Cerebrovascular Disease: Primary and Secondary Stroke Prevention

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Optimizing Primary Stroke Prevention STOP II in Children with Sickle Cell Anemia

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Primary and Secondary Prevention

a 25 year perspective

- An honor to be here among colleagues including Dr Celia Maria Silva who we had the pleasure of hosting in 2001 at Medical College of Georgia

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Primary and Secondary Prevention

a 25 year perspective

- What began as “stroke prevention” grew into projects to protect the brain and then we realized we must also protect the vessels

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Primary and Secondary Prevention

a 25 year perspective

Primary Prevention in Children	Secondary Prevention in Children
Primary Prevention in Adults	Secondary Prevention in Adults

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Primary and Secondary Prevention

a 25 year perspective

Primary Prevention in Children	Secondary Prevention in Children
Primary Prevention in Adults	Secondary Prevention in Adults

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Primary and Secondary Prevention

a 25 year perspective

Primary Prevention in Children REAL PROGRESS !!!!	Secondary Prevention in Children Some new data
Primary Prevention in Adults ---no data	Secondary Prevention in Adults ---no data

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Primary and Secondary Prevention

a 25 year perspective

- Several risk factors for stroke in childhood stand out :
  - Congenital heart disease
  - Trauma
  - Infections
  - Medical illnesses (eg cancer)
  - ***Sickle Cell Disease***

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Primary and Secondary Prevention

a 25 year perspective

- Childhood is just about "stroke free"
  - Rate estimates (both ischemic and hemorrhage):
    - Schoenberg et al (1978) --- 2.5 per 100,000/year
    - Broderick et al (1978)---2.7 per 100,000/year
    - Fullerton et al (1983) ---2.3 per 100,000/year
  - With SCD 285-1000 per 100,000/year!!!!

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Primary and Secondary Prevention

a 25 year perspective

–Why stroke in Sickle Cell Disease?

- An intracranial cerebral large artery "vasculopathy" causing stenosis and occlusion was confirmed early on as major cause of large brain infarctions in Sickle Cell Disease patients

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Medical College of Georgia
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10 cm

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W 1119

,HEAD P

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10 cm

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Medical College of Georgia
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10 cm

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Primary and Secondary Prevention

a 25 year perspective

- **Starting transfusion *after stroke* meant that brain damage had already taken place**
- **Could primary prevention be achieved at least for the highest risk children?**
- **Why not transfuse all SCD children?**
  - **More than 200 children would need to be transfused to prevent one stroke a year**
  - **Side effects and cost prohibitive**

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Primary and Secondary Prevention

a 25 year perspective

- ***A strategy to identify high risk children was needed***
- ***TCD provided that strategy***

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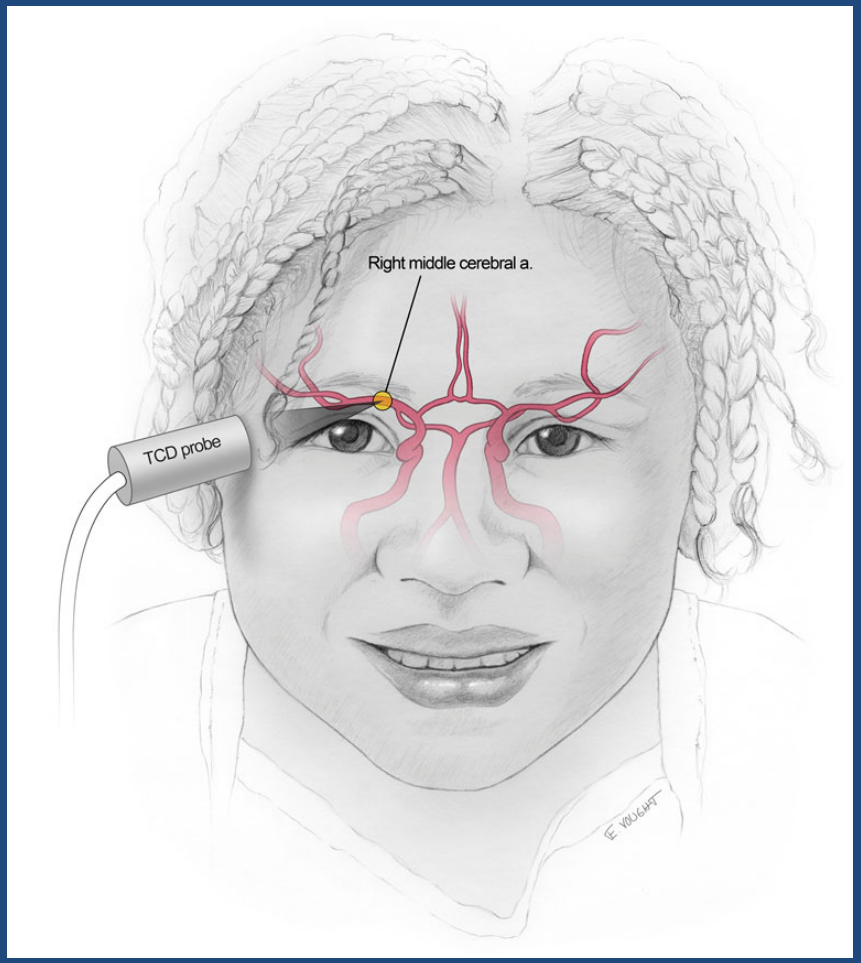
Primary and Secondary Prevention

a 25 year perspective



- **From 1988-1992 a single center prospective study led to a TCD Risk Model**
  - **315 children studied with TCD *before onset of symptoms***
  - **age 3-18 years at first TCD**
  - **mean follow up 64 ± 23 months**
  - **17 developed stroke**
  - **stroke increased with velocity (p<0.001)**
    - **(NEJM 1992)**

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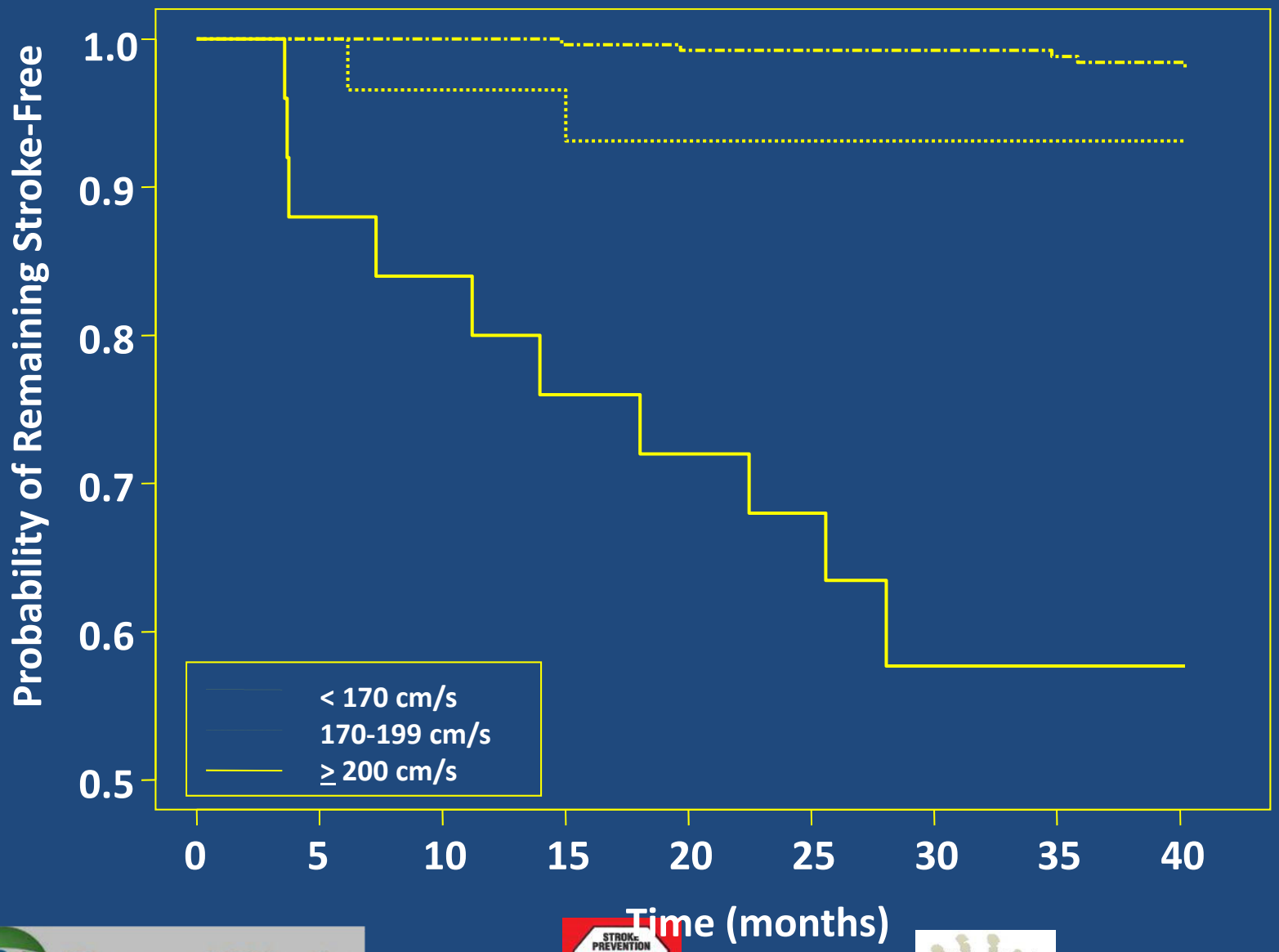
KM of time to stroke as function of TCD



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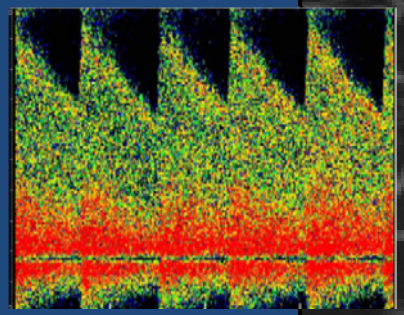
Predictive value of TCD for stroke

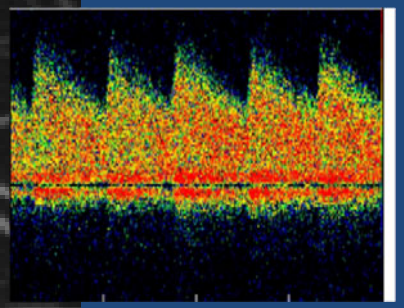
- The probability of remaining stroke-free over time of follow-up or start of chronic transfusion (~ 70 months) was greatest with normal baseline TCD

Right MCA



220 cm/s

Left MCA



130 cm/s

Risk of stroke was higher with abnormal TCD than with normal or conditional TCD ($p < 0.01$)

Adams RJ, et al. Blood. 2004;103:3689-94

STOP Centers (Stroke Prevention Trial in Sickle Cell Anemia)

Primary and Secondary Prevention

a 25 year perspective

- STOP (1994-2000) was a *randomized controlled clinical trial* testing if regular blood transfusion would prevent first stroke in children with SCD identified at high risk by TCD

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Primary and Secondary Prevention

a 25 year perspective

- Randomization criteria
  - homozygous SS disease
  - age 2-16 years
  - two TCD's showing high risk
  - ***no history of stroke***
  - no indication/contraindication to transfusion

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Primary and Secondary Prevention

a 25 year perspective

- **Baseline TCD screening results***
  - **Normal—low risk 68 %**
  - **Conditional ---some risk 17 %**
  - **Inadequate---indeterminate 5%**
  - **Abnormal---high risk 10%**

  - *** no difference across 14 sites and 1934 children**

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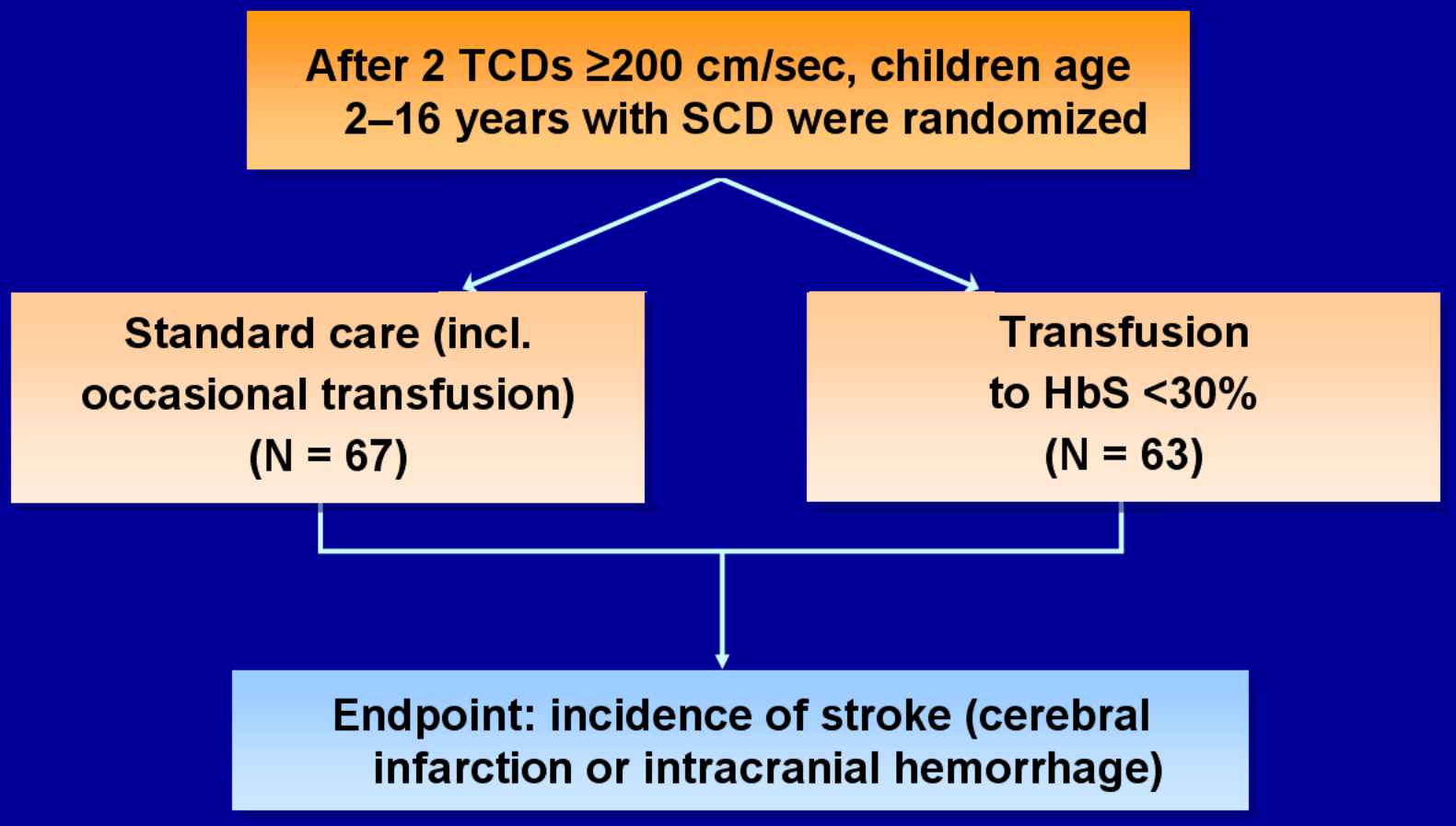
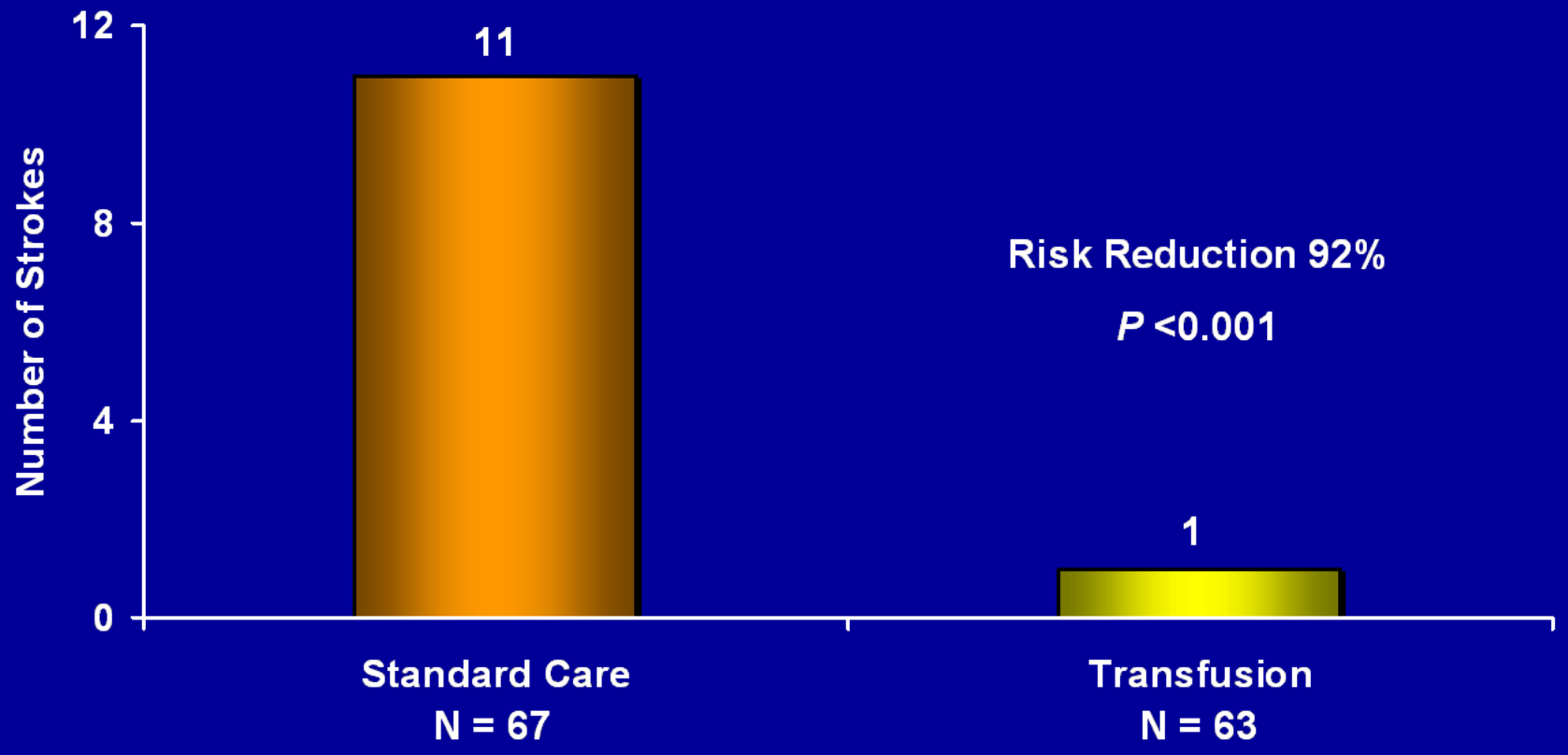
Stroke Prevention Trial in Sickle Cell Anemia: STOP Trial Design



HbS = sickle cell hemoglobin; STOP = Stroke Prevention Trial in Sickle Cell Anemia; TCD = transcranial Doppler

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

STOP Trial Results

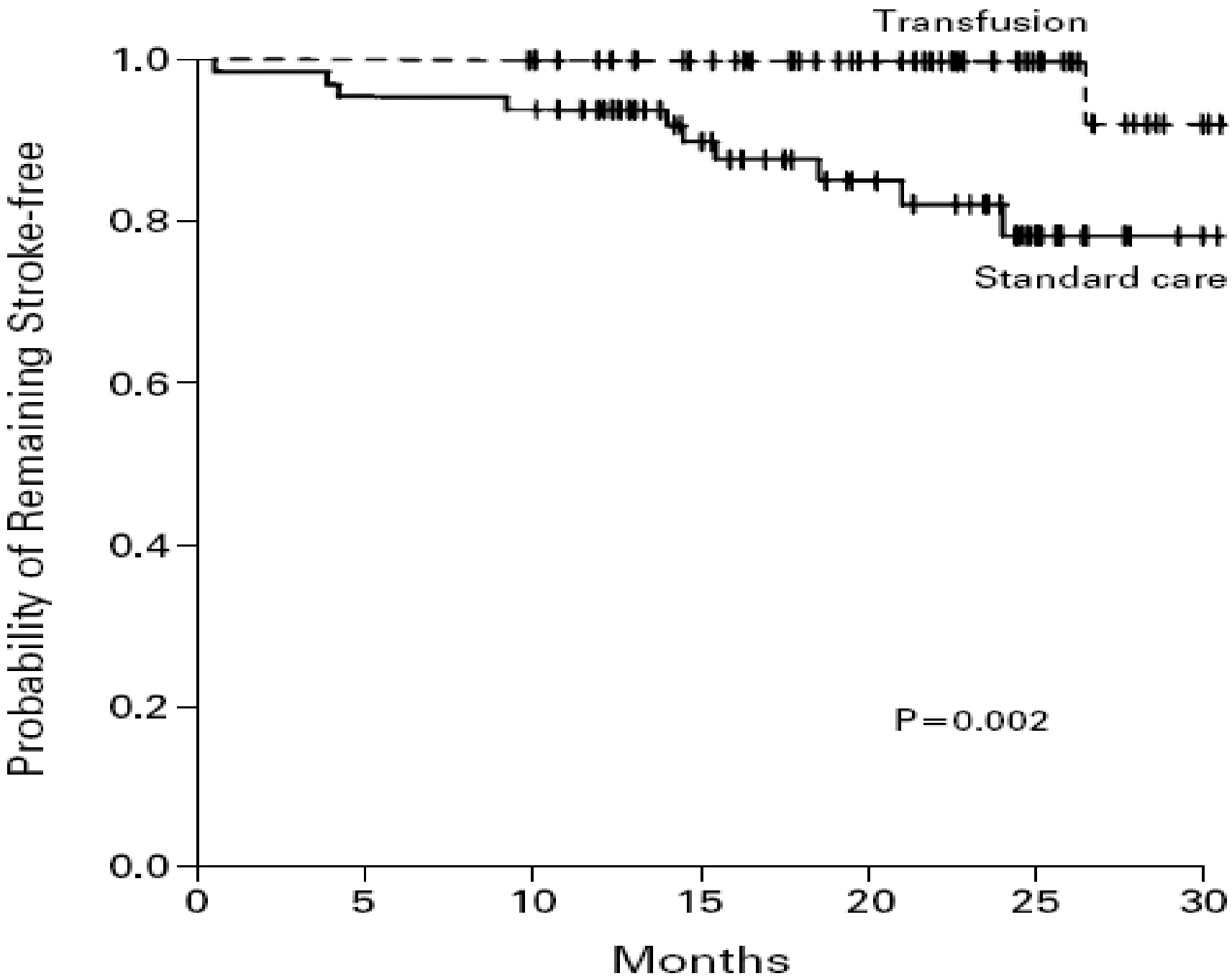


STOP Study halted prematurely in 1997

NIH recommends that all children with SCD should be screened for stroke risk using TCD; those at high risk should receive transfusion therapy.

NIH = National Institutes of Health; SCD = sickle cell disease; STOP = Stroke Prevention Trial in Sickle Cell Anemia; TCD = transcranial Doppler

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


Transfusion
Standard care
P=0.002
Probability of Remaining Stroke-free
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
Months

Primary and Secondary Prevention

a 25 year perspective

- **So TCD screening reduced the NTT (number needed to transfuse to prevent one stroke) from 200 down to 10**

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Primary and Secondary Prevention

a 25 year perspective

- **Screening with TCD starting at age 2 years was/is still recommended for all children with SCD, followed by regular red cell transfusion**

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Primary and Secondary Prevention

a 25 year perspective

- **Despite compelling reduction in stroke risk, acceptance of STOP strategy was limited by concerns about duration and safety of transfusion**

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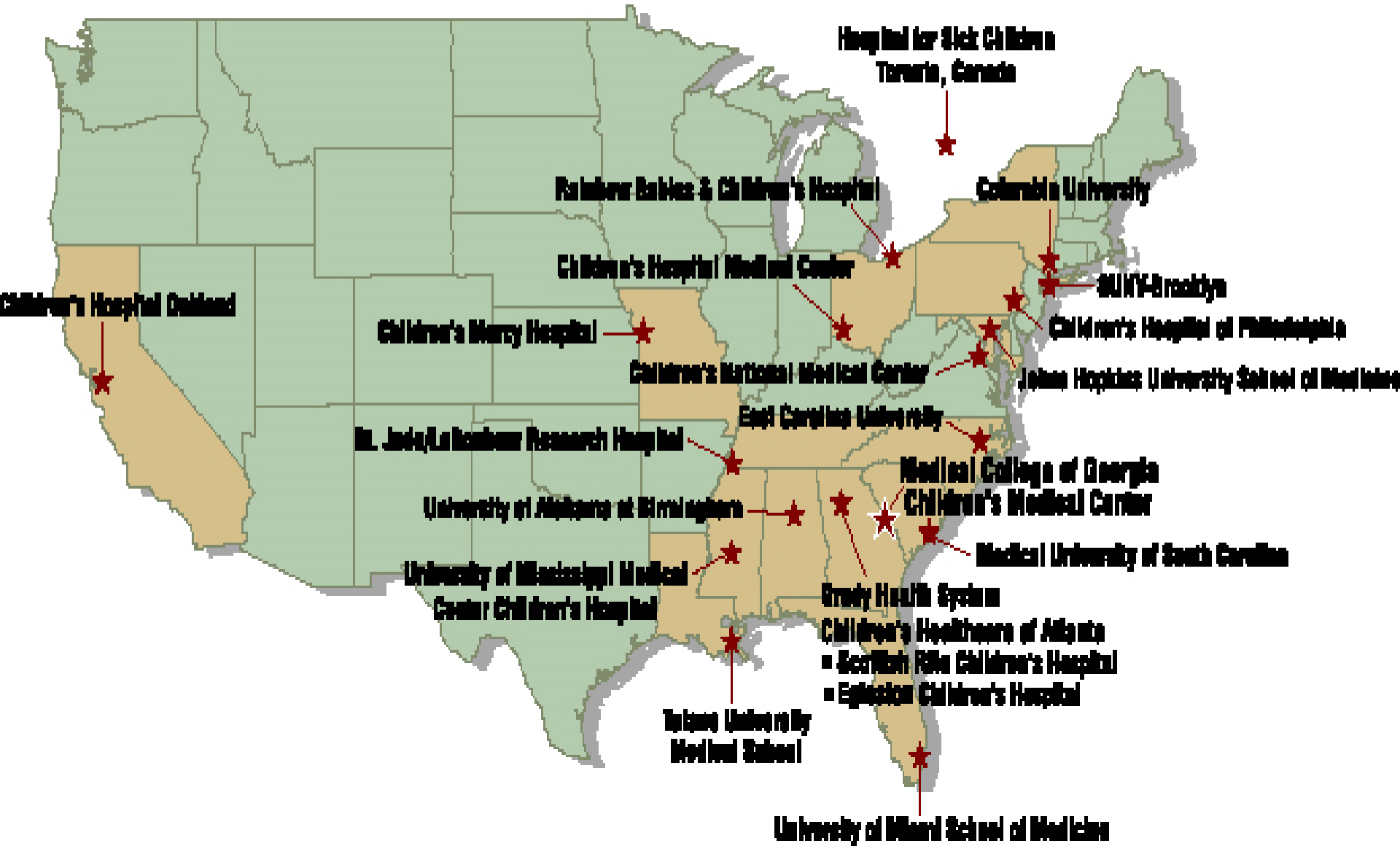
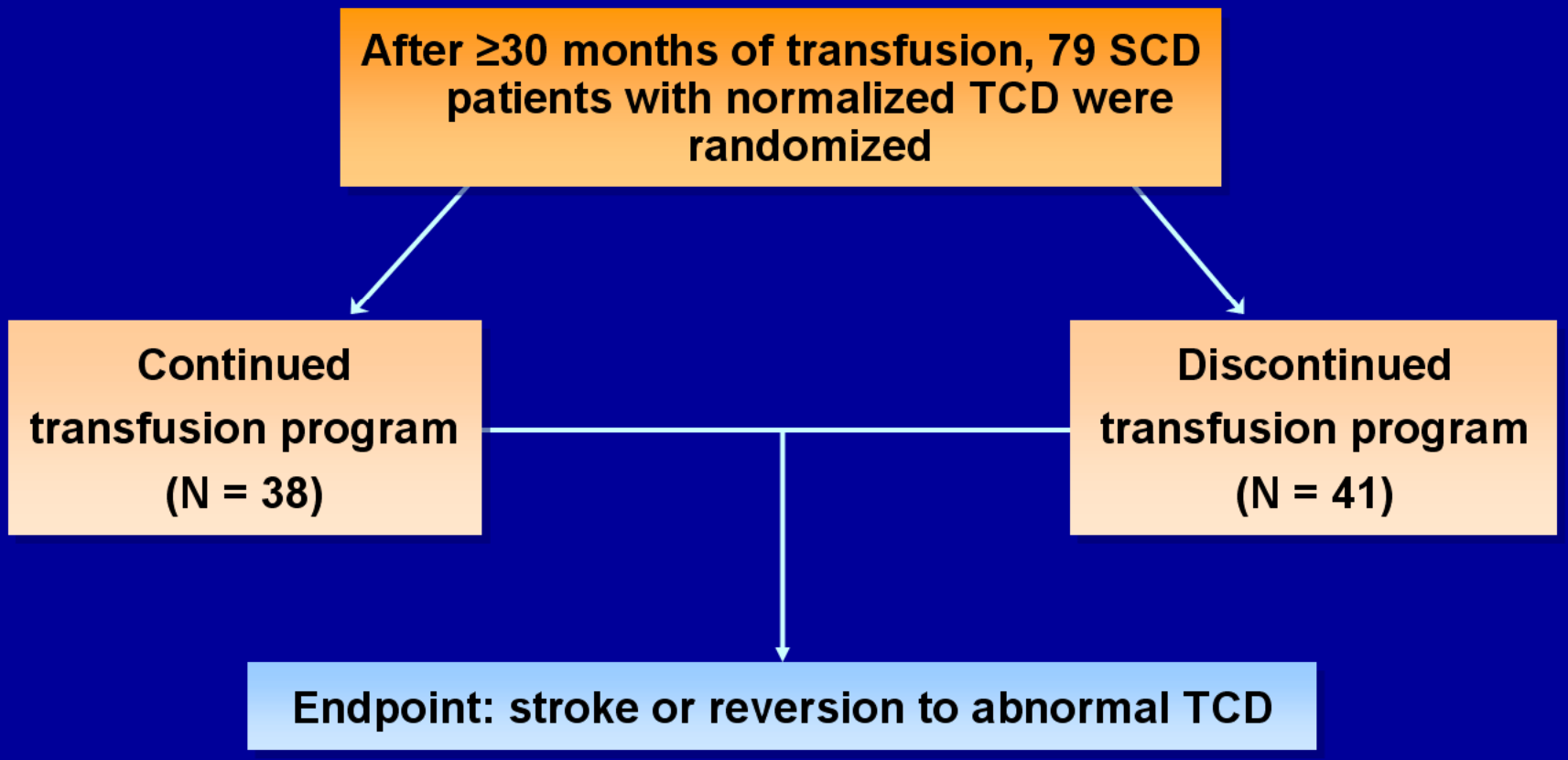
Optimizing Primary Stroke Prevention in Children with Sickle Cell Anemia, or STOP II, Study Sites



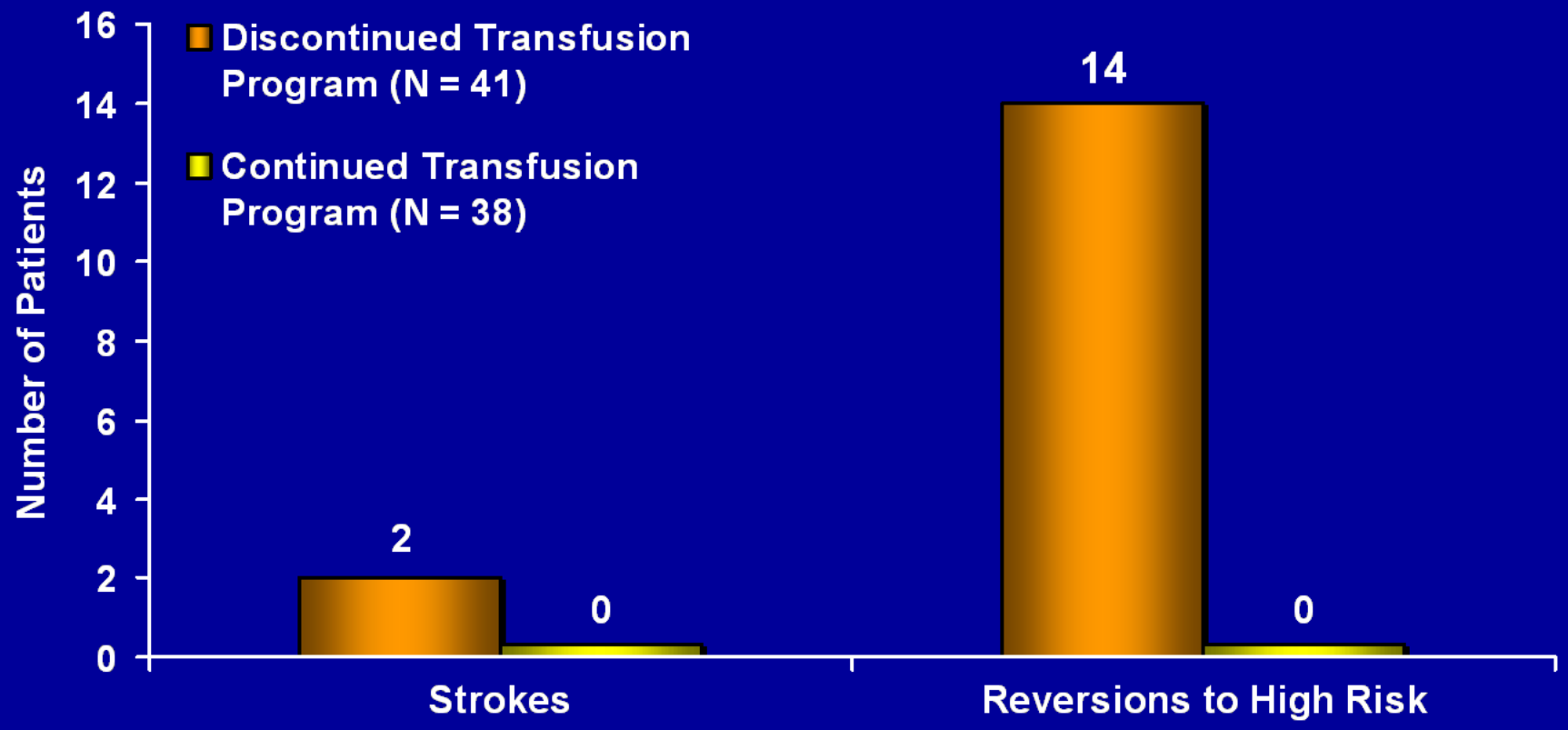
Optimizing Primary Stroke Prevention in Children With Sickle Cell Anemia: STOP 2 Trial Design



SCD = sickle cell disease; STOP = Stroke Prevention Trial in Sickle Cell Anemia; TCD = transcranial Doppler

Adams RJ, et al. *N Engl J Med.* 2005;353:2769-2778.

STOP 2 Trial Results



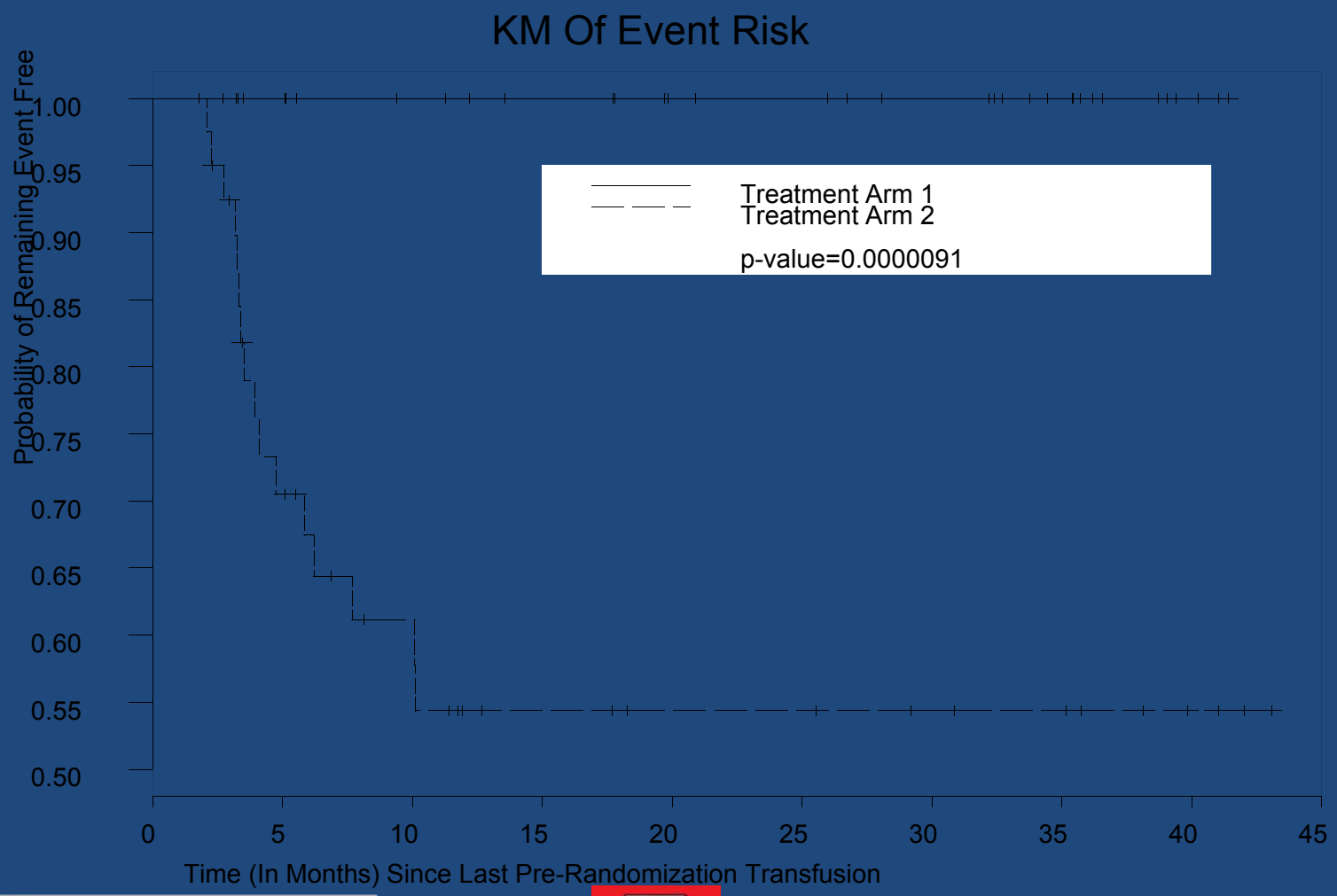
STOP 2 Trial halted prematurely in 2004

NIH recommends that transfusions be continued indefinitely in children with SCD at high risk for stroke

NIH = National Institutes of Health; SCD = sickle cell disease; STOP = Stroke Prevention Trial in Sickle Cell Anemia

Adams RJ, et al. *N Engl J Med.* 2005;353:2769-2778.

KM time to Endpoint



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Primary and Secondary Prevention

a 25 year perspective

- What STOP I and STOP II proved
  - TCD is reliable, valid, and identifies a high-risk cohort for overt stroke (10%/year if untreated)
  - transfusion is highly effective for stroke prevention and has other beneficial effects
  - most children with velocity 200–230 cm/s have minimal stenosis on MRA and transfusion brings TCD down often to < 170 cm/s
  - most children with velocity > 250 cm/s have abnormal MRA and do not normalize on transfusion

MRA, magnetic resonance angiography.

Adams RJ, et al. N Engl J Med. 2005;353:1626-1635.

Primary and Secondary Prevention

a 25 year perspective

- What STOP I and STOP II showed
  - strokes were observed in cases where the last MRA was normal
  - transfusion may fail to prevent stroke in cases with advanced arterial disease
  - hundreds of transfusions were given with lower alloimmunization rates (than in the past) and no hepatitis C infection or serious transfusion reactions were observed

Adams RJ, et al. N Engl J Med. 2005;353:1-13

Primary and Secondary Prevention
a 25 year perspective

- What STOP I and STOP II did not tell us
  - the optimal TCD screening strategy
  - whether or not MRI and MRA have independent contributions to risk after TCD is factored in (confounding present)
  - why is transfusion so effective (how does it work)?
  - would a more liberal HbS target be just as effective as that used in STOP?
  - does this strategy affect brain haemorrhage rates?
  - when, if ever, can transfusion be safely stopped?

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Primary and Secondary Prevention

a 25 year perspective

- What STOP I and STOP II showed
  - whatever is driving stroke risk does not go away, even with prolonged transfusion
  - when transfusion is stopped, high-risk stroke often returns in a few months
  - we have to keep searching for answers to what is driving the stroke risk

Adams RJ, et al. N Engl J Med. 2005; 353:1-13

Primary and Secondary Prevention

a 25 year perspective

- My view is the most important indicator of what happens after transfusion is initiated is the stage of the arterial disease (TCD velocity) when intervention starts
- TCD---early and often to detect newly incident cases is key to prevention of moyamoya

Adams RJ, et al. N Engl J Med. 2005;353:1626-35

Stroke: Evolving Concepts

- The earliest "lesion" is physiologic not morphologic (which is why TCD works well)
  - Cerebral blood flow dysregulation
  - Departure from "normal for SCD hyper CBF" to very high CBF
  - Transcranial Dopper reflects the increased flow
  - At 200-220 cm/sec MRA does not show stenosis
  - At > 250 cm/sec MRA shows marked narrowing
  - Marked asymmmetry indicates morphology change

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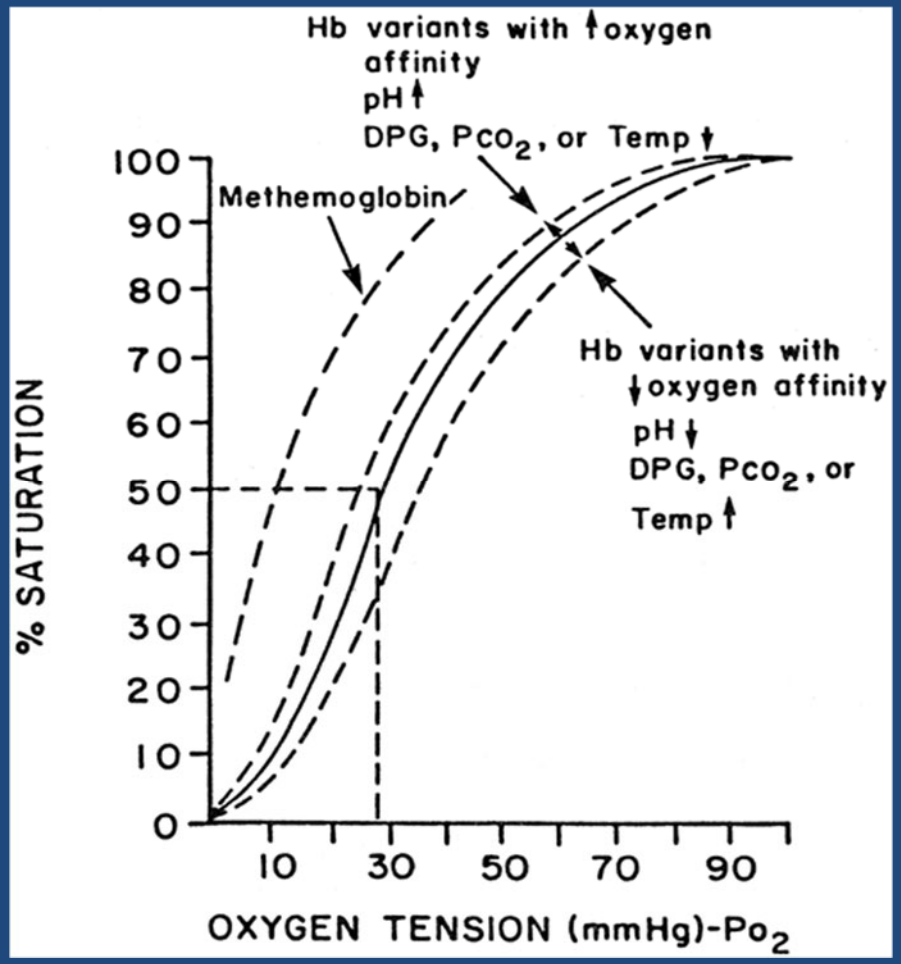
Evolving Concepts

Effect of NO Depletion?

- 1) no simple relationship
- 2) NO administration does not change CBF (CBV)
- 3) Vasoconstriction decreases not increases CBF
- 4) **<u>Critical factor probably is shifting the P50 curve to the left--- Methemoglobin?</u>**



Ancillary studies to STOP/STOP II

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STOP II

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- **Hyacinth I. Hyacinth**, Beatrice E. Gee, Jenifer H. Voeks, Robert J. Adams, Jacqueline M. Hibbert. Frequent red cell transfusions reduced vascular endothelial activation and thrombogenicity in children with sickle cell anemia and high stroke risk. *American Journal of Hematology. (Under review).*
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Primary and Secondary Prevention

a 25 year perspective

- ***With early (age two years) and repeated TCD screening, followed by intervention, we can envision a marked reduction in stroke and severe intracranial arterial disease in SCD***
- ***Is this strategy working?***

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Declining stroke rates in Californian children with sickle cell disease

Heather J. Fullerton, Robert J. Adams, Shoujun Zhao, and S. Claiborne Johnston

- A Clinical Alert from NHLBI was sent to 5000 US physicians September 1997 regarding STOP
- STOP results published in 1998
- STOP may be having an impact
  - Blood 2004

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Stroke in Sickle Cell Disease

Transcranial Doppler Ultrasonography and Prophylactic Transfusion Program Is Effective in Preventing Overt Stroke in Children with Sickle Cell Disease

Henrietta Enninful-Eghan, MPH, Reneé H. Moore, PhD, Rebecca Ichord, MD, Kim Smith-Whitley, MD, and Janet L. Kwiatkowski, MD, MSCE

Objective To assess the impact of our transcranial Doppler ultrasonography (TCD) program on the incidence of first stroke and the rate of transfusion for stroke prevention in children with sickle cell disease.

Study design In this single-institution, retrospective study, we compared the incidence of stroke and of transfusion for stroke prevention in 475 patients observed in the 8-year period before instituting TCD screening with the rate in 530 children in the 8-year period after.

Results The incidence of overt stroke in the pre-TCD period was 0.67 per 100 patient-years, compared with 0.06 per 100 patient-years in the post-TCD period ($P < .0001$). Of the 2 strokes in the post-TCD period, 1 occurred in a child too young for the screening protocol, and 1 occurred in a child with high velocities solely in the anterior cerebral arteries. The rate of transfusion therapy for stroke prevention increased from 0.67 per 100 patient-years to 1.12 per 100 patient-years since instituting our program ($P = .008$).

Conclusions Our program has been successful in reducing the rate of first overt stroke, but with increased use of transfusion. Additional modifications to screening might further reduce the risk of first stroke, and studies of alternative treatments may be beneficial. *(J Pediatr 2010;* ■:■-■*).*

Incidence of Stroke

	Pre-TCD	Post-TCD
Number	475	530
Person-years of follow-up	3,137	3,578
Overt stroke	21	2
- Ischemic	19	2
- Hemorrhagic	2	0
Other neuro event	3	6
Indeterminate	2	1
Incidence rate - overt stroke (per 100 pt yr)	**0.67**	**0.06***

* *p* value < 0.001

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Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort

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- **Newborn cohort follow up 217 children**
- **Early and yearly TCD since 1992**
- **Transfusion for abnormal TCD/or MRA**
- **Cumulative age 18 risk of overt stroke < 2% (much lower than 11% from CSSCD)**

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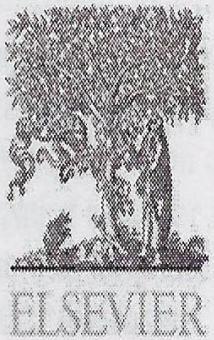

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Trends in comorbid sickle cell disease among stroke patients

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ABSTRACT

Background: Stroke is a major complication of sickle cell disease (SCD). In an era of chronic red cell transfusions for stroke prophylaxis in children and greater life expectancy, nationwide data on stroke rates among pediatric and adult patients with SCD are scarce. We evaluated recent time trends in stroke hospitalization among children (0–17 years) and adults (>17 years) with SCD in the United States.

Methods: Data were obtained from the Nationwide Inpatient Sample. Pediatric (n=26,380) and adult

Primary and Secondary Prevention

a 25 year perspective

Ovbiagele and Adams (2011) examined data from hospitalized stroke –National Inpatient Sample—between 1997 and 2006 looking at time trends related to stroke and SCD

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Primary and Secondary Prevention

a 25 year perspective

- **Pediatric strokes with co morbid SCD represented 8.7% of the 1997 (pre STOP) sample but only 4.8% in 2006 (p=0.04)**
- **In contrast adults stroke patients with SCD were 0.3% of all hospitalized stroke in 1997 vs .5% in 2006 (p-0.01)**

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ONLINE FIRST

Changing Ethnic Disparity in Ischemic Stroke Mortality in US Children After the STOP Trial

Laura L. Lehman, MD; Heather J. Fullerton, MD, MAS

Importance: A prior report showed higher stroke mortality in US black children compared with white children (1979-1998), a disparity likely due in part to sickle cell disease, which leads to a high risk of childhood ischemic stroke. We hypothesized that this disparity has diminished since the publication of the Stroke Prevention Trial in Sickle Cell Anemia (STOP trial) in 1998 demonstrating the efficacy of long-term blood transfusions for primary stroke prevention.

Objective: To evaluate the demographics and secular trends in mortality from ischemic and hemorrhagic stroke (as a primary cause of death) in US children (<20 years) and determine if there has been a decrease in the disparity between white and black children since the publication of the STOP trial in 1998.

Design: We used death certificate data from the National Center for Health Statistics, 1988 through 2007.

Setting: United States.

Participants: Children who died in 1988 through 2007 in the United States.

Intervention: Publication of the STOP trial.

Main Outcome Measures: Incidence rate ratios were calculated as the measure of relative risk.

Results: Among 1.6 billion person-years of US children (1988-2007), there were 4425 deaths attributed to stroke, yielding an average of 221 deaths per year; 20% were ischemic; 67%, hemorrhagic; and 12%, unspecified. The relative risk of ischemic stroke mortality for black vs white children dropped from 1.74 from 1988 through 1997 to 1.27 from 1998 through 2007. The ethnic disparity in hemorrhagic stroke mortality, however, remained relatively stable between these 2 periods: black vs white relative risk, 1.90 (1988-1997) and 1.97 (1998-2007).

Conclusions and Relevance: The excess risk of death from ischemic, but not hemorrhagic, stroke in US black children has decreased over the past decade. This may be related to the implementation of an effective ischemic stroke prevention strategy for children with sickle cell disease.

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Primary and Secondary Prevention

a 25 year perspective

- Strategy is clearly working but are there alternatives to red cell transfusion?

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Hydrea for Primary Stroke Prevention

- TWITCH study is now testing whether HU can maintain the stroke prevention obtained after at least 12 months of transfusion after a positive TCD
- RCT with a TCD velocity endpoint
- Similar to STOP II but uses HU instead of no therapy
- Midway through the study now

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Primary and Secondary Prevention

a 25 year perspective

Primary Prevention in Children STOP Protocol HU ?	Secondary Prevention in Children
Primary Prevention in Adults	Secondary Prevention in Adults

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Primary and Secondary Prevention

a 25 year perspective

- Regular red cell transfusion became the standard of care in 1980's without a trial and is now routine. It is probably very effective
- Does HU work?

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SWiTCH: aims and study design

Aim: to compare 30 months of HU and phlebotomy (alternative) with transfusions and deferasirox (standard) for the prevention of secondary stroke and reduction of transfusional iron overload

161 paediatric patients with sickle cell anaemia (83 male, 78 female), documented stroke, and iron overload enrolled in SWiTCH (US10)

134 patients randomized 1:1

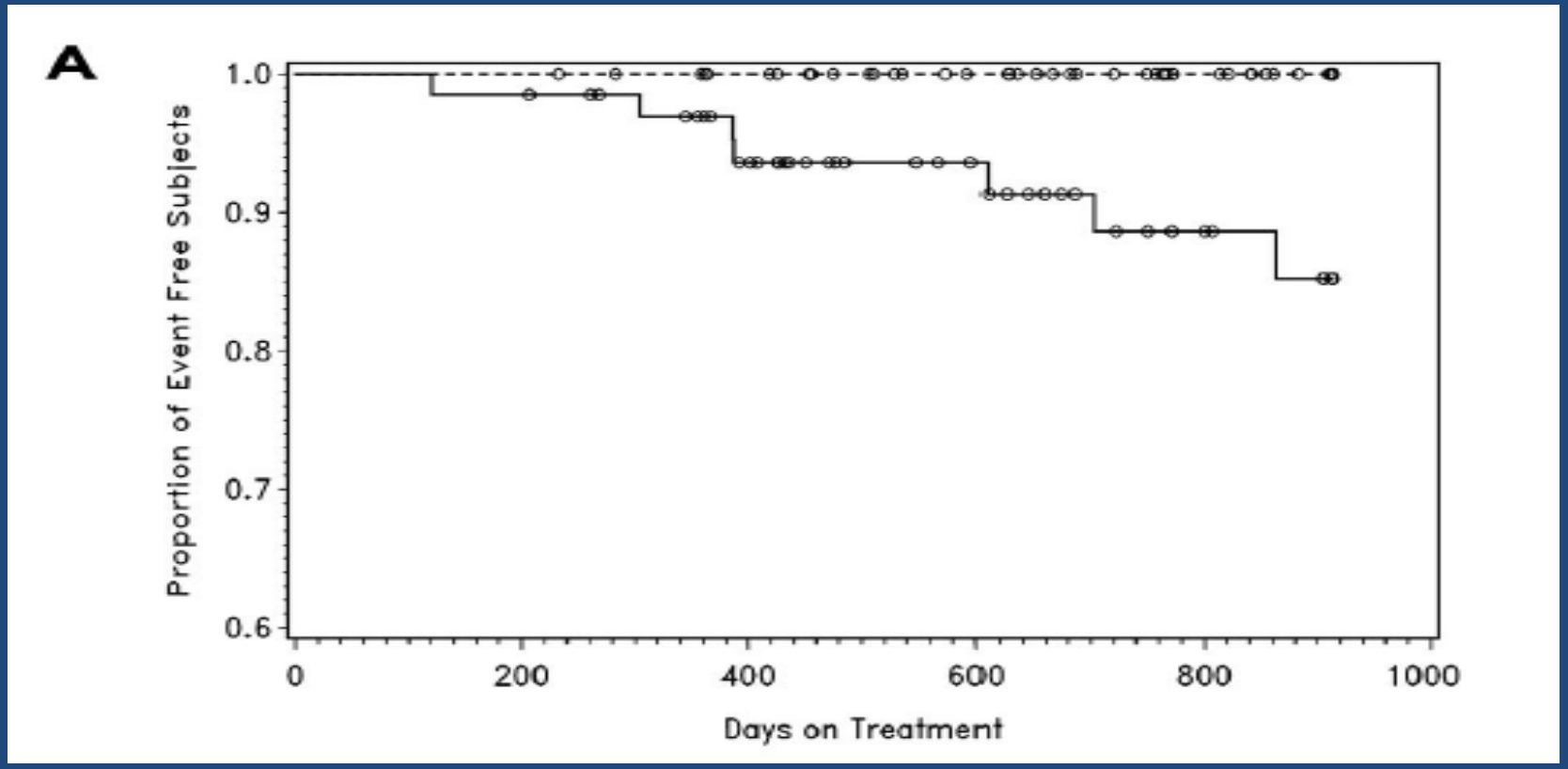
Alternative arm
67 patients
HU + phlebotomy

Standard arm
67 patients
Transfusions + deferasirox

Prediction: increased occurrence of recurrent stroke events in alternative arm counterbalanced by better management of iron overload with phlebotomy

Ware RE, Helms RW. Blood. [Epub ahead of print 2012 Feb 7]

SWITCH: K-M stroke



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Primary and Secondary Prevention

a 25 year perspective

- SWITCH halted by DSMB in 2010 when liver iron endpoint was not sufficiently better to balance the stroke risk in HU arm (10% on HU vs 0% with continuation of transfusion)
- TCD was used at baseline for correlation to MRA but otherwise played no role in SWITCH

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Primary and Secondary Prevention

a 25 year perspective

Primary Prevention in Children STOP Protocol HU ?	Secondary Prevention in Children Transfusion BMT (probably)
Primary Prevention in Adults	Secondary Prevention in Adults

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Primary and Secondary Prevention

a 25 year perspective

Primary Prevention in Children	Secondary Prevention in Children
Primary Prevention in Adults NO DATA	Secondary Prevention in Adults NO DATA

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Brain Magnetic Resonance Imaging Abnormalities in Adult Patients With Sickle Cell Disease

Correlation With Transcranial Doppler Findings

Gisele Sampaio Silva, MD, PhD; Perla Vicari, MD, PhD; Maria Stella Figueiredo, MD, PhD; Henrique Carrete Junior, MD, PhD; Marcos Hideki Idagawa, MD; Ayrton Roberto Massaro, MD, PhD

Background and Purpose—Brain imaging abnormalities were reported in up to 44% of children with sickle cell disease (SCD). The prevalence of neuroimaging abnormalities in adult patients with SCD and their relationship to transcranial Doppler is still unclear. Our objectives were to study the frequency of MRI and MR angiography abnormalities in adults with SCD and to define what transcranial Doppler velocities are associated with intracranial stenoses detected by MR angiography.

Methods—We examined all adult patients (>16 years) with SCD followed in the hematology outpatient clinic at our university hospital with MRI, MR angiography, and transcranial Doppler.

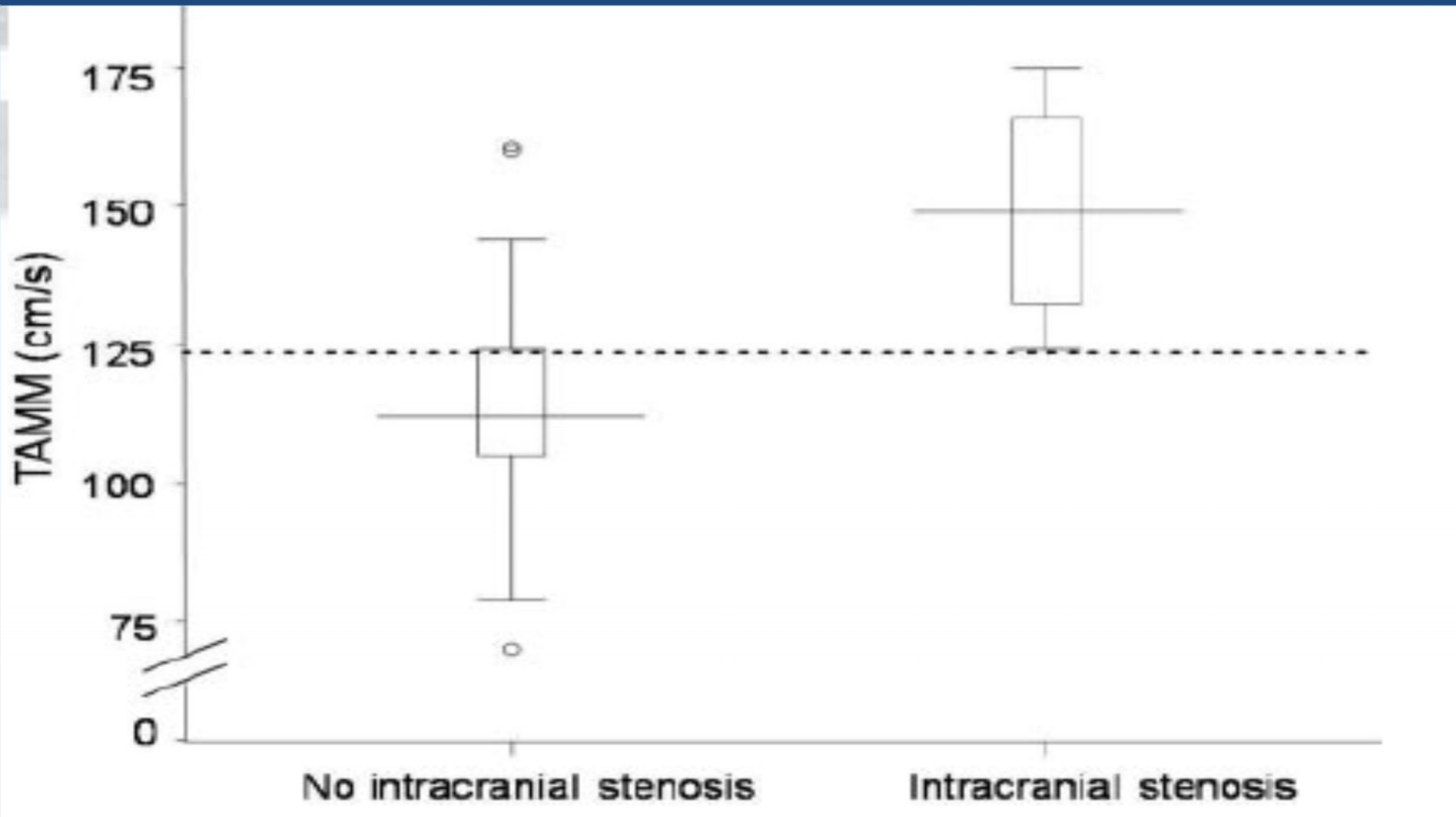
Results—We evaluated 50 patients. The overall prevalence of MRI abnormalities was 60%. Abnormal MRI findings were more frequent when vessel tortuosity or stenoses were present on MR angiography ($P<0.01$). Patients with intracranial stenoses had significantly higher time-averaged maximum mean velocities ($P=0.01$). A time-averaged maximum mean velocity of 123.5 cm/s allowed the diagnosis of middle cerebral artery or internal carotid artery intracranial stenosis with sensitivity of 100% and specificity of 73% with an area under the receiver operator characteristic curve of 0.91 (CI, 0.79 to 1.00).

Conclusions—The frequency of brain imaging abnormalities detected by MRI/MR angiography in adults with SCD was higher than that described for children. Transcranial Doppler velocities in adult patients with intracranial stenoses were lower than those described for the pediatric population with SCD. (*Stroke*. **2009;40:00-00.**)

Key Words: magnetic resonance imaging ■ sickle cell anemia ■ stroke ■ transcranial Doppler ultrasonography

American Stroke Association

Adults with SCD



Primary and Secondary Prevention

a 25 year perspective

- Reduction in stroke in children is now a reality but these gains may be lost if we cannot continue stroke prevention into adulthood

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Primary and Secondary Prevention

a 25 year perspective

- Important brain issues exist across the spectrum of adults with SCD
- Adult SCD neurological problems including stroke are increasing
- “neurologically intact” adults will not score on tests as well as their peers without SCD even if no “silent” brain lesions on MRI

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JAMA. 2010 May 12; 303(18): 1823–1831. doi:10.1001/jama.2010.562.

Neuropsychological Dysfunction and Neuroimaging Abnormalities in Neurologically Intact Adults With Sickle Cell Anemia

Elliott P. Vichinsky, MD, Lynne D. Neumayr, MD, Jeffrey I. Gold, PhD, Michael W. Weiner, MD, Randall R. Rule, PhD, Diana Truran, BA, Jeffrey Kasten, BA, Barry Eggleston, MS, Karen Kesler, PhD, Lillian McMahon, MD, Eugene P. Orringer, MD, Thomas Harrington, M Karen Kalinyak, MD, Laura M. De Castro, MD, Abdullah Kutlar, MD, Cynthia J. Rutherford, MD, Cage Johnson, MD, Joel David Bessman, MD, Lanetta B. Jordan, MD, MPH, and F. Daniel Armstrong, PhD [on behalf of for the Neuropsychological Dysfunction and Neuroimaging Adult Sickle Cell Anemia Study Group]

Primary and Secondary Prevention

a 25 year perspective

Research needs to be initiated now!!!!

It took 12 years from beginning TCD studies to the publication of STOP clinical trial results ---I did my first TCD in 1986—I was young---I had hair ☺

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Primary and Secondary Prevention

a 25 year perspective

- Hierarchy of Clinical Research
  - Case reports
  - Retrospective chart reviews ("prevalent cases")
  - Prospective cohort studies ("incident cases")
  - Randomized clinical trials (RCT's test treatments)
    - "Phase 4 Open label" studies
  - Critical to have a "research pipeline" and a long range perspective

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Primary and Secondary Prevention

a 25 year perspective

- Good compassionate clinical care is important to change the outcome of the individual patient
- Good clinical research is important to improve the outcome off an entire group of patients
- RCT's still give the most valuable data

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Primary and Secondary Prevention

a 25 year perspective

- Opportunities for Brazil
  - Cooperative environment among 3+ centers
  - More continuity between pediatric and adult medical services
  - Young researchers and potential researchers
  - "Human resources" are the most critical part

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Primary and Secondary Prevention

a 25 year perspective

- Some potential studies
  - 1) long term follow up of all TCD + cases
  - 2) Chart review of all neurologic cases among adults with SCD in your centers to identify rates
  - 3) Prospective cohort study of all adult patients with TCD, TRV, GFR, etc and clinical follow up
  - 4) Extend HU research (participate with US)
  - 4) Large (simple) trials of adjunctive therapies such as aspirin, nutrition and anti-inflammatory agents or statins

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Primary and Secondary Prevention

a 25 year perspective

- One idea would be to form a close intra- national collaborative which could negotiate with NIH as a group to enhance Brazilian participation in RCT's and increase enrollment in these studies

- Another would be an assessment of current and needed clinical "research infrastructure"

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Primary and Secondary Prevention

a 25 year perspective

- While the cutting edge science is important to advance our knowledge it is the simple widely applicable tests/treatments that have the biggest clinical impact, especially in areas of low resources (e g Africa)

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The “Ronald Reagan Endpoint”

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Some of the STOP TEAM

Thanks

- To NHLBI, to the coordinators, TCD examiners—especially Judy Luden– site investigators and consultants as well as NERI our Data Center
- Patients and families that participated in STOP and STOP II
- Many dedicated pediatric clinicians caring for these children especially Dr Virgil McKie at MCG—the hematologists made this work possible by taking a chance on a new approach

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Obrigado

Medical University of South Carolina