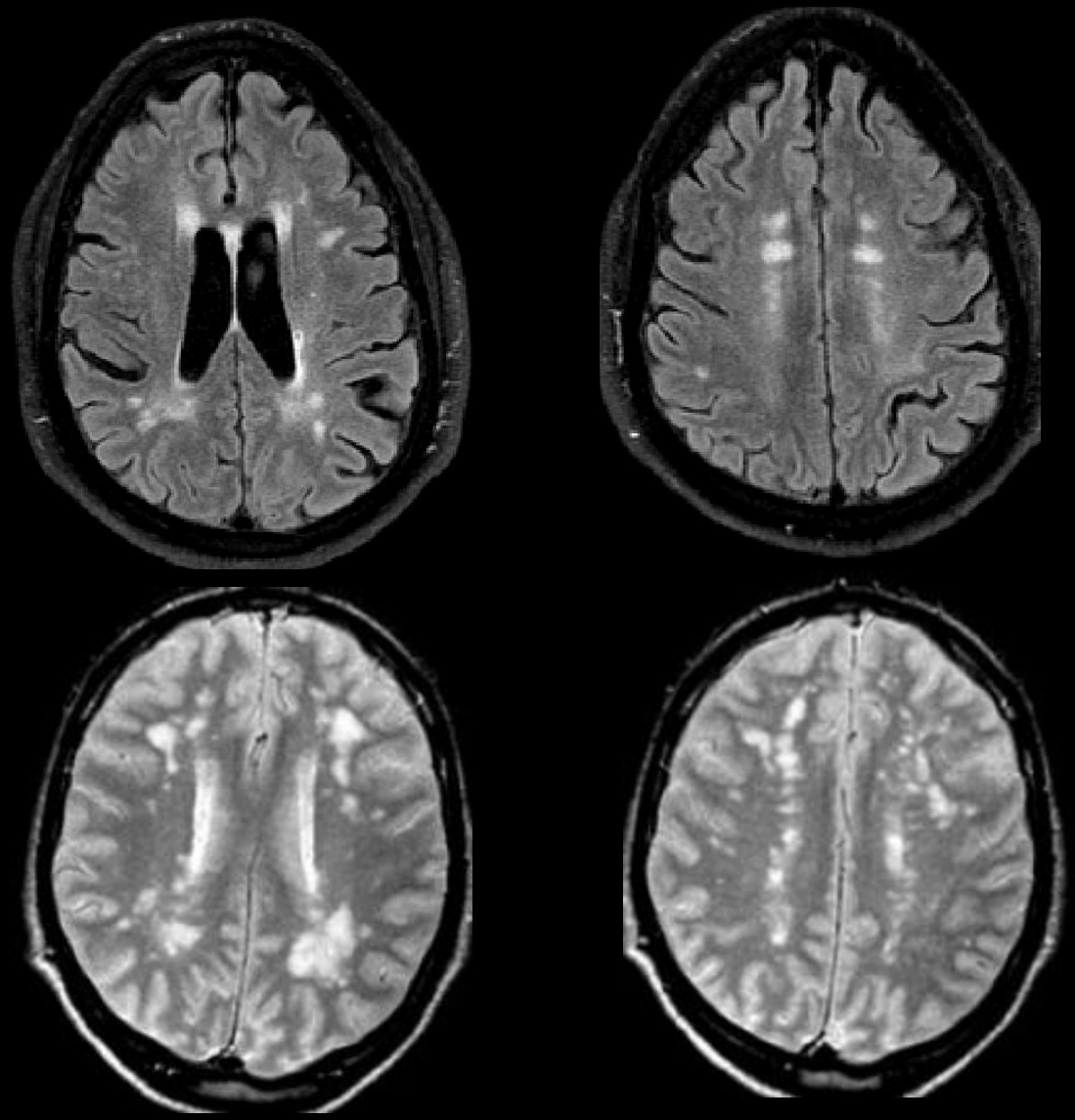
Ford et al., *Blood*, 2018.

Cerebral oxygen metabolic stress surrounding regions of white matter disruption and SCIs



Wang et al. Neurology 2021.

Lesion Patterns in Cerebral SVD



Age
Hypertension
Diabetes

Multiple Stroke Mechanisms in Patients with SCD

- Moyamoya intracranial vasculopathy
- Cerebral small vessel disease
- Hypercoagulable State
- Cardiomyopathy

- Anemia / low CaO2
- Hb polymerization / abnormal rheology
- High cardiac output / flow
- Cerebral autoregulation
- Turbulent flow, Vascular stenosis
- Endothelial injury
- Tissue Ischemia
- Blood brain barrier compromise
- Neuro-inflammation

Therapeutic Targets in Sickle Cell Disease
Ultimate goal to reduce vaso-occlusive crises

Targeted Stroke Mechanism	Therapeutic
Anemia / low CaO_2 / HbS polymerization	Exchange Transfusion * Hydroxyurea + Voxelotor
Vascular stenosis	EC-IC Bypass / EDAS procedure +
Endothelial injury / adhesion Blood brain barrier compromise	Crizanlizumab + L-glutamine
Inflammation	Minocycline (animal models)
Genetic Mutation	BMT + Gene therapies

* Proven to prevent strokes in the setting of elevated TCD velocity or presence of SCIs
+ Data supporting the therapeutic for stroke protection or ongoing studies towards this end.

ORIGINAL ARTICLE

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

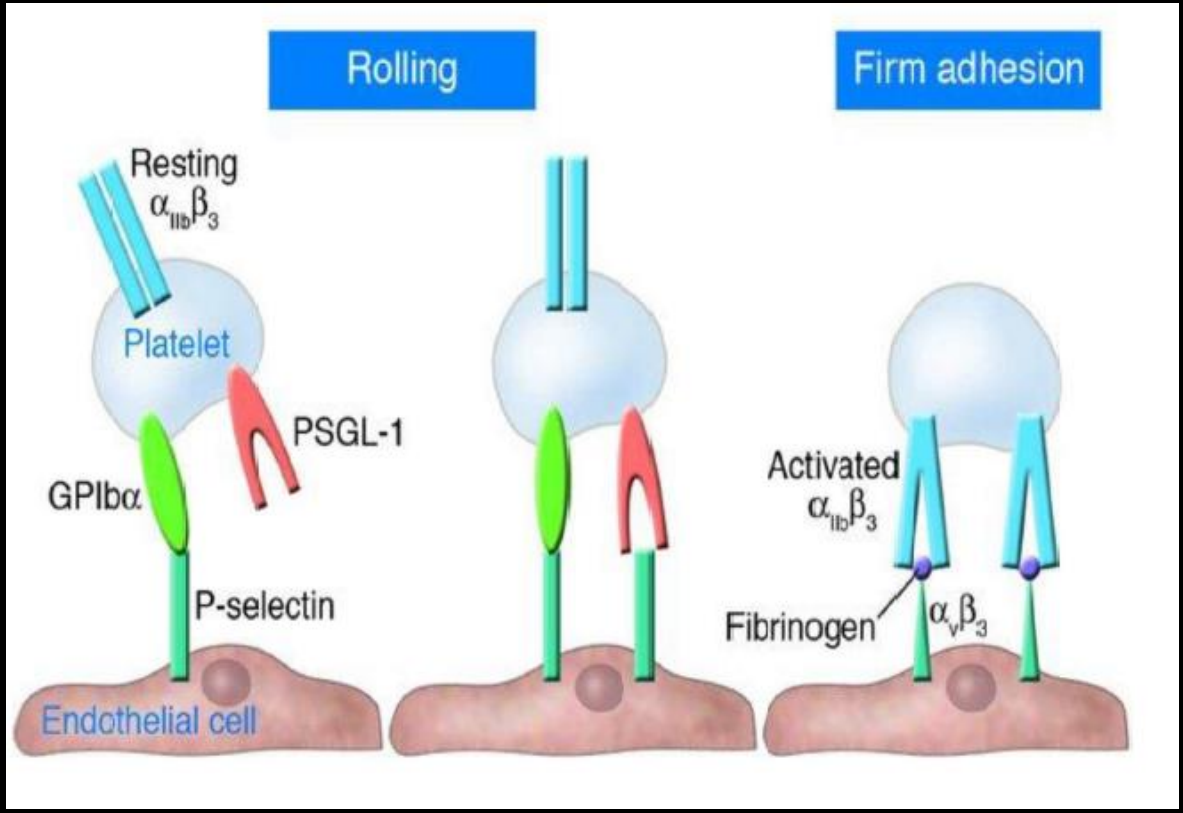
K.I. Ataga, A. Kutlar, J. Kanter, D. Liles, R. Cancado, J. Friedrisch, T.H. Guthrie, J. Knight-Madden, O.A. Alvarez, V.R. Gordeuk, S. Gualandro, M.P. Colella, W.R. Smith, S.A. Rollins, J.W. Stocker, and R.P. Rother

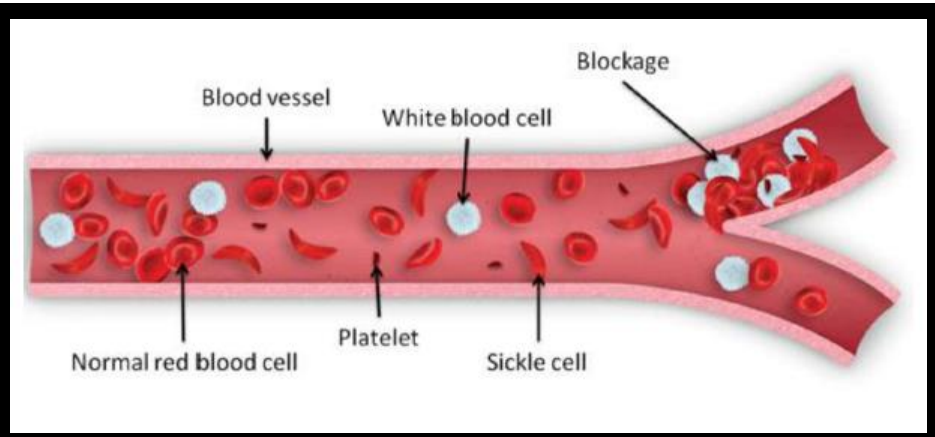
N Engl J Med 2017;376:429-39.

SUSTAIN Trial

- Vascular adhesion molecules of great interest in SCD to understand pathophysiology of systemic microvascular occlusion
- Adhesion of both Sickle RBCs and WBCs to the endothelial wall → obstruction and tissue ischemia
- Formation of aggregates – platelets/RBCs/WBCs -→ may obstruct microcirculation

Endothelial protection





- P-selectin: Responsible for initiation of adhesion of leukocytes to the endothelium during inflammation
- Translocation of endothelial P-selectin to the cell surface results in the prompt adhesion of sickle erythrocytes to vessels and the development of vascular occlusion in transgenic mice with SCD.
- Transgenic mice with SCD that are deficient in P/E-selectin have defective leukocyte recruitment to the vessel wall and are protected from vaso-occlusion

Fernando Alfonso, and Dominick J. Angiolillo JACC 2013;61:2056-2059

Traditional stroke treatments and SCD

- Antiplatelet agents
- Blood pressure / cholesterol
  - Patients with SCD tend to be “hyper-metabolic” and have lower blood pressure and lower cholesterol chronically, especially with younger age, may factor into adults with SCD
- Alteplase – case reports, 1 GWTG study suggestive of safety of alteplase, however specific populations enriched in HbSS or those with moyamoya have not been adequately studied
- Exchange transfusion - Extrapolota

* Proven to prevent strokes in the setting of elevated TCD velocity or presence of SCIs
+ Data supporting the therapeutic for stroke protection or ongoing studies towards this end.

Traditional stroke treatments and SCD

- STOP 1 and 2 data show benefit of exchange transfusion when selected by high TCD velocities
- Patients with “overt stroke” have high risk of recurrence
- Exchange transfusion better than manual transfusion for prevention of future stroke

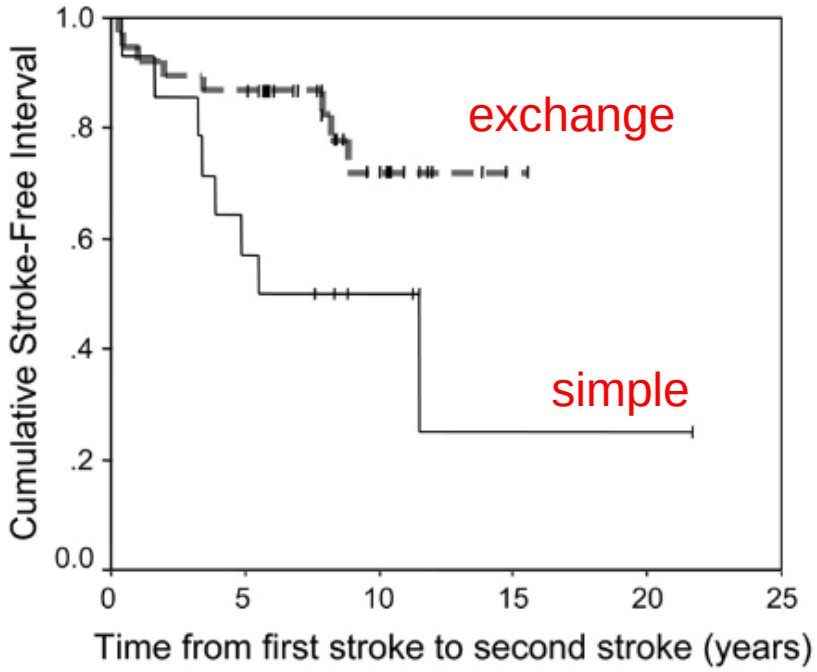
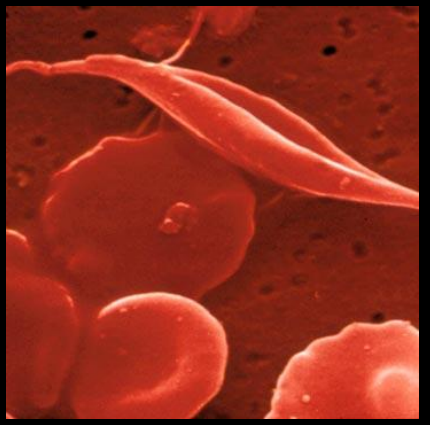


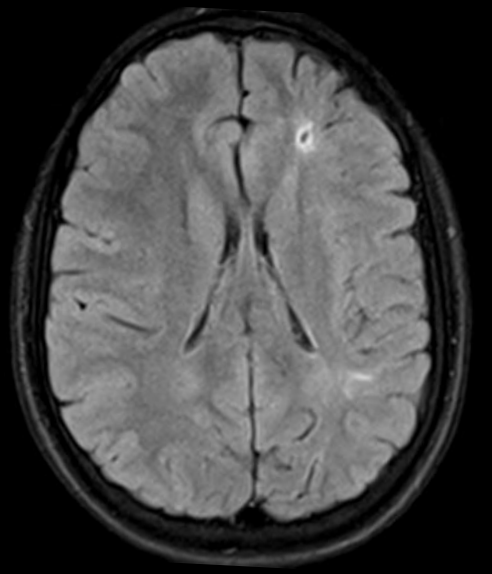
Figure. Initial simple transfusion for first overt stroke in children with SCA who presented within 24 hours of symptom onset is associated with increased risk of recurrent stroke compared with exchange transfusion. Initial exchange transfusion, n = 38; initial simple transfusion, n = 14; RR = 5.0; 95% CI = 1.3 to 18.6; log-rank test; $P = .02$. All children received scheduled chronic blood transfusion therapy for at least 5 years after the first stroke. Solid line, simple transfusion; broken line, exchange transfusion; dashes, censored events.

Hulbert et al. J Pediatr 2006;149:710-2

Summary

- Cerebral ischemia and stroke are common in children and adults with SCD.
- The brain engages innate compensatory to prevent stroke, however when the brain cannot meet cerebral metabolic demand, stroke is imminent
- A surrogate biomarker, TCDV, (which provides a metric of cerebral hemodynamic /metabolic stress) can be leveraged to select patients at high risk of stroke and offer treatment
- SCD provides a model of cerebral ischemic vulnerability which may apply to other SVDs or neurological diseases.
- Multiple nove stroke/disease mechanisms may be targeted in SCD and may apply to other cerebrovascular diseases.





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