Sickle Cell Disease and the Brain

Kevin Kuo, MD, FRCPC
Red Blood Cell Disorders Program
Toronto General Hospital

July 28, 2012

Disclosure

- Nothing to disclose

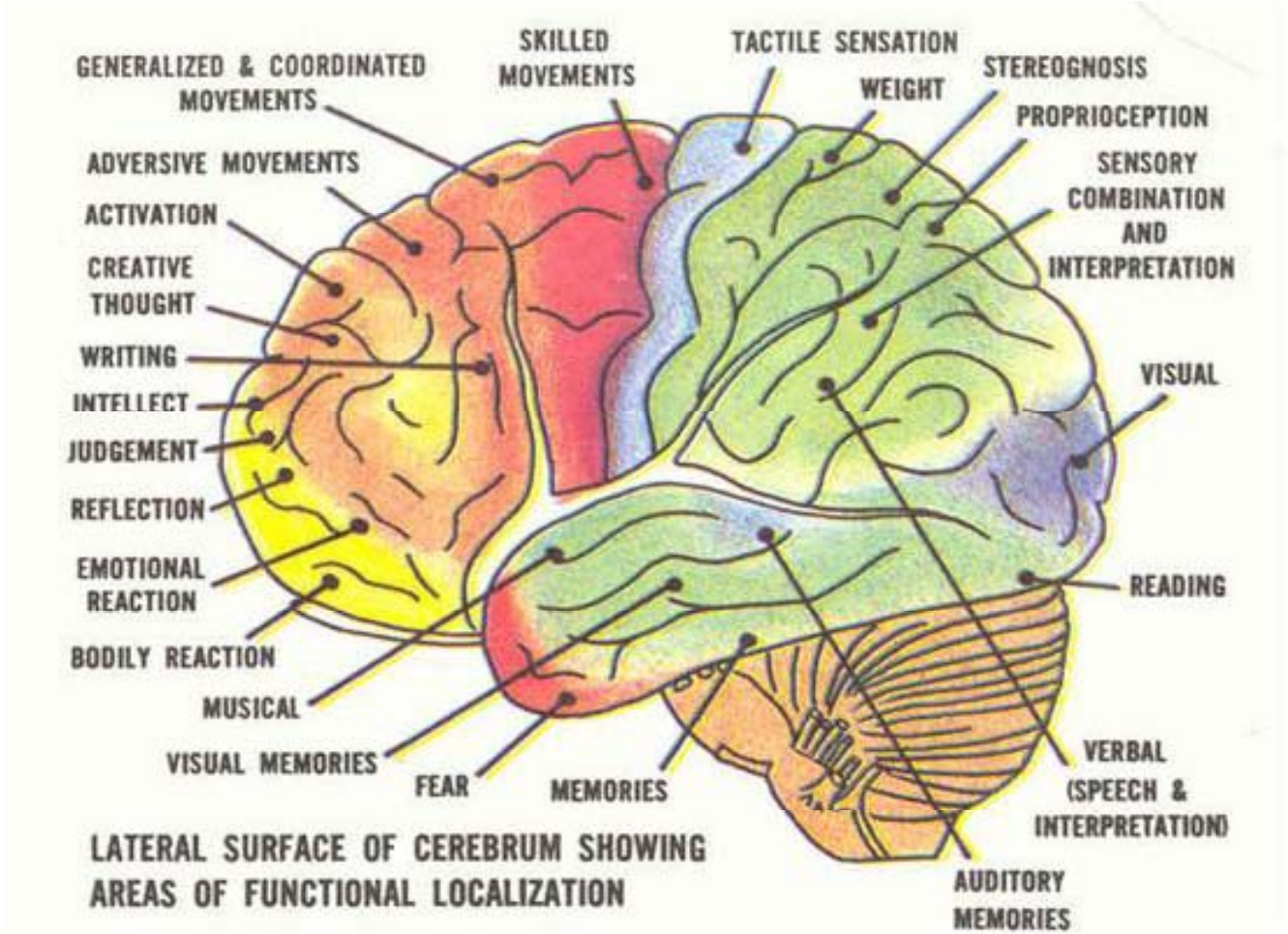
Outline

- Signs and symptoms of stroke
- Epidemiology of stroke
- Treatment and prevention of stroke
- Chronic transfusion and stroke
  - STOP and STOP2 studies
- Hydroxyurea as an alternative
  - SWiTCH and TWiTCH studies
- Uncertainties in the diagnosis and management of Silent Infarct
  - SIT study
- Discussion

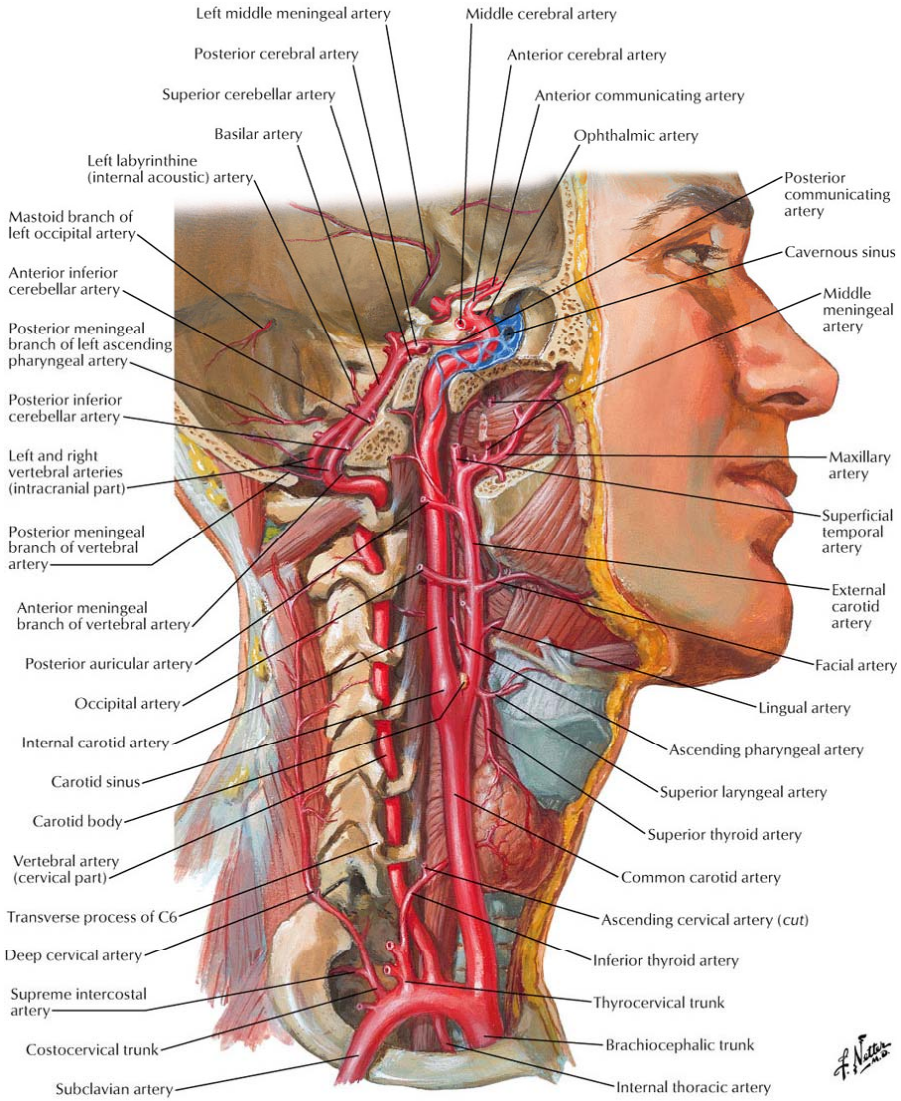
What is stroke?

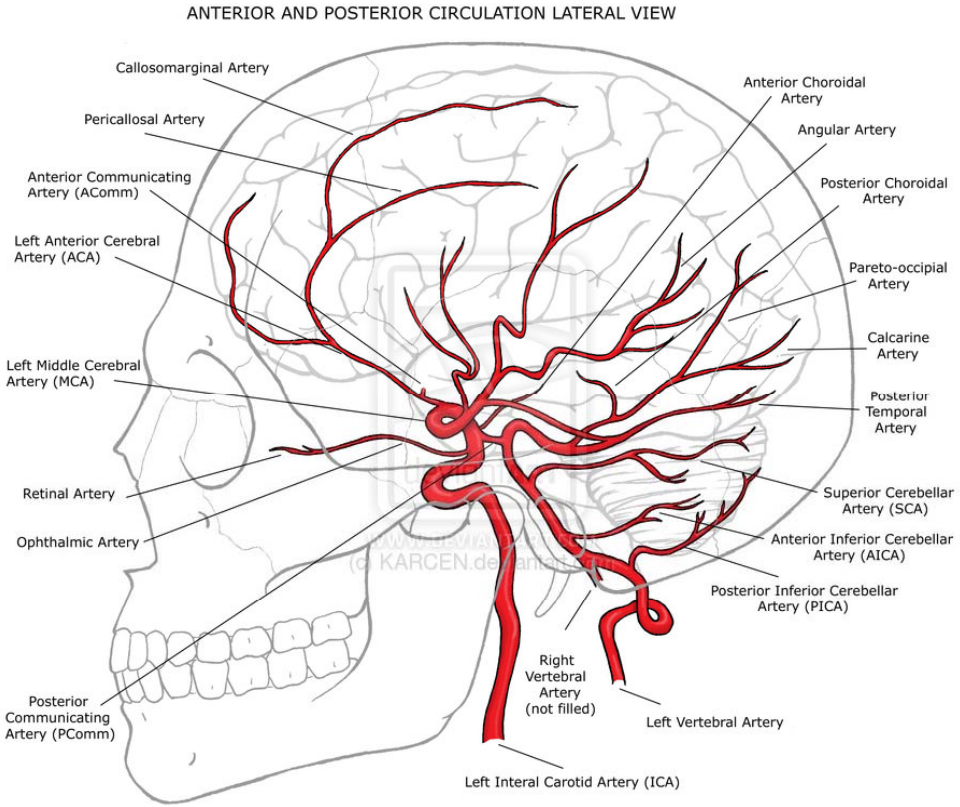
- Sudden loss of blood circulation to an area of the brain
- Corresponding loss of neurological function
- Ischaemic
  - Large artery
  - Small vessel
  - Cardioembolic
- Haemorrhagic
- Transient Ischaemic Attack (TIA)
  - Temporary loss of blood circulation
  - Symptoms usually resolve in 24 hours

Brain Anatomy



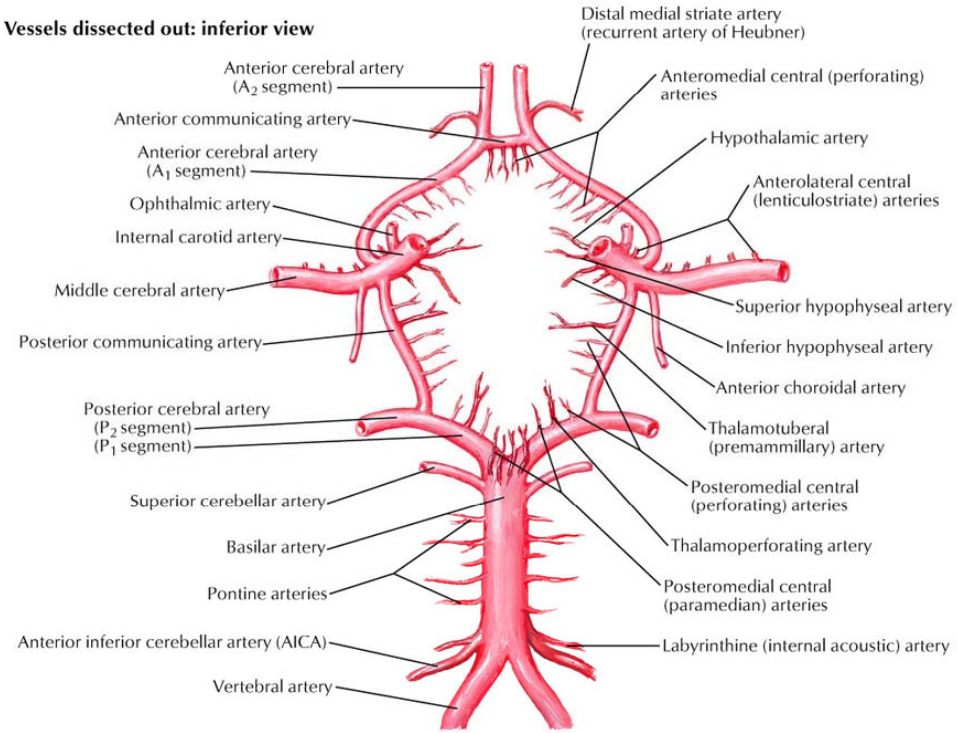
http://www.becindonesia.com/smg/wp-content/uploads/2009/07/Brain-Functions.jpg



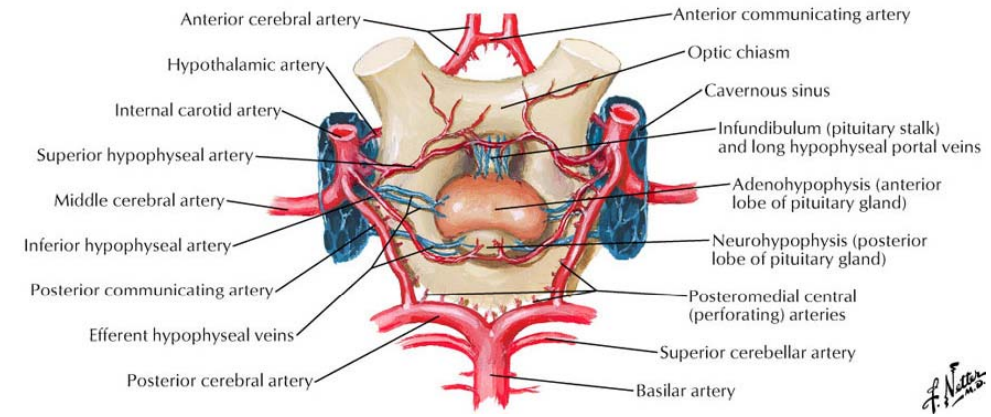


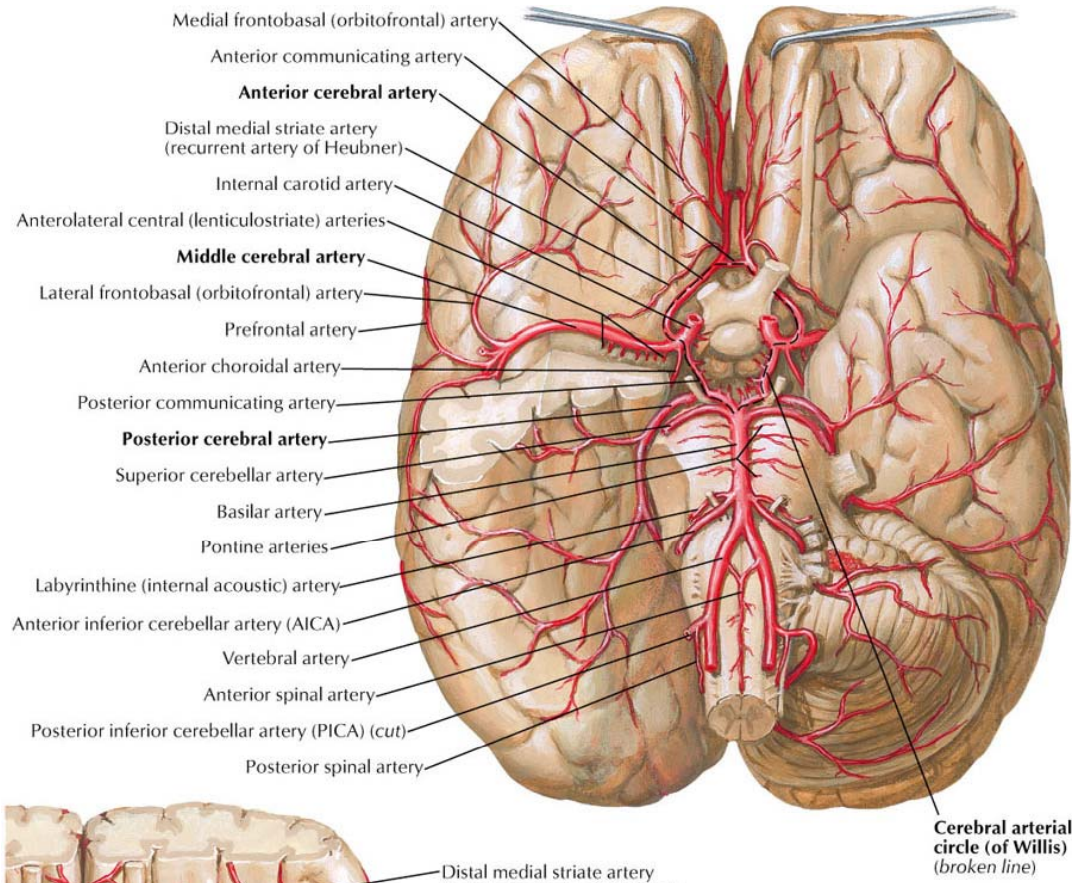
Netter, F. Atlas of Human Anatomy
http://karcen.deviantart.com/art/Cerebral-Circulation-167535443

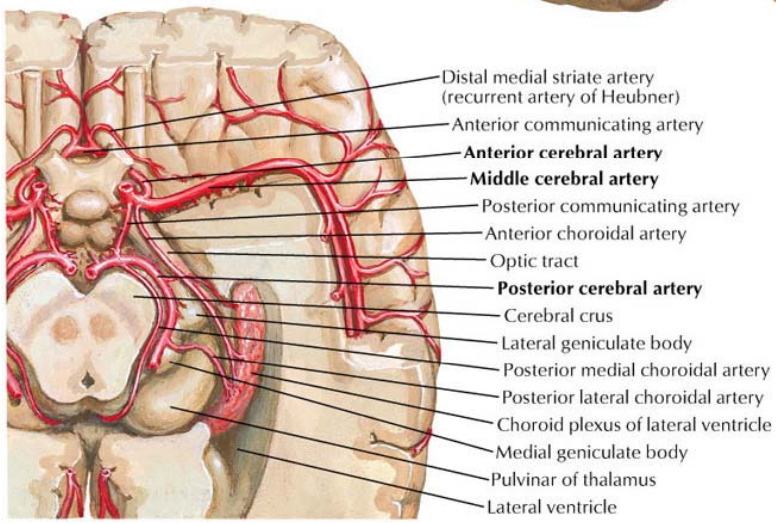
Vessels dissected out: inferior view

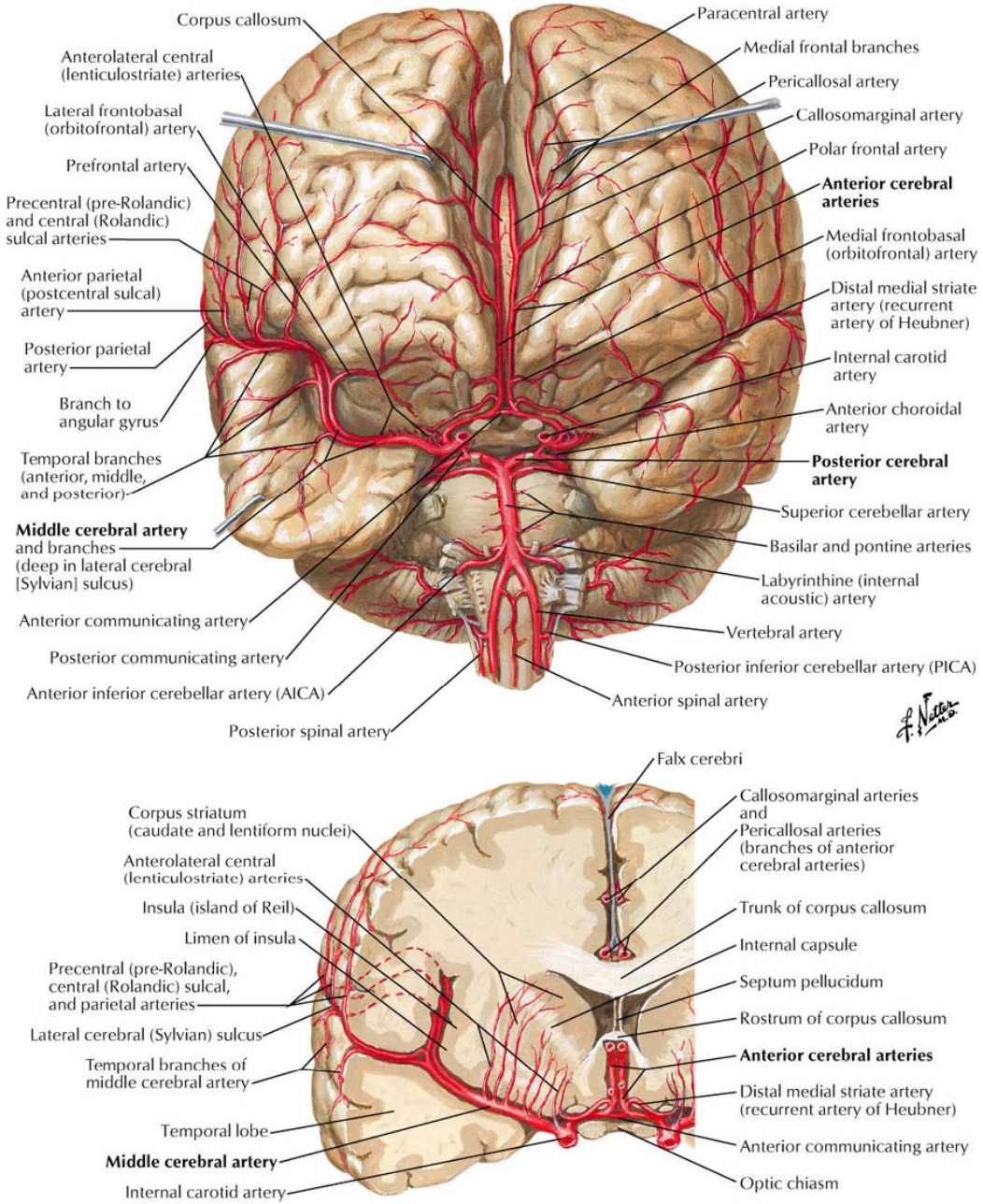


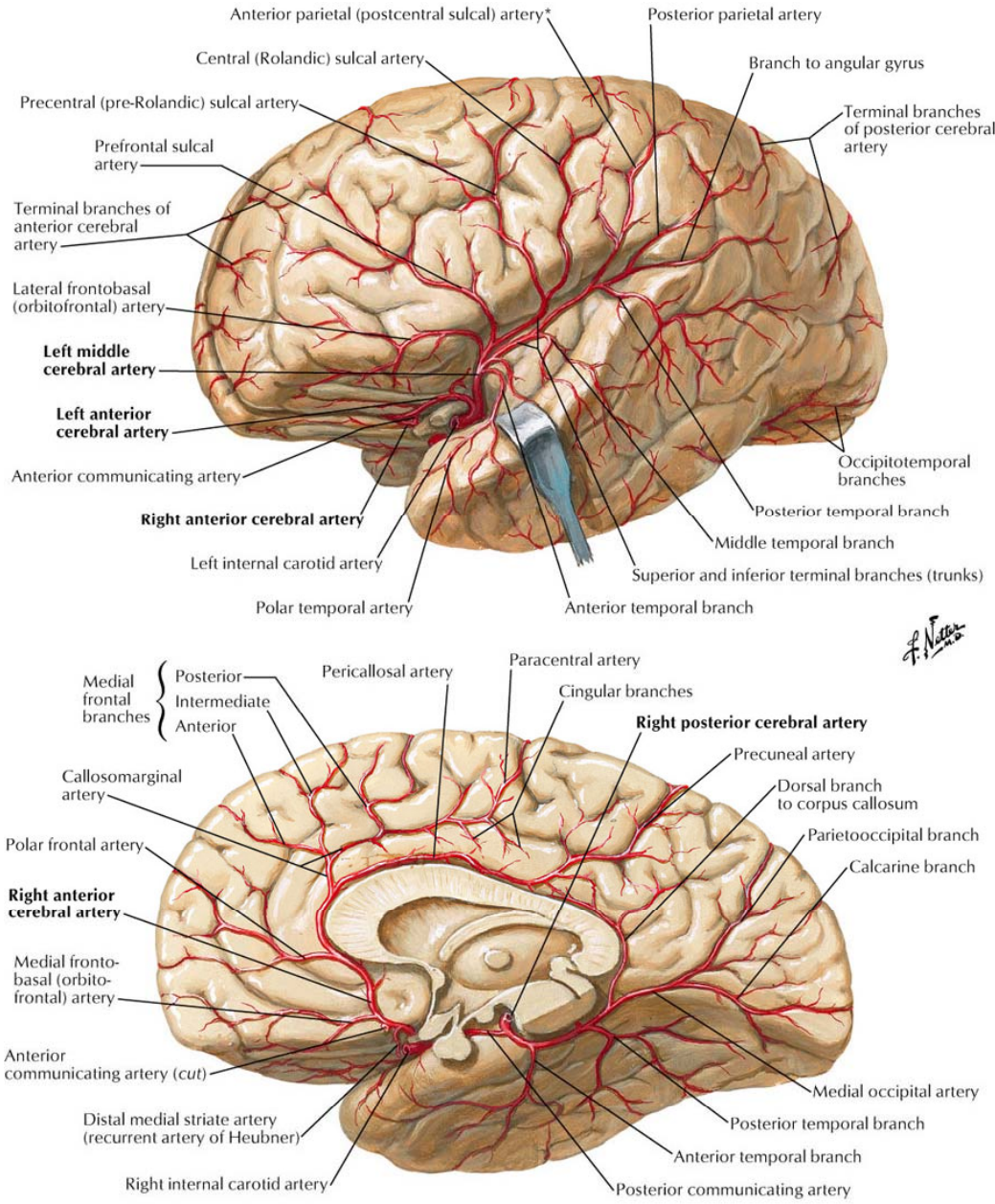
Vessels in situ: inferior view




Medial frontobasal (orbitofrontal) artery
Anterior communicating artery
Anterior cerebral artery
Distal medial striate artery (recurrent artery of Heubner)
Internal carotid artery
Anterolateral central (lenticulostriate) arteries
Middle cerebral artery
Lateral frontobasal (orbitofrontal) artery
Prefrontal artery
Anterior choroidal artery
Posterior communicating artery
Posterior cerebral artery
Superior cerebellar artery
Basilar artery
Pontine arteries
Labyrinthine (internal acoustic) artery
Anterior inferior cerebellar artery (AICA)
Vertebral artery
Anterior spinal artery
Posterior inferior cerebellar artery (PICA) (cut)
Posterior spinal artery
Cerebral arterial circle (of Willis) (broken line)

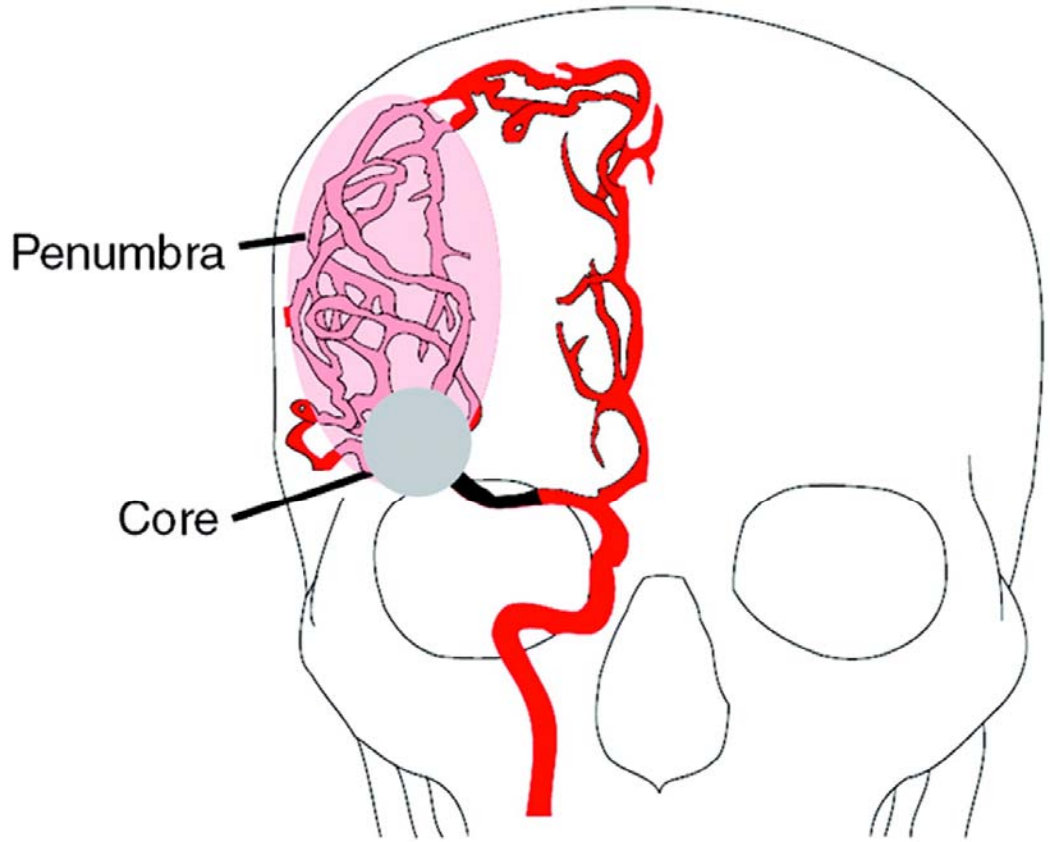

Distal medial striate artery (recurrent artery of Heubner)
Anterior communicating artery
Anterior cerebral artery
Middle cerebral artery
Posterior communicating artery
Anterior choroidal artery
Optic tract
Posterior cerebral artery
Cerebral crus
Lateral geniculate body
Posterior medial choroidal artery
Posterior lateral choroidal artery
Choroid plexus of lateral ventricle
Medial geniculate body
Pulvinar of thalamus
Lateral ventricle


Corpus callosum
Anterolateral central (lenticulostriate) arteries
Lateral frontobasal (orbitofrontal) artery
Prefrontal artery
Precentral (pre-Rolandic) and central (Rolandic) sulcal arteries
Anterior parietal (postcentral sulcal) artery
Posterior parietal artery
Branch to angular gyrus
Temporal branches (anterior, middle, and posterior)
Middle cerebral artery and branches (deep in lateral cerebral [Sylvian] sulcus)
Anterior communicating artery
Posterior communicating artery
Anterior inferior cerebellar artery (AICA)
Posterior spinal artery
Paracentral artery
Medial frontal branches
Pericallosal artery
Callosomarginal artery
Polar frontal artery
Anterior cerebral arteries
Medial frontobasal (orbitofrontal) artery
Distal medial striate artery (recurrent artery of Heubner)
Internal carotid artery
Anterior choroidal artery
Posterior cerebral artery
Superior cerebellar artery
Basilar and pontine arteries
Labyrinthine (internal acoustic) artery
Vertebral artery
Posterior inferior cerebellar artery (PICA)
Anterior spinal artery
Falx cerebri
Corpus striatum (caudate and lentiform nuclei)
Anterolateral central (lenticulostriate) arteries
Insula (island of Reil)
Limen of insula
Precentral (pre-Rolandic), central (Rolandic) sulcal, and parietal arteries
Lateral cerebral (Sylvian) sulcus
Temporal branches of middle cerebral artery
Temporal lobe
Middle cerebral artery
Internal carotid artery
Callosomarginal arteries and Pericallosal arteries (branches of anterior cerebral arteries)
Trunk of corpus callosum
Internal capsule
Septum pellucidum
Rostrum of corpus callosum
Anterior cerebral arteries
Distal medial striate artery (recurrent artery of Heubner)
Anterior communicating artery
Optic chiasm



*Note: Anterior parietal (postcentral sulcal) artery also occurs as separate anterior parietal and postcentral sulcal arteries.

Anatomy of a Stroke

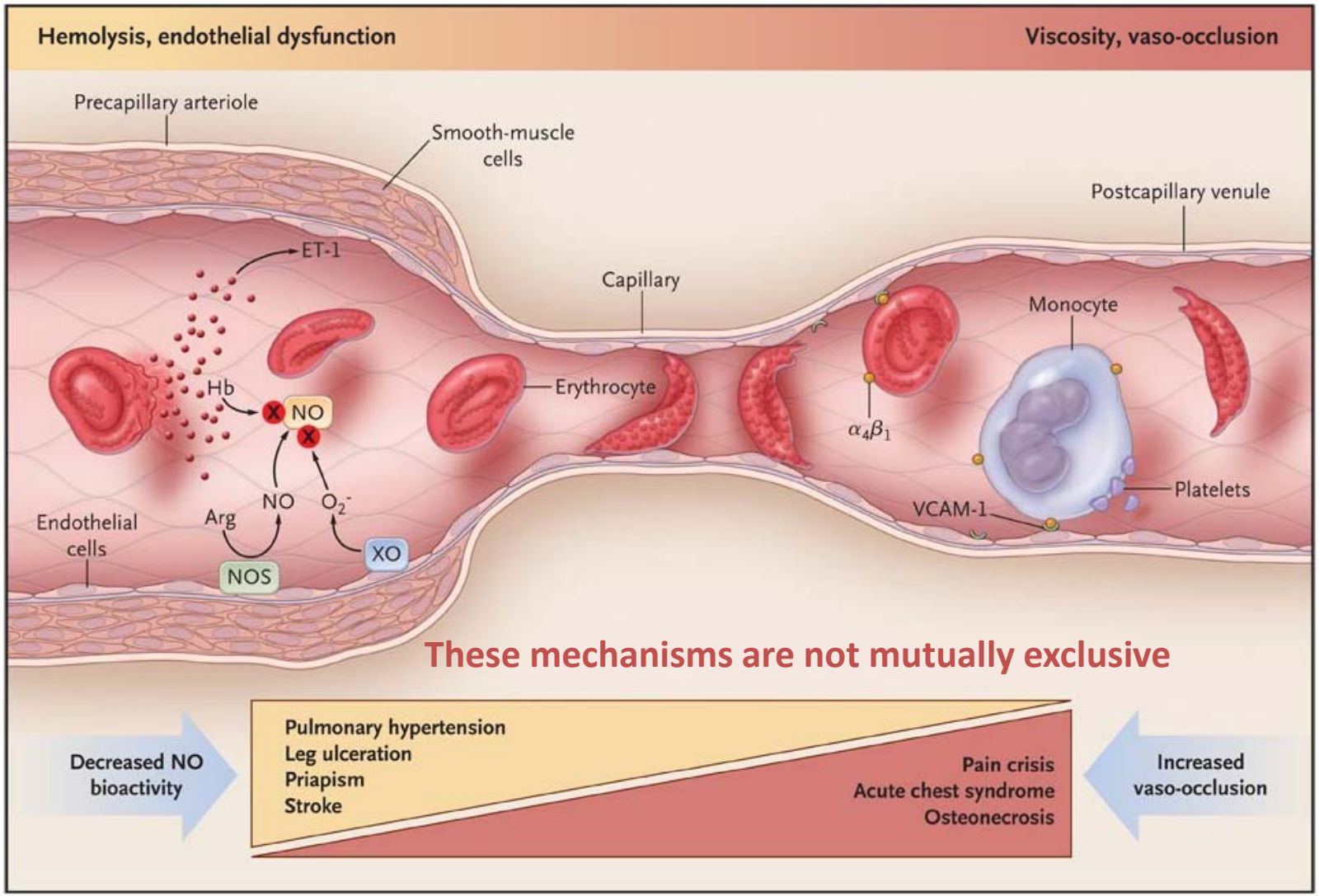


http://www.ajnr.org/content/27/4/728/F2.large.jpg

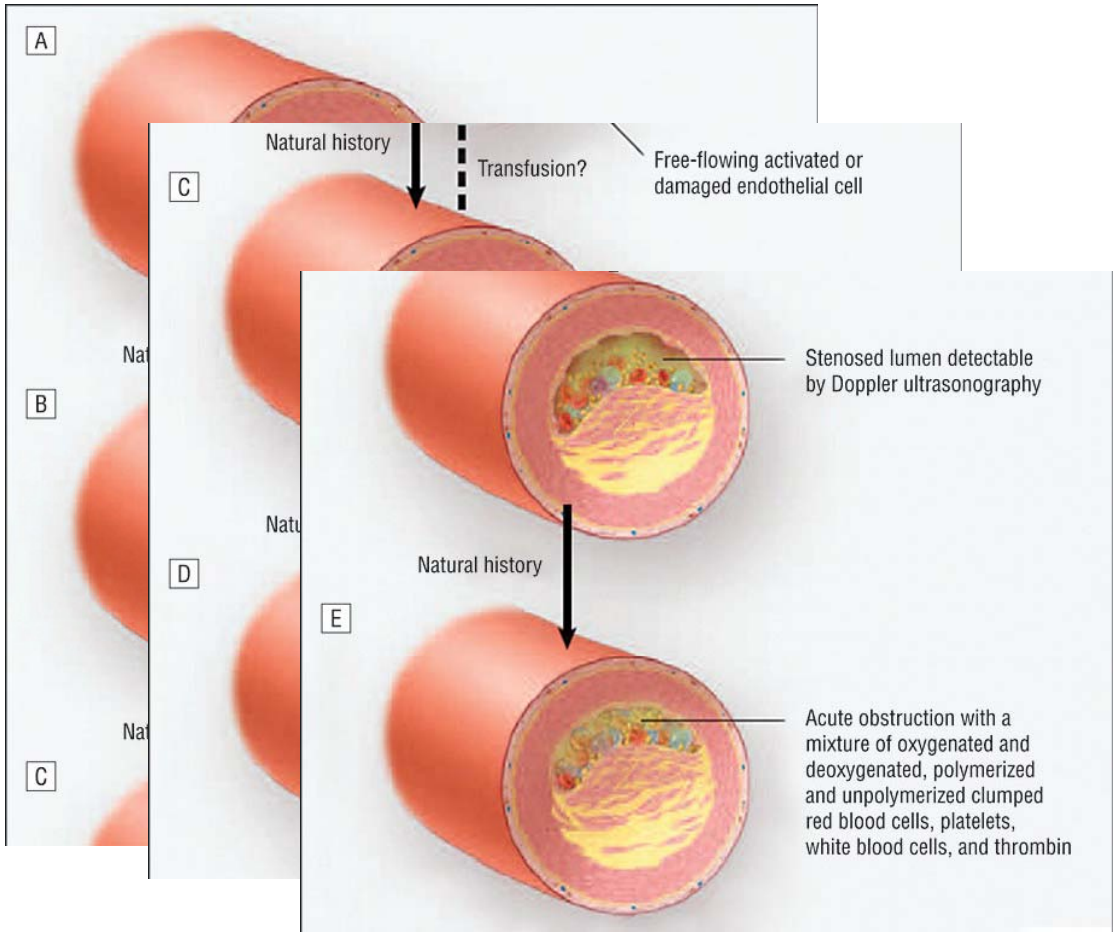
Signs and Symptoms of Stroke

- One-sided weaknesses and/or sensory changes (numbness, tingling)
- Loss of balance
- Vision loss
- Slurring of speech
- Seizures
- Typically one or few symptoms predominates

Spectrum of SCD Complications

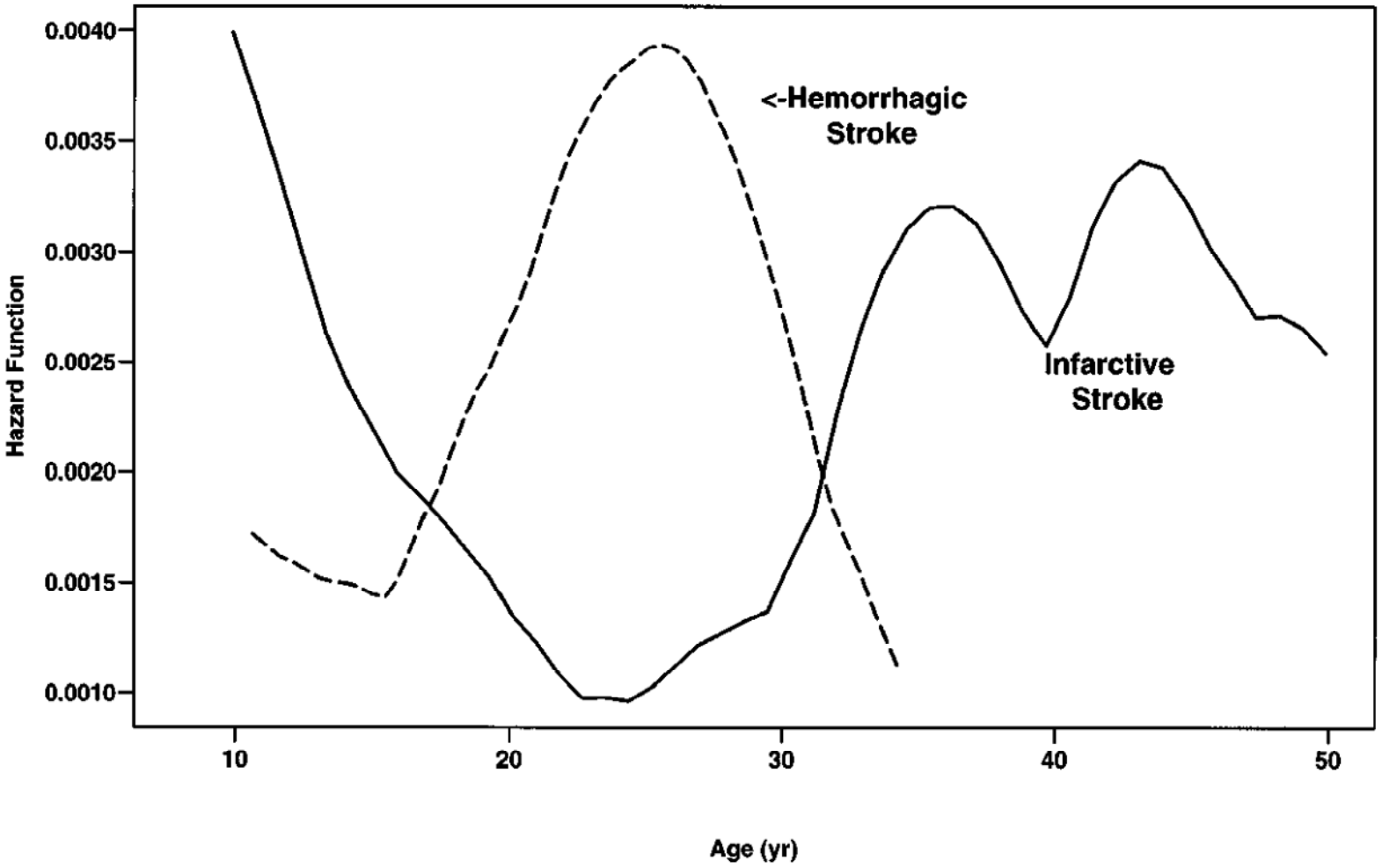


Natural History of Cerebral Vasculopathy in SCD



Adams RJ. Big strokes in small persons. Arch Neurol. 2007 Nov;64(11):1567-74

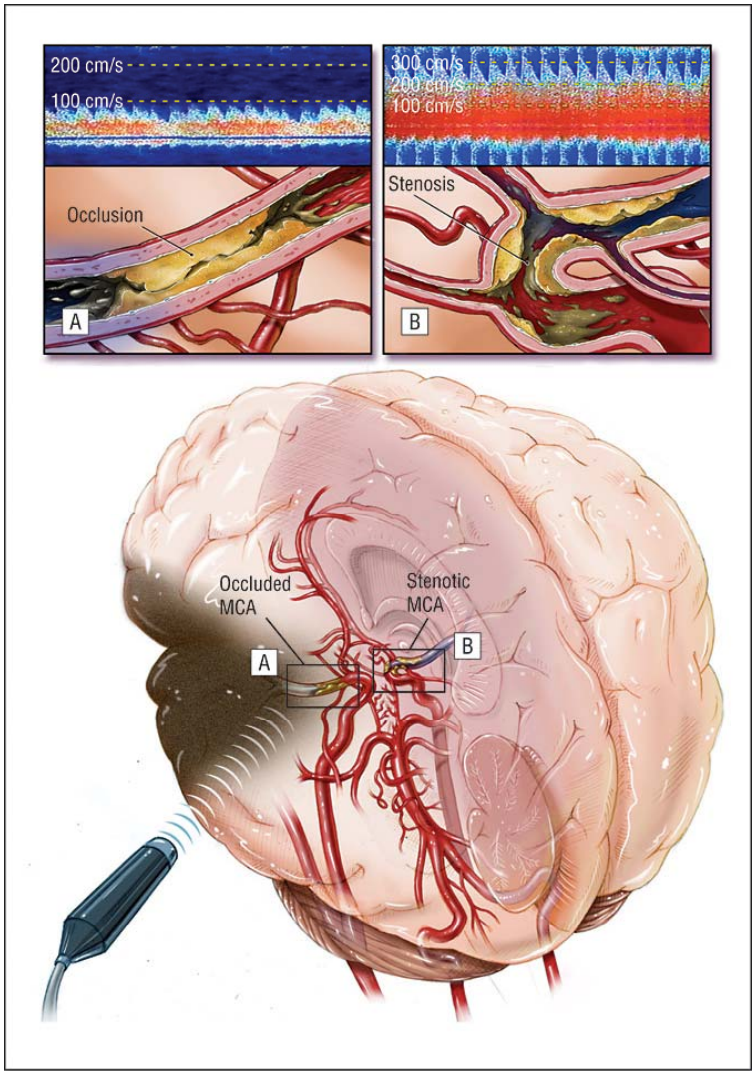
Risk of Hemorrhagic and Infarctive Stroke Changes with Age



Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998 Jan 1;91(1):288-94.

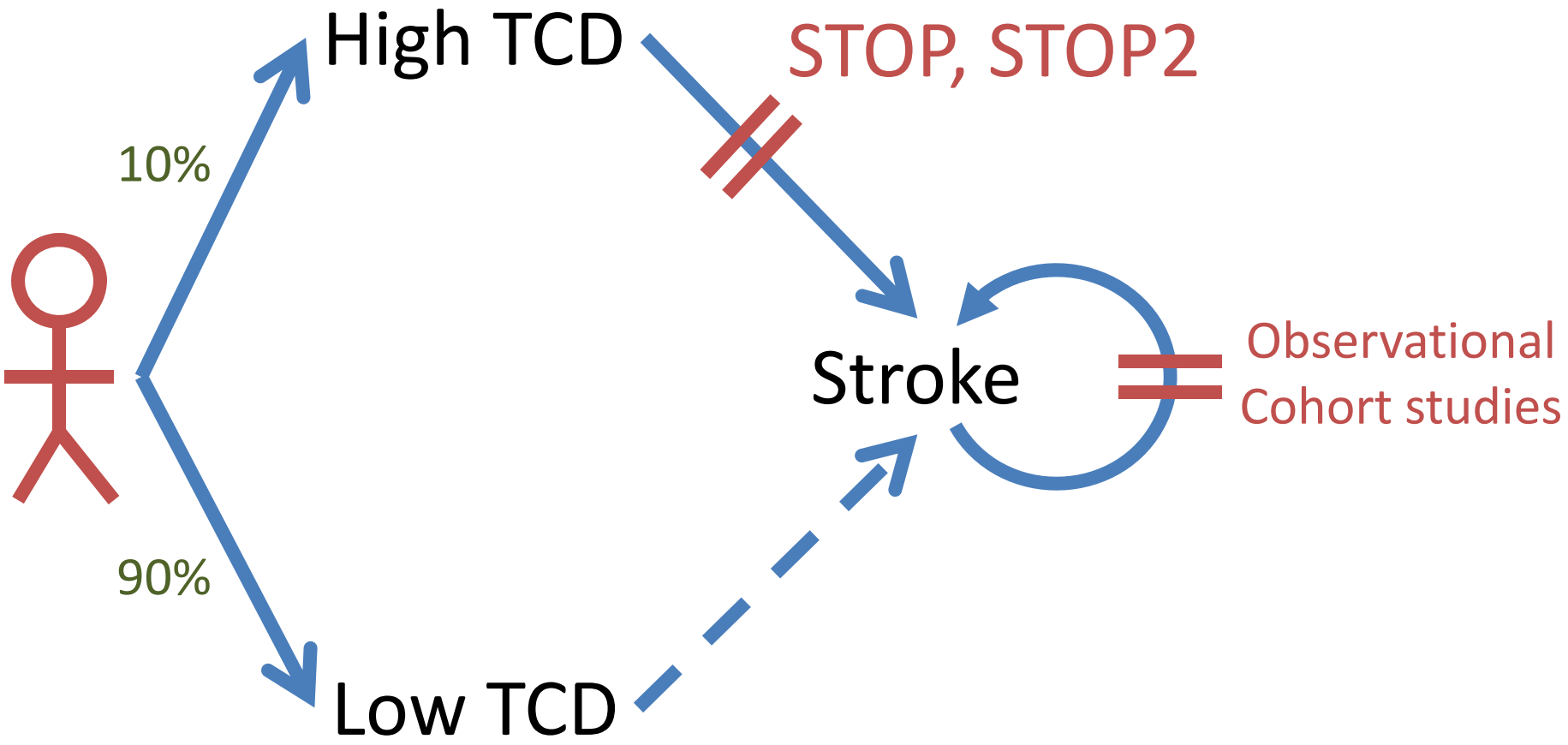
Measurement of Transcranial Doppler Velocity Via Ultrasonography

- Standard of care
- Ultrasound Doppler aimed at the MCA
- Measures peak velocity of blood flow
- High velocity = stenosis and vasculopathy
  (like a narrowed garden hose)
- > 200 cm/s (= abnormal) associated with 40% risk of stroke within 3 years
- Performed annually
- From the time when the baby can lay still (~ 2 years-old) until the bone window closes (early/late teens)



Adams RJ. Big strokes in small persons. Arch Neurol. 2007 Nov;64(11):1567-74

Epidemiology of CVA in SCD



STOP Study Design

- Patients:
  - SCD patients (SS, S/β^0 thal), Age 2 to 16
  - Transcranial Doppler Velocity > 200 cm/s
  - No history of stroke

- Study design:
  - Randomized to transfusion vs. no transfusion (standard of care)
  - Transfusion target: pre-transfusion HbS < 30%, Hb < 120, Hct < 0.360
  - Patients can achieve target by simple or exchange transfusion

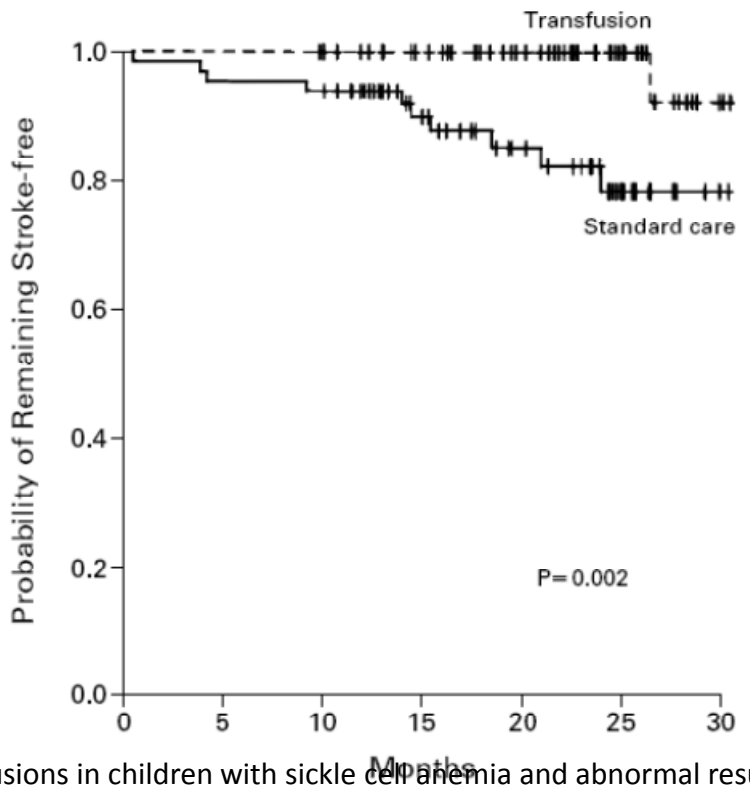
- Primary end-point:
  - cerebral infarction and hemorrhage, diagnosed by MRI

Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998 Jul 2;339(1):5-11

STOP Study Results

	Transfusion	Control
Stroke	1	11
No stroke	62	56

- RRR = **0.903**



Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998 Jul 2;339(1):5-11

STOP2 Study

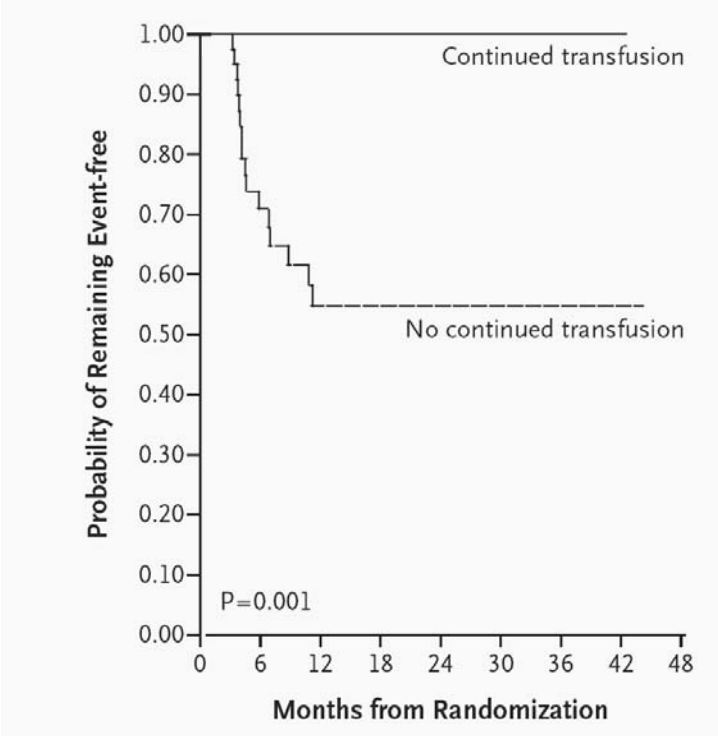
- Patients:
  - SCD patients (SS, S/β^0 thal), Age 2 to 16, from STOP study
  - On transfusion for > 30 months with HbS < 30% 2/3 of the time
  - Normal TCD, No stroke
- Study design:
  - Randomized to continued transfusion vs. no transfusion
  - Transfusion target: pre-transfusion HbS < 30%, Hb < 120, Hct < 0.360
  - Patients can achieve target by simple or exchange transfusion
- Primary end-point:
  - Stroke or reversion to abnormal TCD velocities

Adams RJ, Brambilla D; Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) Trial Investigators. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med. 2005 Dec 29;353(26):2769-78.

STOP2 Study Results

	Transfusion	Control
Stroke/Abnormal TCD	0/0	2/14
No stroke	38	25

- All strokes or reversion to abnormal TCD velocities occurred within first 10 months
- Both strokes occurred after reversion to abnormal TCD velocities



Adams RJ, Brambilla D; Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) Trial Investigators. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med. 2005 Dec 29;353(26):2769-78.

Chronic Transfusion in SCD

Methods of Transfusion

- Simple “top-up” transfusion
- Exchange transfusion:
  - Automated exchange
  - Manual RBC Exchange Transfusion

Potential Costs with Chronic Transfusion in SCD Patients

- Potential non-infectious risks
- Alloimmunization
- Potential infectious risks (minimal)
- Transfusional iron overload
  - Side effects from iron chelators
- Financial costs to patients (loss time from work, school, etc.)

Alloimmunization in SCD Patients

- Discrepancies between donor pool and recipient ethnicities
- 8 to 47% has been reported
- Dependent on patient age, number of donor units exposed, extent of phenotype matching
- Potential Consequences
  - Delayed hemolytic transfusion reaction (11%)
  - Autoantibody formation

Chou ST, Westhoff CM. Molecular biology of the Rh system: clinical considerations for transfusion in sickle cell disease. Hematology Am Soc Hematol Educ Program. 2009:178-84.

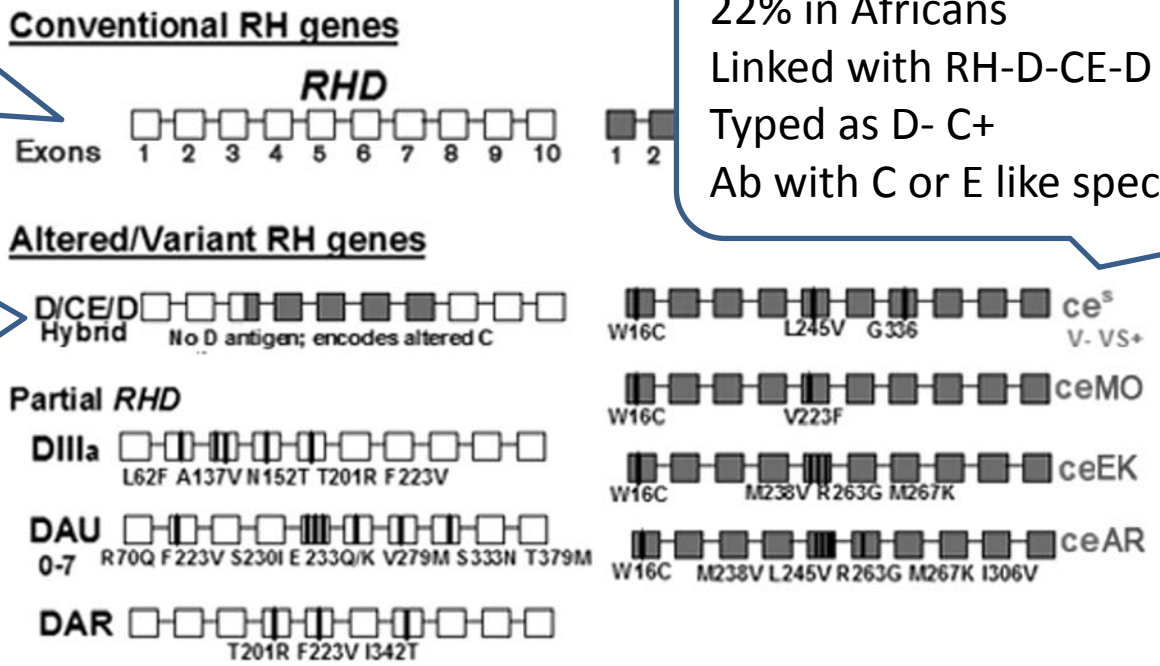
Alloimmunization Examples
RHD and RHCE

- Altered C and e Ag are frequent in Africans
- Cannot be distinguished serologically, but recognized as foreign by the immune system

66% premature stop
19% gene deletion
(>90% in Caucasians)

15% RHD-CE-D hybrid
Typed as D- C+
(none in Caucasians)

22% in Africans
Linked with RH-D-CE-D
Typed as D- C+
Ab with C or E like specificities



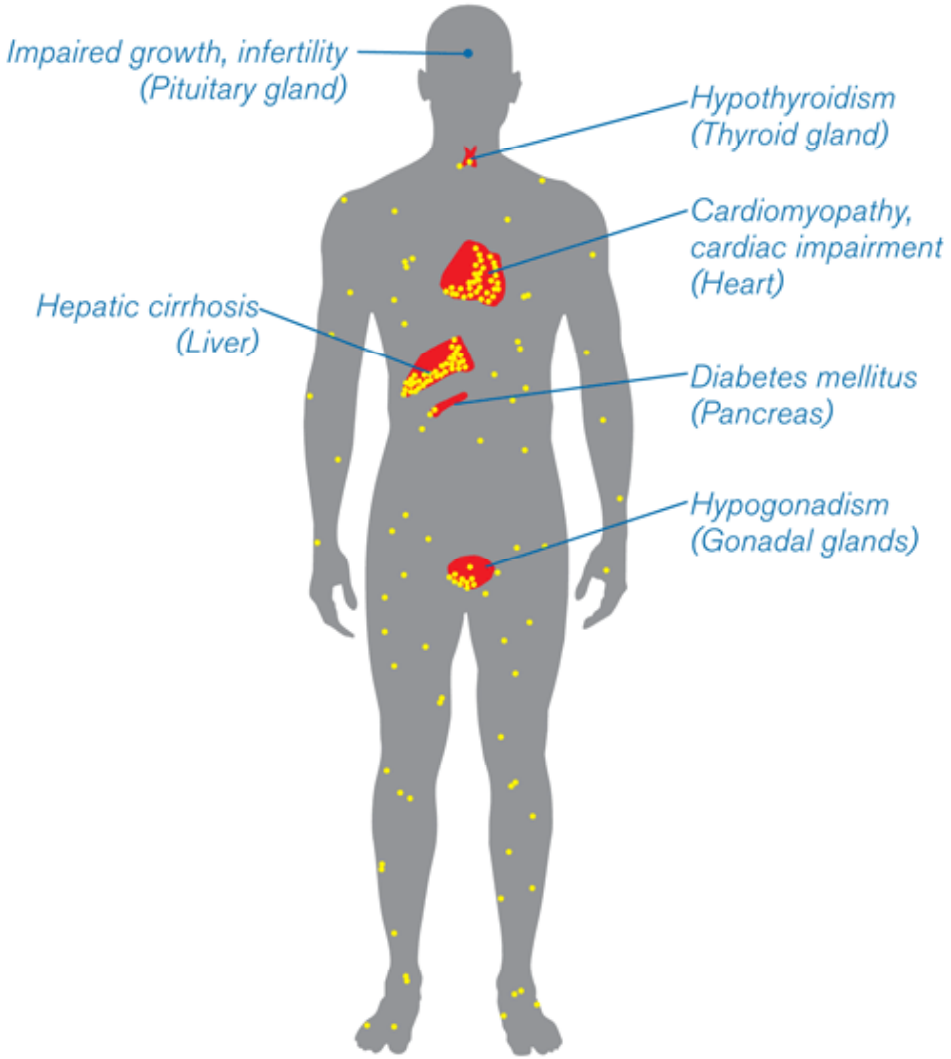
Chou ST, Westhoff CM. Molecular biology of the Rh system: clinical considerations for transfusion in sickle cell disease. Hematology Am Soc Hematol Educ Program. 2009:178-84.

Antigen-Matching

C/c E/e Kell matched

	Group A (n = 20)	Group B (n = 26)
Total number of antibodies	31	108
Common Rh alloantibodies	0	22 18 anti-E 4 anti-C
Complex Rh antibodies*	22 11 anti-D (D+ patients) 8 anti-e (e+ patients) 3 anti-C (C+ patients)	30 4 anti-D (D+ patients) 6 anti-e (e+ patients) 20 anti-C or -Ce (C+ patients)
Other antibodies	9 2 anti-Jk^b 1 anti-Fy^a 4 anti-M 1 anti-N 1 anti-Js^a	56 8 anti-K 6 anti-S 6 anti-Fy^a 4 anti-Jk^b 2 anti-Jk^a 1 anti-M 1 anti-Go^a 1 anti-N 1 anti-Js^a 1 anti-Kp^a 1 anti-Yta 1 anti-Le^a 1 anti-Le^b
***RH* alleles**		
Hybrid *RHD-CE-D* and *RHCE*ce^s*	3	20
Only altered *RHCE*ce*	11	6
Partial *RHD* and altered *RHCE*ce*	9	14

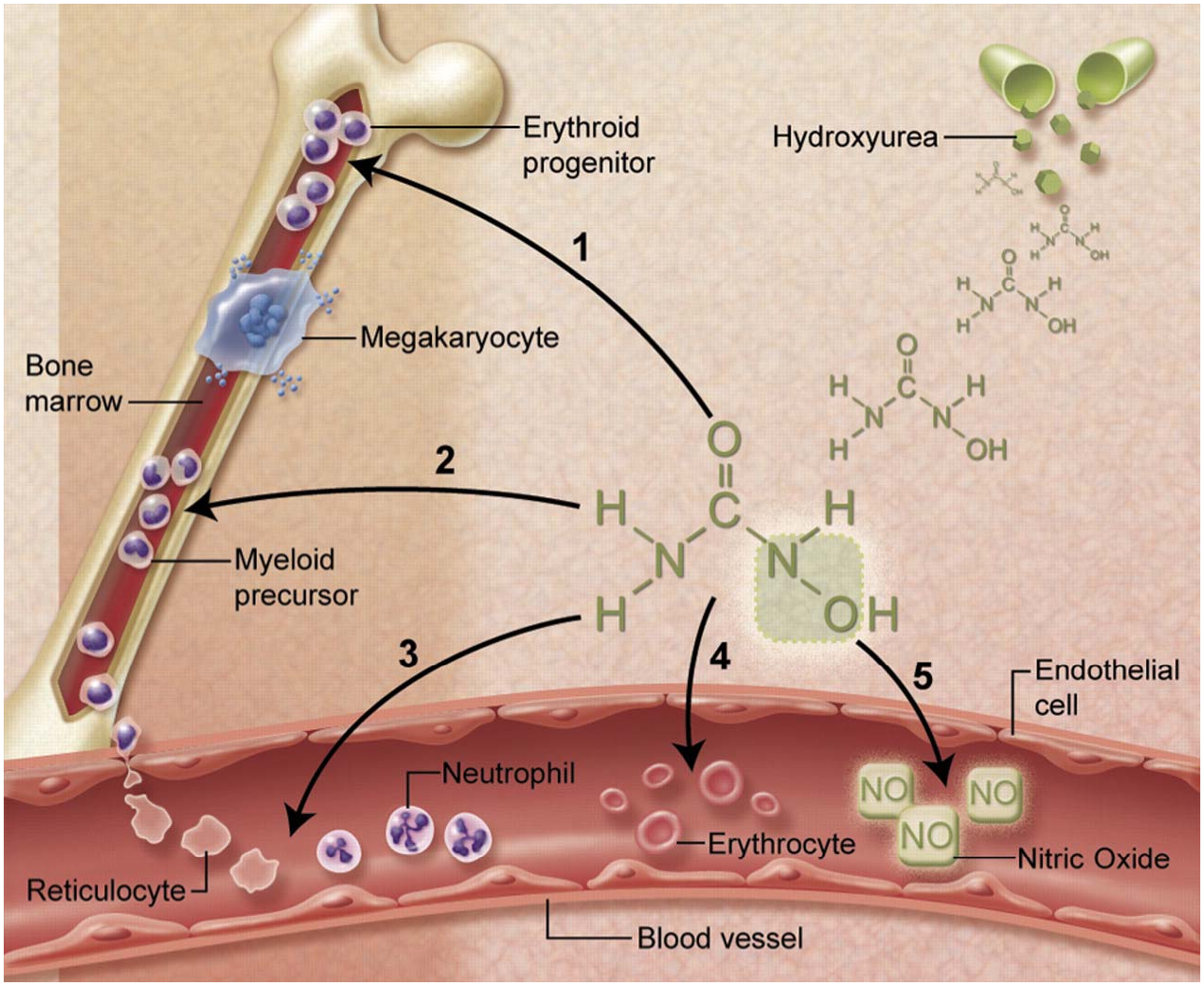
Transfusional Iron Overload



http://www.sld.cu/sitios/prevemi/temas.php?idv=24514

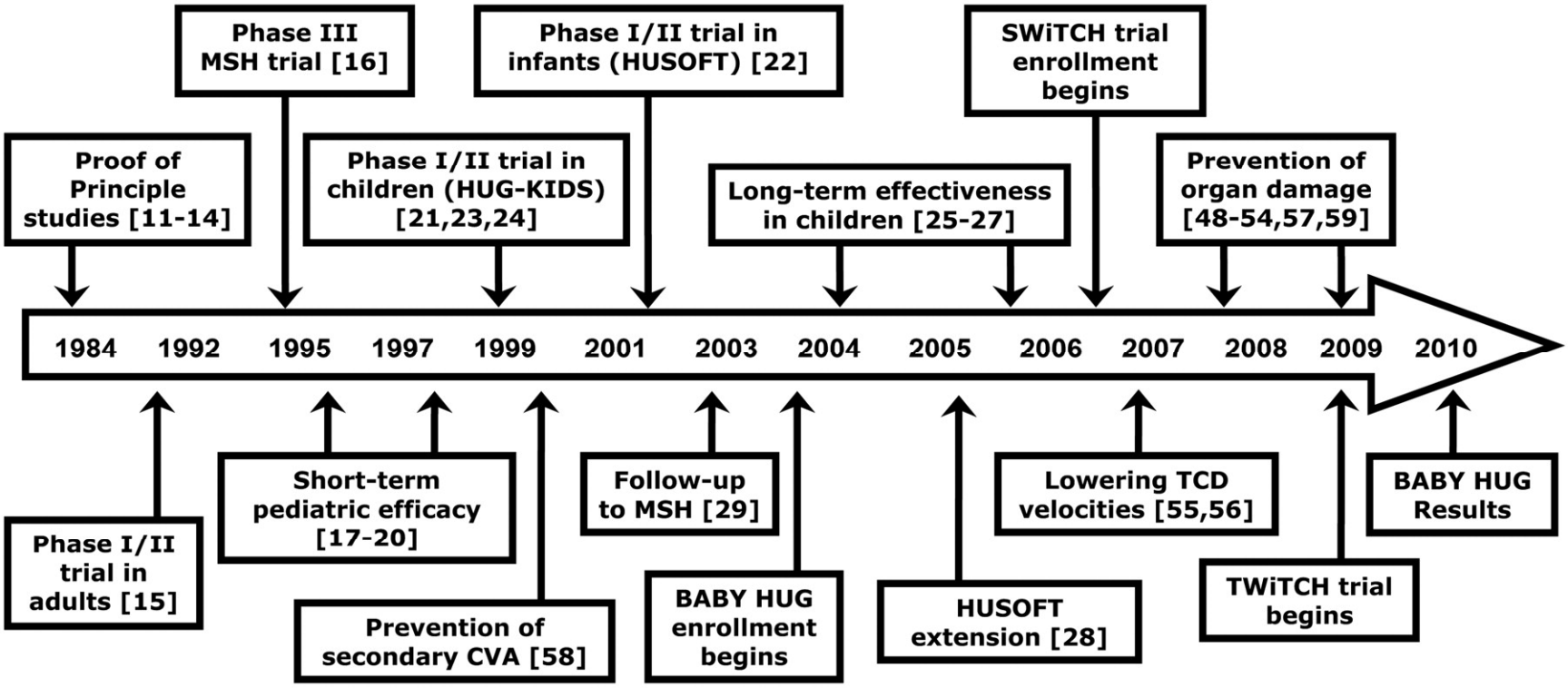
Hydroxyurea as a Potential Alternative to Transfusion in the Treatment and Prevention of Stroke

Multiple Beneficial Effects of Hydroxyurea for SCD



Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood. 2010 Jul 1;115(26):5300-11.

Clinical Studies of Hydroxyurea in SCD



Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood. 2010 Jul 1;115(26):5300-11.

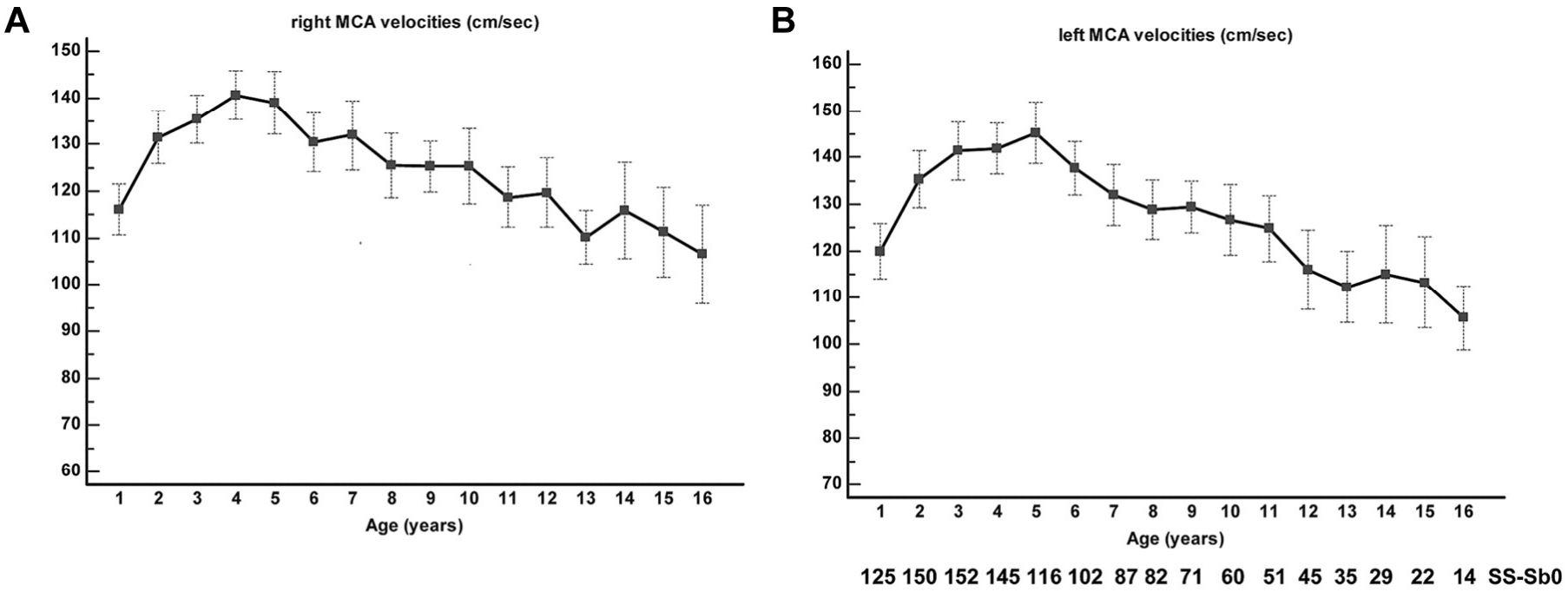
SWiTCH

- Phase III multicenter RCT, Non-inferiority
- 30 months, N = 133
- Hydroxyurea + phlebotomy vs. transfusions + chelation
- Composite primary endpoint: stroke recurrence and iron burden
- 12% had recurrent stroke prior to enrollment
- interim data analysis was performed after 1/3
- No difference in LIC
- Stroke recurrence rate: 7/67 vs. 0/66 transfusion + chelation

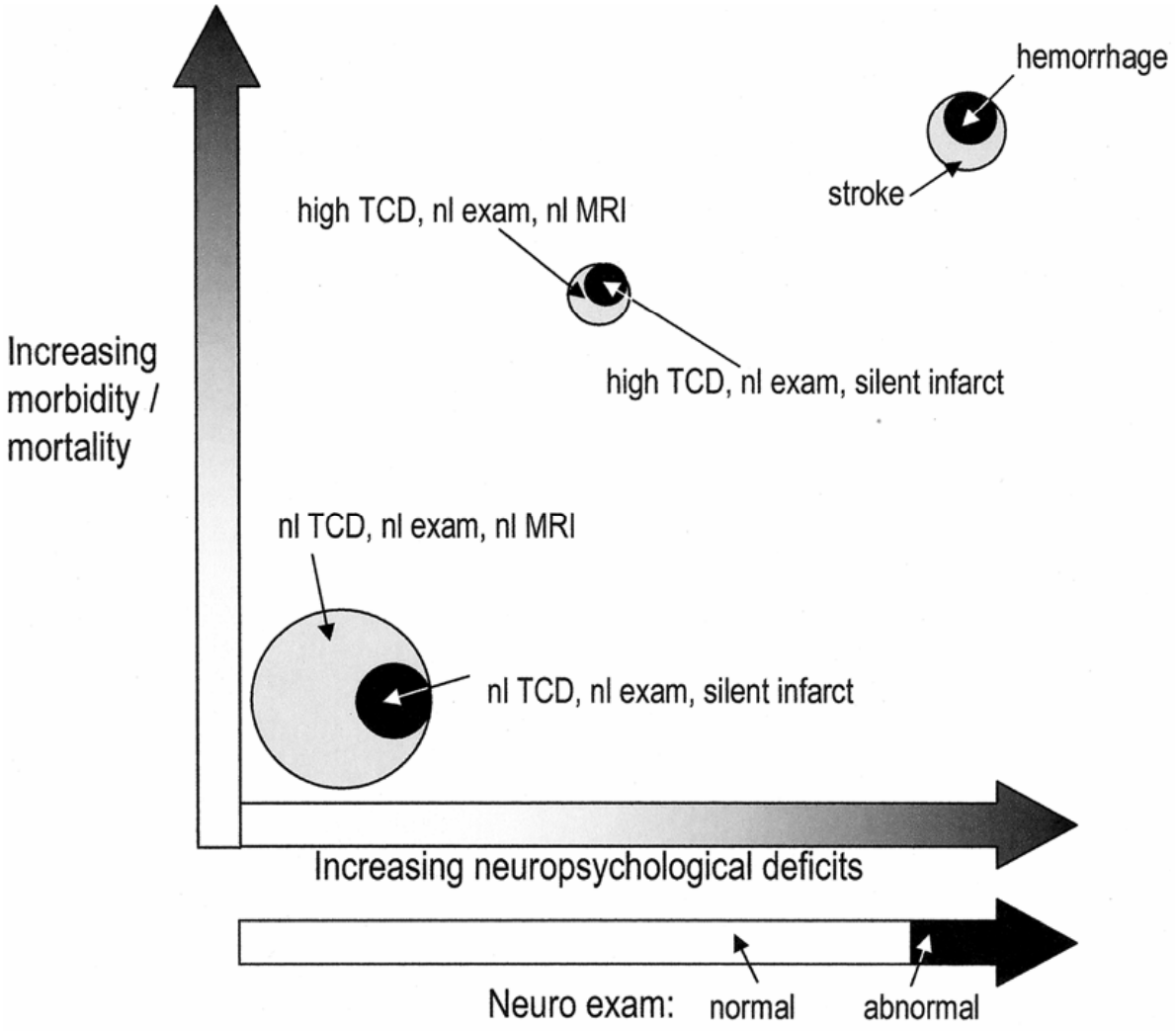
TWiTCH

- N = 148 planned enrollment (ages 4 to 15)
- SCA + abnormal TCD
- Transfusions + chelation vs. Hydroxyurea + phlebotomy
- Treatment duration: 24 months
- Outcome measurements: LIC, TCD, MRI

TCD Velocities Decrease with Age



Neurological Events in SCD

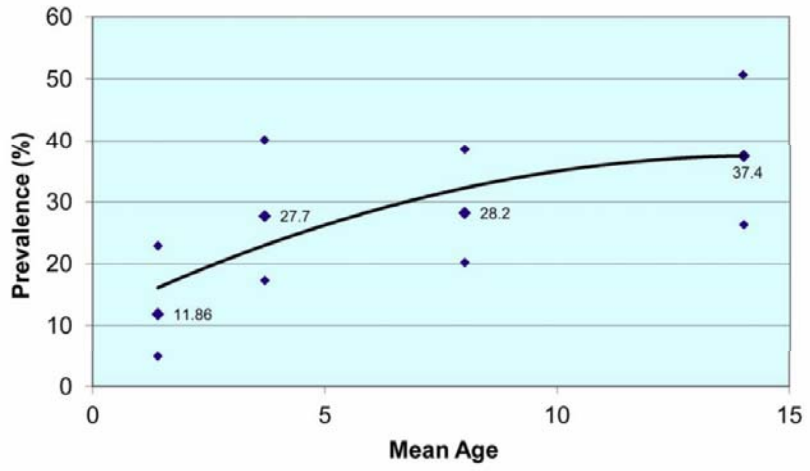


Silent Cerebral Infarcts (SCI)

- No signs or symptoms of stroke
- Normal neurologic examination
- Abnormal MRI
- Lack of concordance with TCD velocity
- Definition of abnormal MRI is constantly evolving
  - Improved imaging technologies
  - Different definitions between adults and kids
  - Area under intensive research
- What were classified as SCI previously may had subtle signs of stroke

Epidemiology of SCI

- Constantly shifting definition and lack of consensus amongst researchers
- Patient selection bias (very ill vs. not so ill)
- Lack of longitudinal studies with large number of patients
- Best guess in kids:



- In adults: 13% in SCA vs. 2% in age- and ethnicity-matched controls without SCA

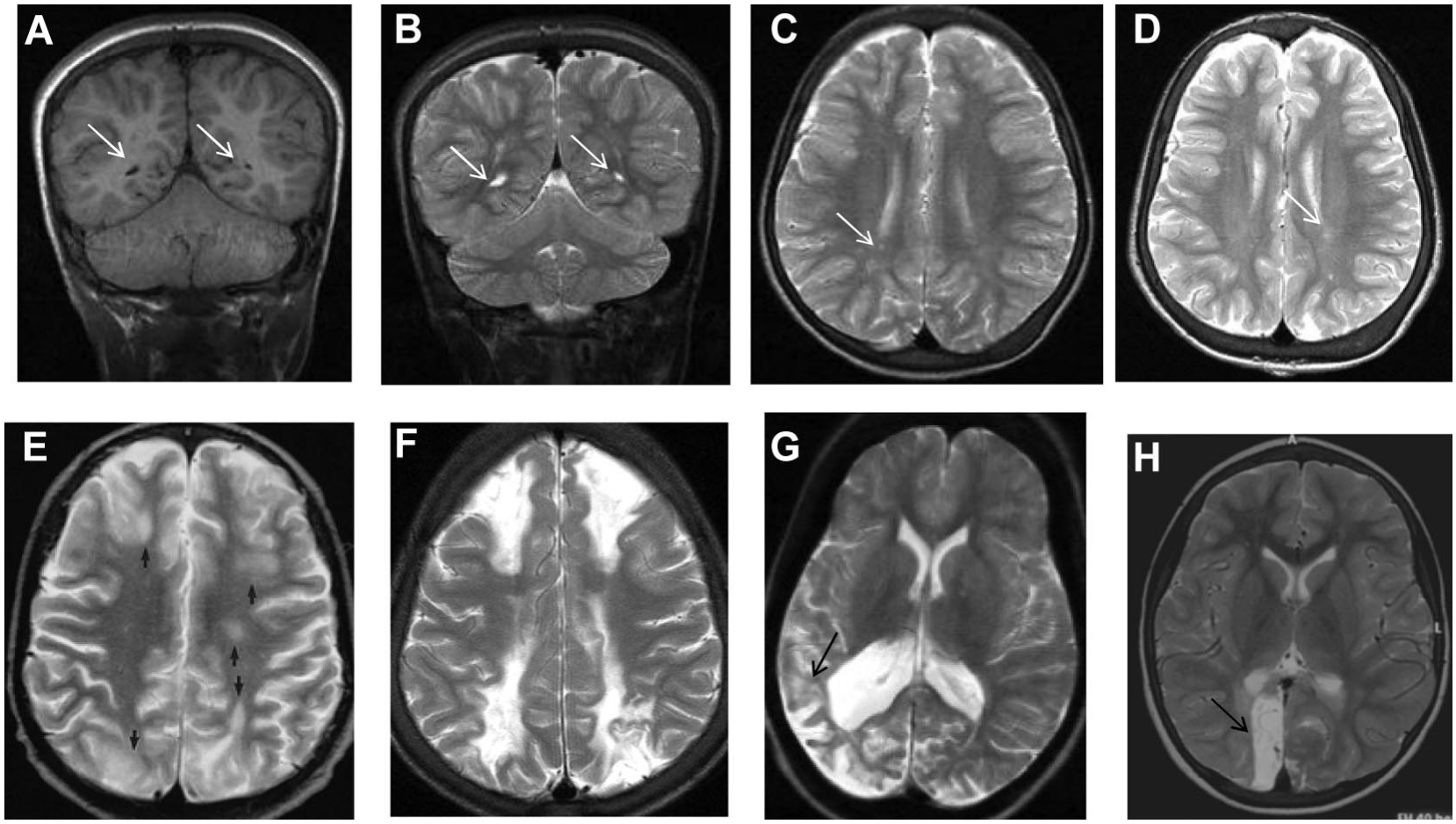
Risk Factors for SCI

- Low baseline hemoglobin level
- Higher blood pressure
- Male
- May be:
  - History of seizures
  - High white blood cell count
  - SEN β^S globin gene haplotype

Anatomic Location of SCI

- (in decreased order of likelihood)
- Deep white matter
  - Frontal lobe
  - Parietal lobe
- Basal ganglia
- Thalamus
- Temporal lobes

Detection of SCI by MRI

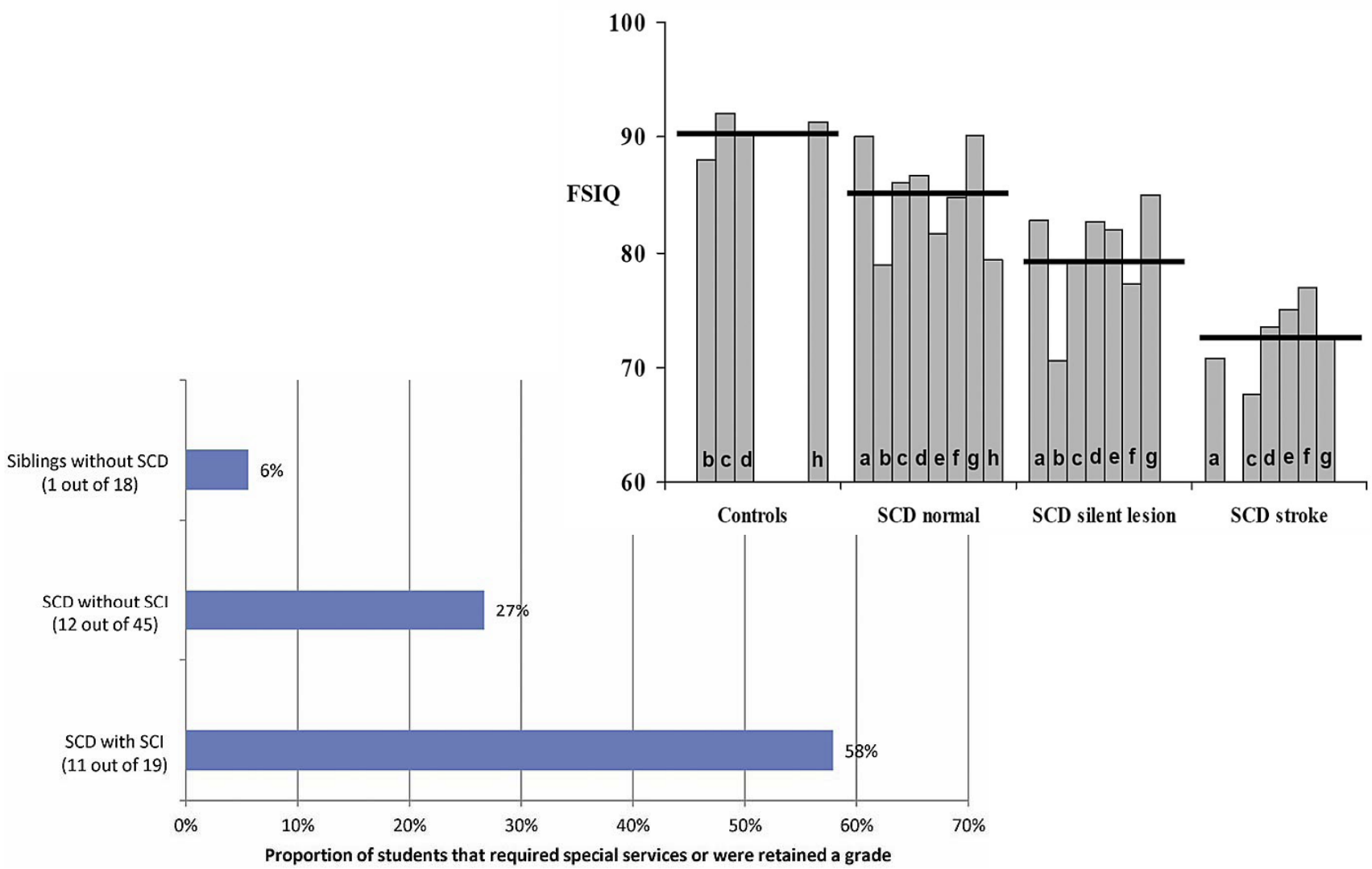


Effects of Silent Cerebral Infarcts

- Lower global intellectual function
- Executive functions
  - selective attention, card sorting, working memory, processing speed
- Visual motor speed
- Coordination
- Visual memory
- Verbal comprehension
- Vocabulary
- Abstract reasoning

- Poor academic achievement

Effects of Silent Cerebral Infarcts



Potential Treatments for SCI

- Currently no therapy has been proven to prevent the occurrence or progression of SCI
- Transfusions
  - reduce the risk of stroke in patients with SCI and abnormal TCD velocities (STOP secondary analysis)
  - Currently being evaluated as an potential option in the SIT study
- Hydroxyurea and HSCT
  - evidence from single arm studies

Silent Cerebral Infarct Multi-center Transfusion (SIT) Trial

- Study hypothesis: monthly prophylactic blood transfusion therapy in children with SCI will result in an 86% reduction in strokes or new or progressive SCIs
- Multi-center randomized-controlled trial (29 sites in US, Canada, UK, and France) over 8.5 years
- Population: Children with history of SCI
- Randomization: blood transfusion or observation x 36 months
- N = 1,880 (planned enrolment)
- Outcome: Strokes, New or enlarged SCI
- Instrument: screening, pre-randomization (baseline), and exit MRI using a designated, prospective imaging protocol

Vendt BA, McKinstry RC, Ball WS, et al. Silent Cerebral Infarct Transfusion (SIT) Trial Imaging Core: Application of Novel Imaging Information Technology for Rapid and Central Review of MRI of the Brain. J Digit Imaging. 2008 Apr 9
Casella JF, King AA, Barton B, et al. Design of the silent cerebral infarct transfusion (SIT) trial. Pediatr Hematol Oncol. 2010 Mar;27(2):69-89

Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease

Monica L. Hulbert,[1] Robert C. McKinstry,[2,3] JoAnne L. Lacey,[2] Christopher J. Moran,[2] Julie A. Panepinto,[4] Alexis A. Thompson,[5] Sharada A. Sarnaik,[6] Gerald M. Woods,[7] James F. Casella,[8] Baba Inusa,[9] Jo Howard,[9] Fenella J. Kirkham,[10] Kofi A. Anie,[11] Jonathan E. Mullin,[12] Rebecca Ichord,[13] Michael Noetzel,[3,14] Yan Yan,[3] Mark Rodeghier,[15] and Michael R. DeBaun[16]

[1]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [2]Department of Radiology, Washington University School of Medicine, St Louis, MO; [3]Department of Pediatrics, Washington University School of Medicine, St Louis, MO; [4]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; [5]Department of Pediatrics, Northwestern University School of Medicine, Chicago, IL; [6]Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI; [7]Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO; [8]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD; [9]Guy's and St Thomas's National Health Service Foundation Trust, London, United Kingdom; [10]University College Institute of Child Health, London, United Kingdom; [11]Imperial College School of Medicine, Central Middlesex Hospital, London, United Kingdom; [12]Case Western Reserve University School of Medicine, Cleveland, OH; [13]Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA; [14]Department of Neurology, Washington University School of Medicine, St Louis, MO; [15]Statistical Collaborator, Chicago, IL; and [16]Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN

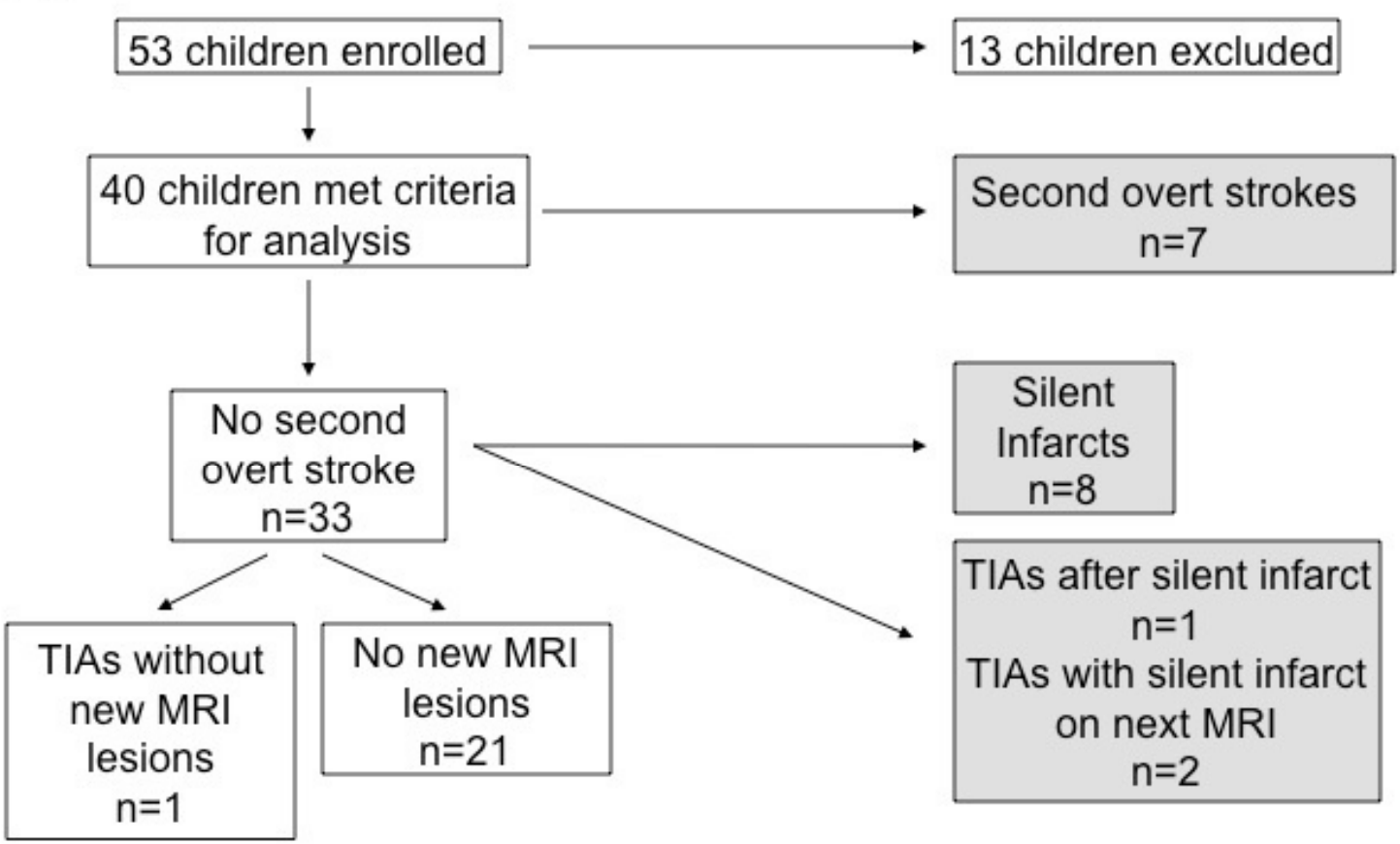
Submitted January 15, 2010; accepted September 2, 2010. Prepublished online as *Blood* First Edition paper, October 12, 2010; DOI 10.1182/blood-2010-01-261123.

An Inside *Blood* analysis of this article appears at the front of this issue.

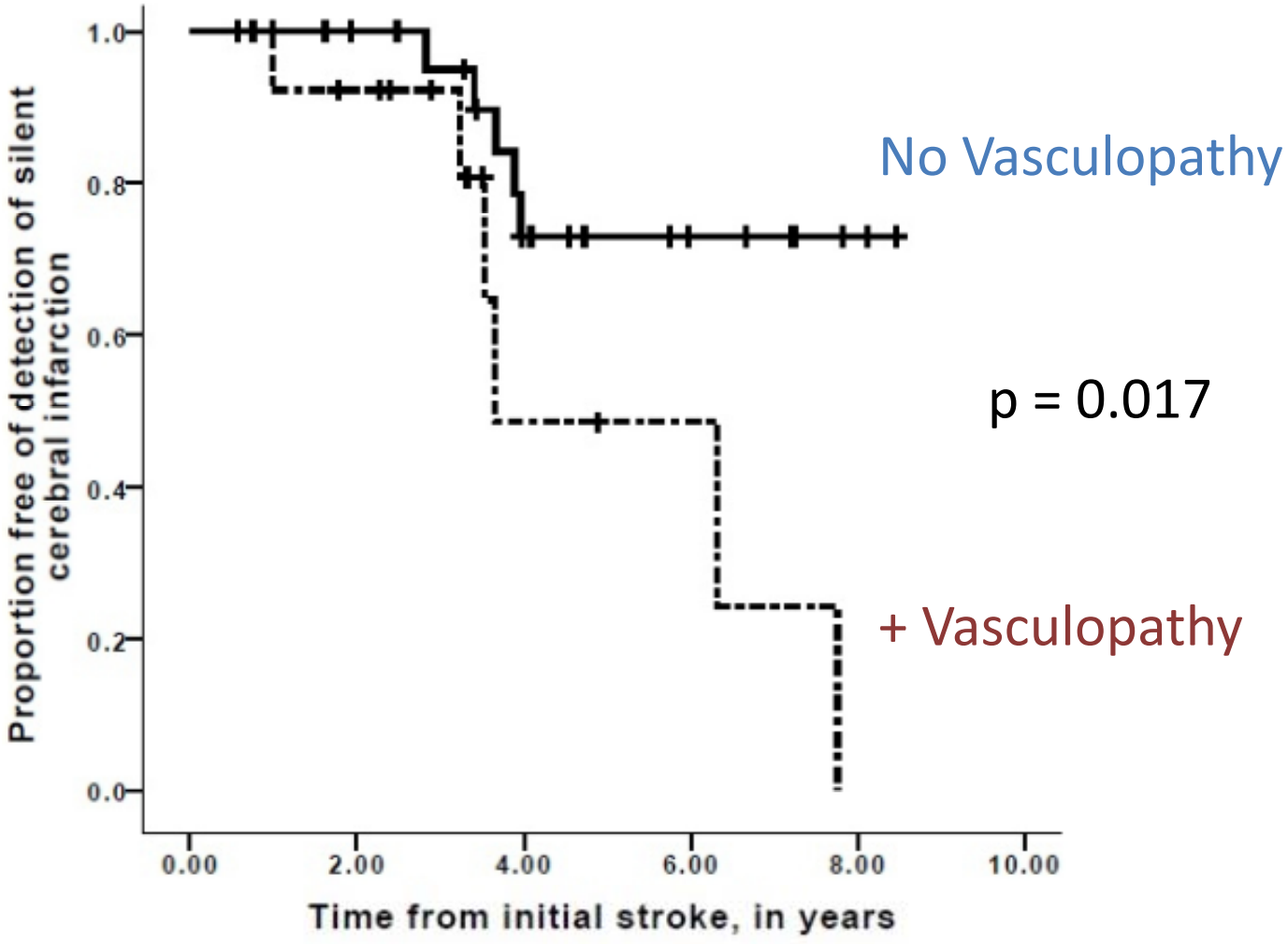
The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Results

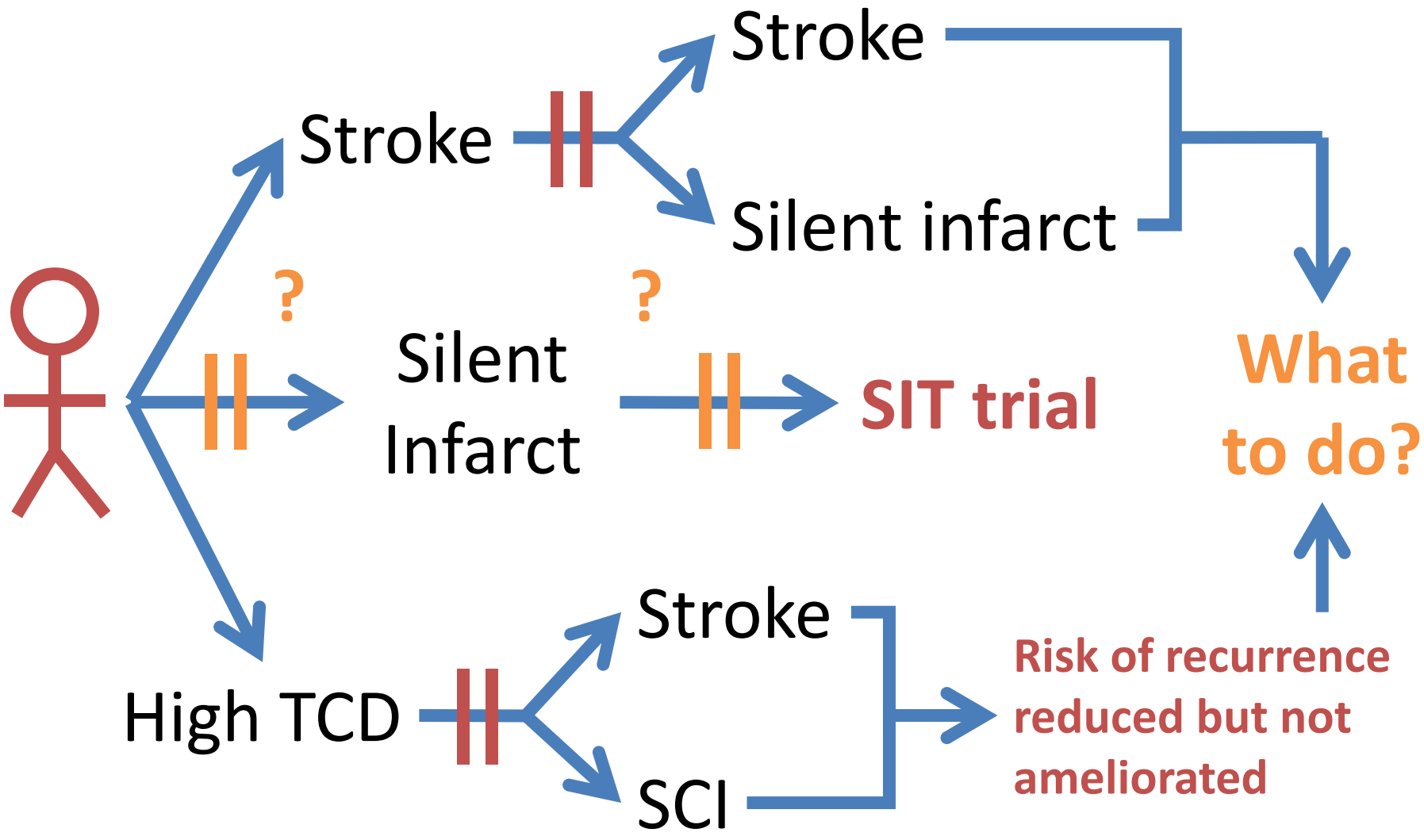
- Median age at first stroke 5.4 years-old
- Median duration of follow-up 5.5 years



Progressive Vasculopathy and Silent Infarcts



Where to Go in the Post-STOP Era



More Questions than Answers

- When to do screening MRI?
- How often should we evaluate SCA patients for SCI?
- Hydroxyurea as a therapeutic option?
- Bone marrow transplantation?
- Gene-therapy?
- Other novel therapeutic agents?

Discussion