Treatment of SCD: Bridging the Gap between Efficacy and Effectiveness

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Objectives

- Gain understanding of the current efficacious treatments for SCD
- Recognize the key barriers to implementing these efficacious treatments
- Appreciate health systems changes needed to optimize treatment outcomes for SCD

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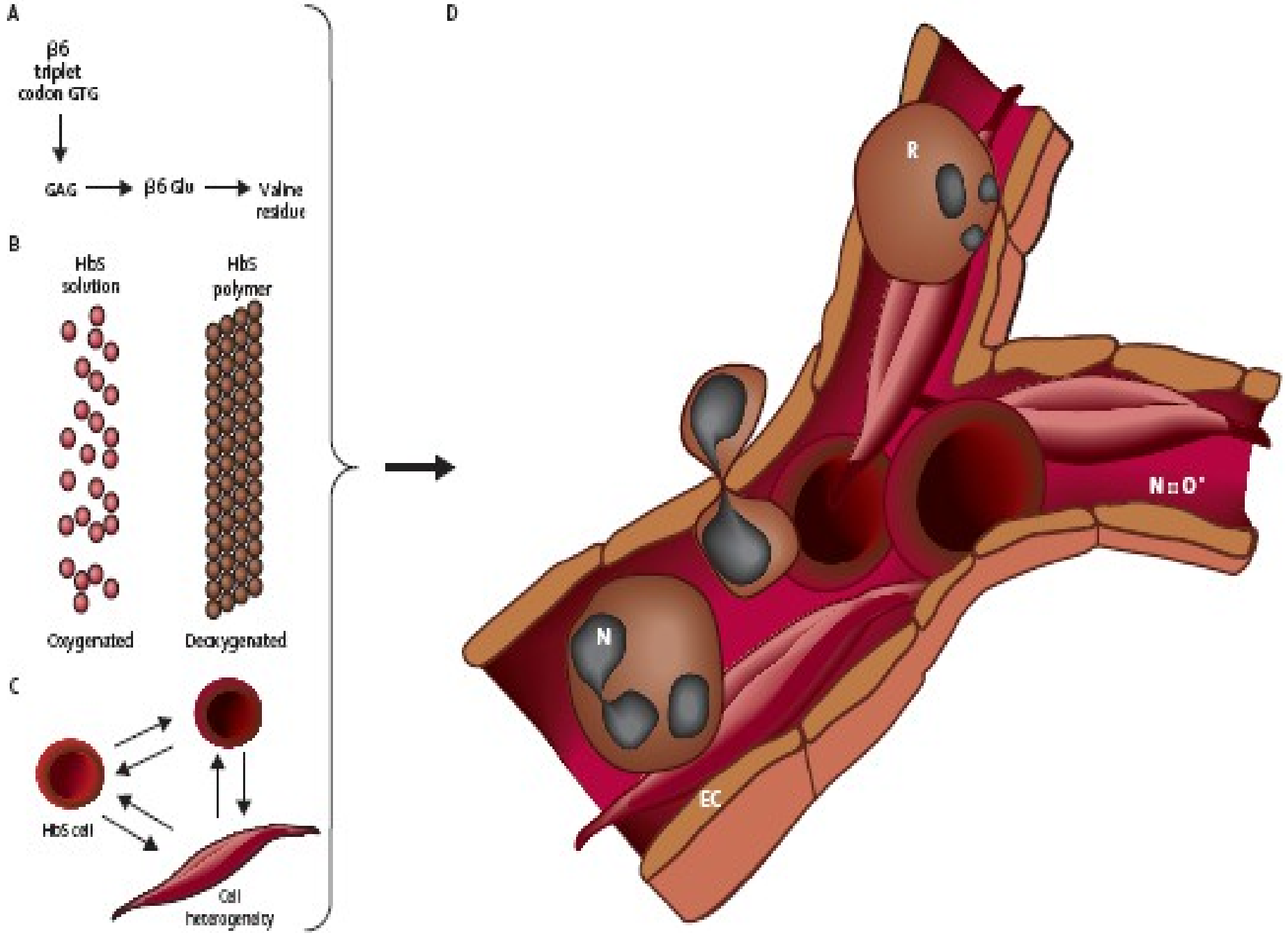
A
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triplet
codon GTG
GAG
β6 Glu
Valine
residue
B
HbS
solution
HbS
polymer
Oxygenated
Deoxygenated
C
HbS cell
Cell
heterogeneity
D
R
N
EC
N□O•

Major RCTs in SCD

- Penicillin prophylaxis in SCD
  - Oral penicillin reduces incidence pneumococcal sepsis
    - Gaston et al. NEJM 1986:314:1593-99
- Prophylactic Penicillin Study II
  - Discontinuation of penicillin prophylaxis can be considered at age 5 yrs
    - Falletta et al. J. Pediatr.1995;127:685-90
- Multicentre Study of Hydroxyurea
  - HU reduces frequency of painful episodes, ACS, transfusions, hospitalizations
    - Charache et al. NEJM.1995;332:317-22

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Major RCTs in SCD

- Preoperative transfusion in SCD
  - Simple Tx to Hb 100 g/L is as effective as exchange Tx to reduce Hb S to 30%
    - **Vichinsky et al. NEJM 1995;333:206-13**
- Prophylactic transfusion in pregnancy
  - Prophylactic Tx to Hb 100 g/L vs. Tx to Hb < 60 g/L or for emergent situations did not improve obstetric or perinatal outcome
    - **Koshy et al. NEJM 1988;319:1447-52**

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Major RCTs in SCD

- Stroke prevention in SCD (STOP I)
  - Children at risk of stroke based on abnormal TCD velocity benefit from prophylactic transfusions
    - Adams et al. NEJM 1998;3395-11
- Optimizing primary stroke prevention in SCD (STOP II)
  - Prophylactic transfusions for patients with high-risk TCD cannot be stopped safely at 30 months
    - Adams et al. NEJM 2005;353:5-11

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Major RCTs in SCD

- Hydroxyurea in very young children with SCA: a multicentre, randomized, controlled trial (BABY HUG)
  - On the basis of the safety and efficacy data from this trial, hydroxyurea can now be considered for all very young children with sickle-cell anaemia
    - **Wang et al. The Lancet 2011; 377(9778):1663-1672.**
- Stroke with Transfusions Changing to Hydroxyurea (SWiTCH)
  - Transfusions and chelation still remain a better way to manage children with SCA, stroke and iron overload
    - **Ware et al. Blood 2012;119(17):3925-3932**

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Major RCTs in SCD

- Controlled Trial of Transfusions for Silent Cerebral Infarcts in Sickle Cell Anemia
  - Recurrent blood transfusions significantly reduces the incidence of the recurrence of cerebral infarcts in children with SCA (6% vs. 14%)
    - **Debaun et al. NEJM 2014;371:699-710**
- Hydroxyurea versus Chronic Transfusion for Maintenance of TCD Velocities in Children with SCA- TWiTCH trial
  - Hydroxyurea can substitute for chronic blood transfusions to maintain TCD velocities and help prevent strokes
    - **Ware et al. The Lancet online Dec 6, 2015**

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Strategies for Management of SCD

- Integrating new preventive care strategies
  - Newborn screening and antibiotic prophylaxis
  - Immunizations
  - Stroke prevention
  - Early recognition of end organ damage
- Management of acute complications
  - Painful episodes
  - Acute chest syndrome
  - Management of infections (hyposplenic state)
  - Multiple organ failure

egies to modify disease outcomes

- Hydroxyurea therapy and other mechanistic approaches

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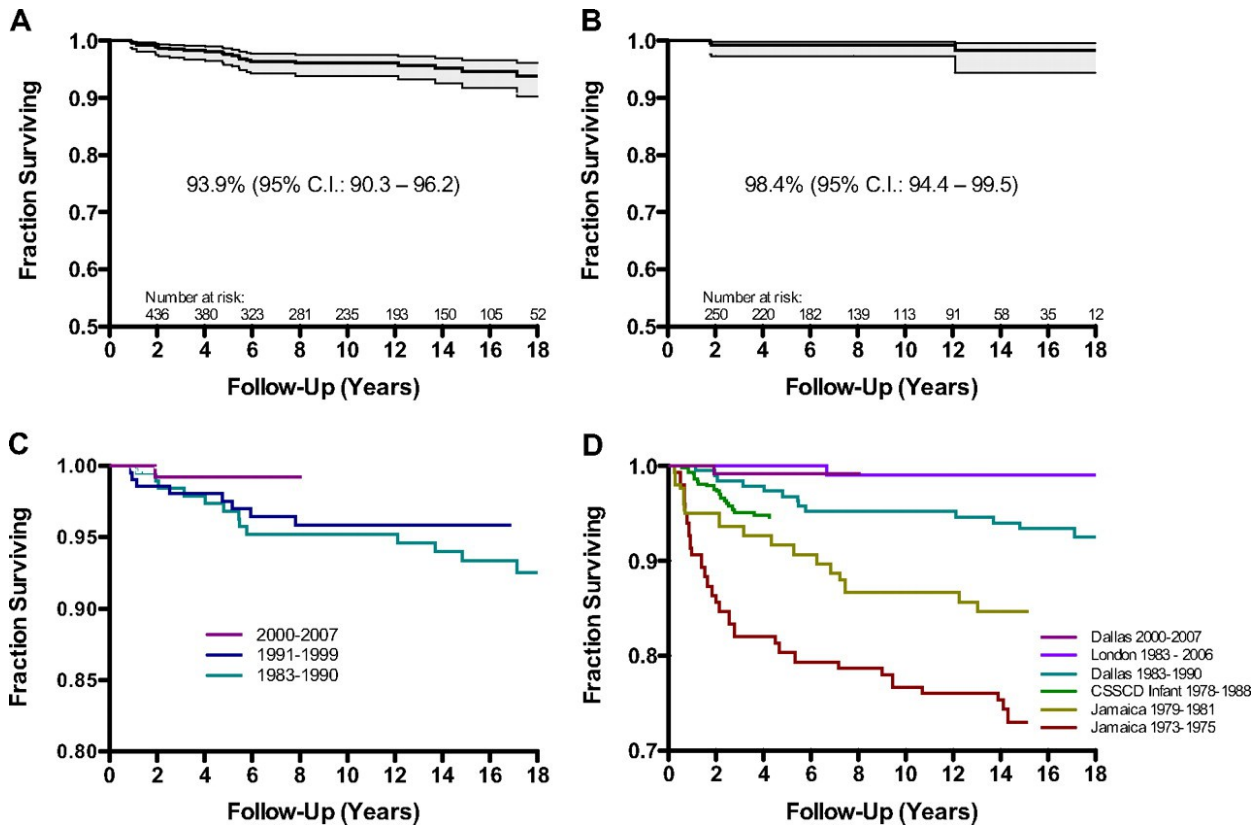
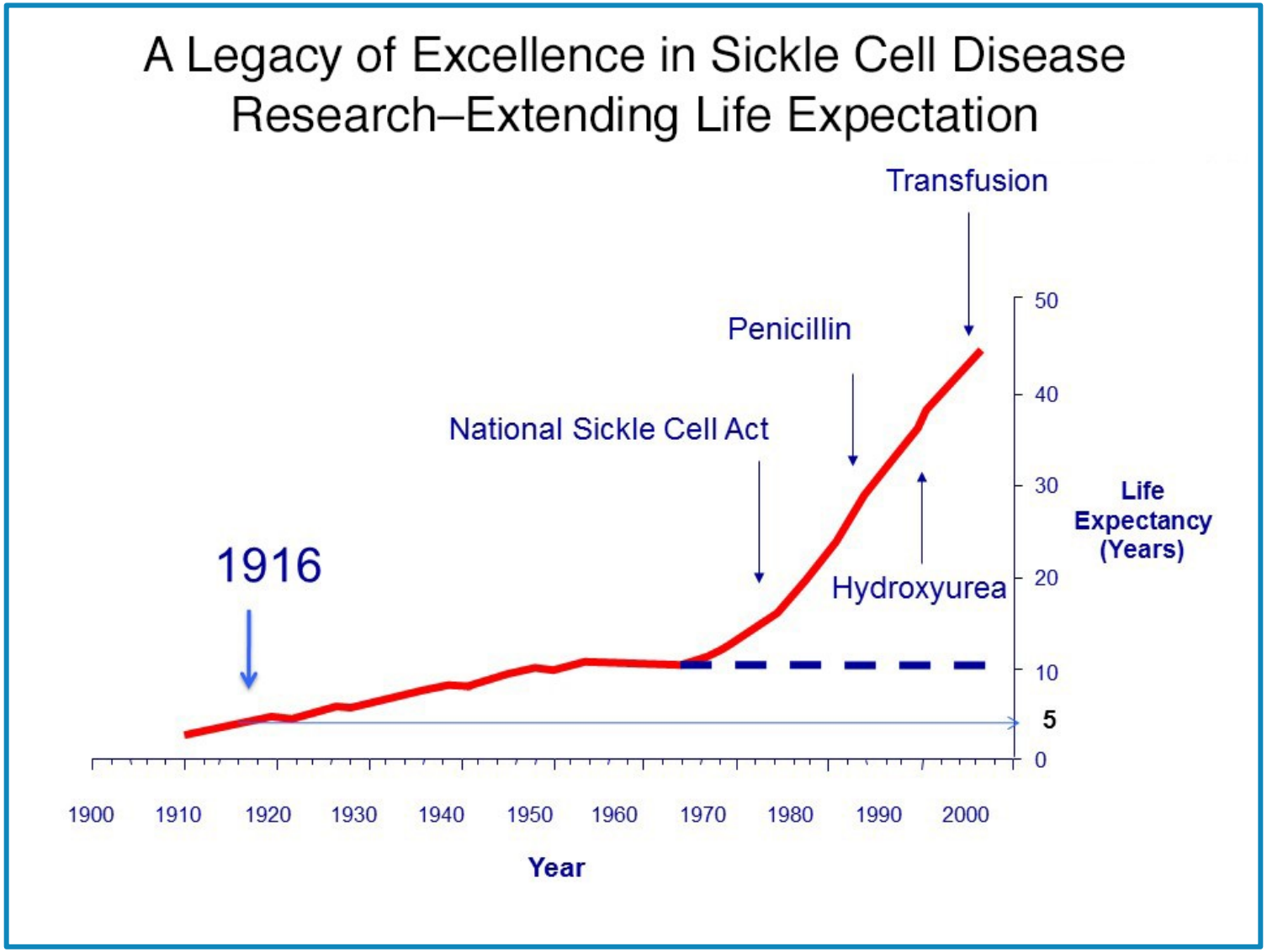
Survival of children with sickle cell disease

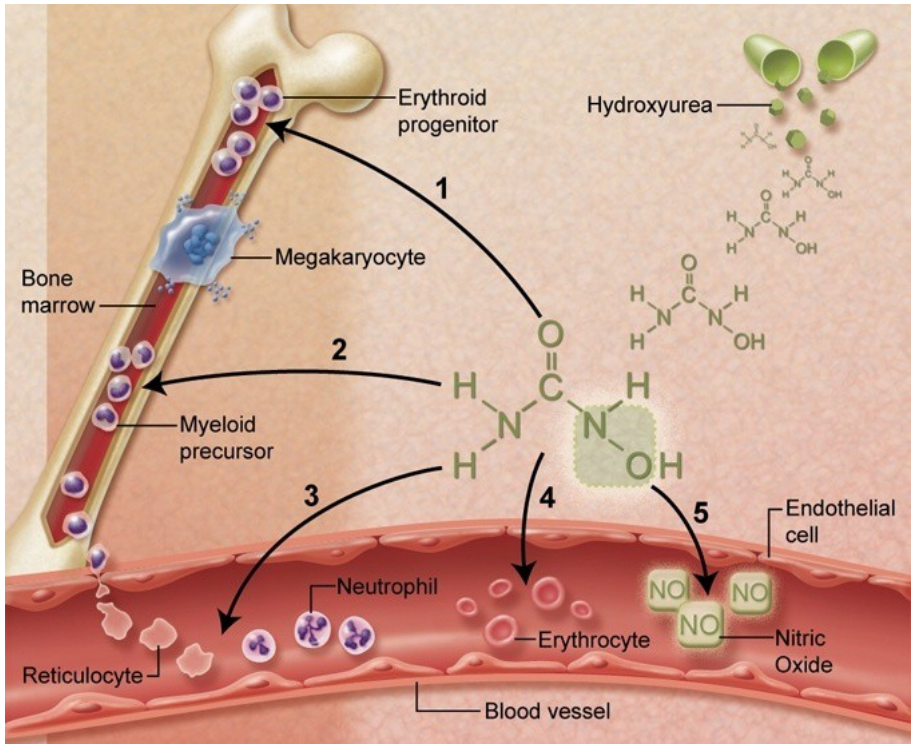


Quinn, C. T. et al. Blood 2010;115:3447-3452

SCD in USA: Improving Survival

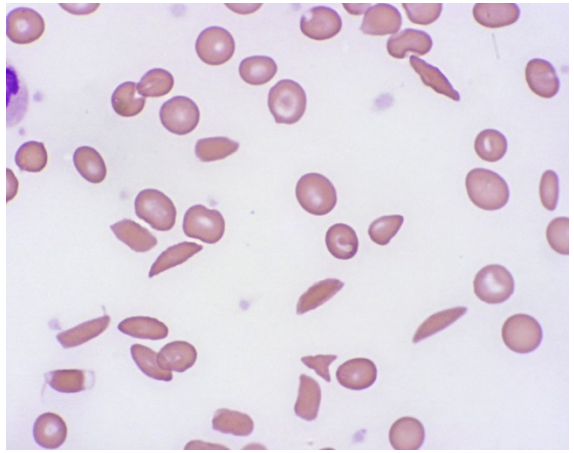


Hydroxyurea for Sickle Cell Anemia
Multiple Potential Mechanisms of Action

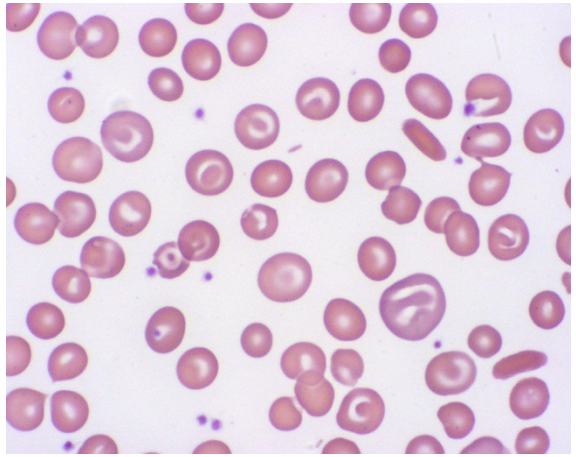


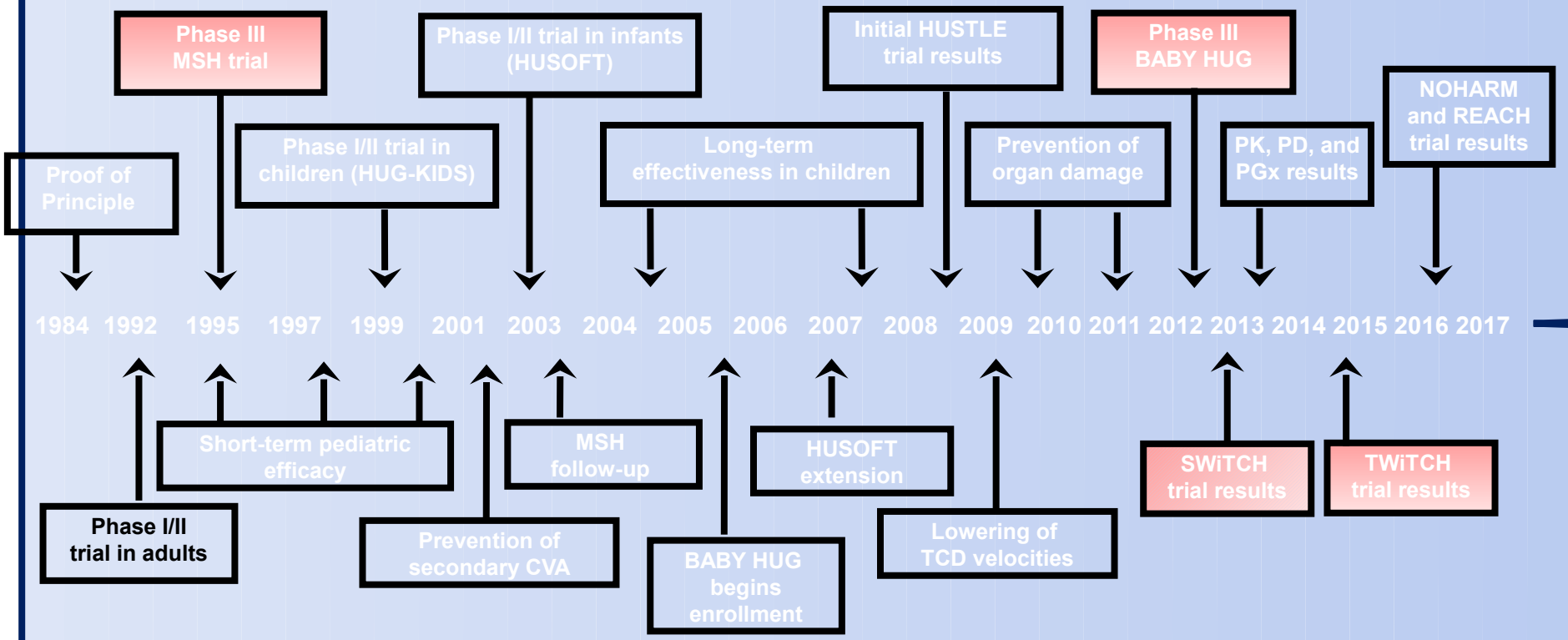
Ware, Blood 2010

Before Hydroxyurea



Taking Hydroxyurea




Proof of Principle
Phase III MSH trial
Phase I/II trial in children (HUG-KIDS)
Phase I/II trial in infants (HUSOFT)
Long-term effectiveness in children
Initial HUSTLE trial results
Prevention of organ damage
Phase III BABY HUG
PK, PD, and PGx results
NOHARM and REACH trial results
1984 1992 1995 1997 1999 2001 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
Phase I/II trial in adults
Short-term pediatric efficacy
Prevention of secondary CVA
MSH follow-up
BABY HUG begins enrollment
HUSOFT extension
Lowering of TCD velocities
SWiTCH trial results
TWiTCH trial results

Clinical Outcomes: BABY HUG compared to MSH

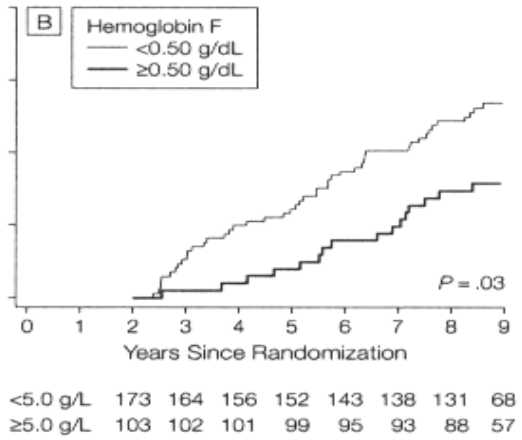
	BABY HUG†			MSH		
	HU	PL	p-value	HU	PL	p-value
Patients	96	97		152	147	
Pain	177	372	**0.002**	2.5/y	4.5/y	**<0.001**
Acute Chest	8	27	**0.017**	25	51	**<0.001**
Dactylitis	24	123	<0.001	—	—	—
Hospitalized*	232	321	**0.050**	1.0/y	2.4/y	**<0.001**
Transfusion‡	35	60	**0.033**	48	73	**<0.001**

†data indicate no. of episodes
*in BABY HUG, all hospitalizations; in MSH, hospitalization for pain only
‡in BABY HUG, no. of transfusions; in MSH, no. of pts. receiving transfusion

Increased Survival with Hydroxyurea

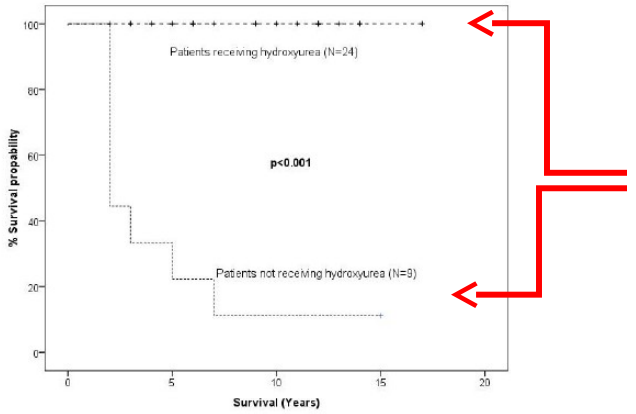
Steinberg et al., JAMA 2003

- 9 years of follow-up
- 40% reduction in mortality



Voskaridou et al., Blood 2009

- 17-year single center trial
- 131 patients (34 HbSS)
- Significant reduction in mortality
  - SS > S/β0-thal > S/β+-thal



Steinberg et al., Am J Hematol 2010

- 17.5 years of follow-up
- Significant decrease in mortality

Lobo et al. ASH abstract 2011

Harmful Effects of Hydroxyurea Therapy

- Evidence
  - 3 RCTs (over 500 pts)
  - Over 40 observational studies (> 3000 pts)
  - Results
    - BM suppression – high quality evidence, reversible
    - Leg ulcers in adults- moderate quality evidence
    - Leukemia- low evidence
    - Reproductive effects- very low evidence

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Case Presentation

7 year old male, SCA, seen at SCD clinic after 4

years in Canada.

2004 4 VOC admissions

2005 4 VOC admissions

2006 2 VOC admissions

2007 4 VOC admissions

2008 2 admissions in addition Jan to April 30 days missed from school

Start of Hydroxyurea April 2008

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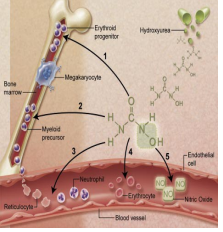
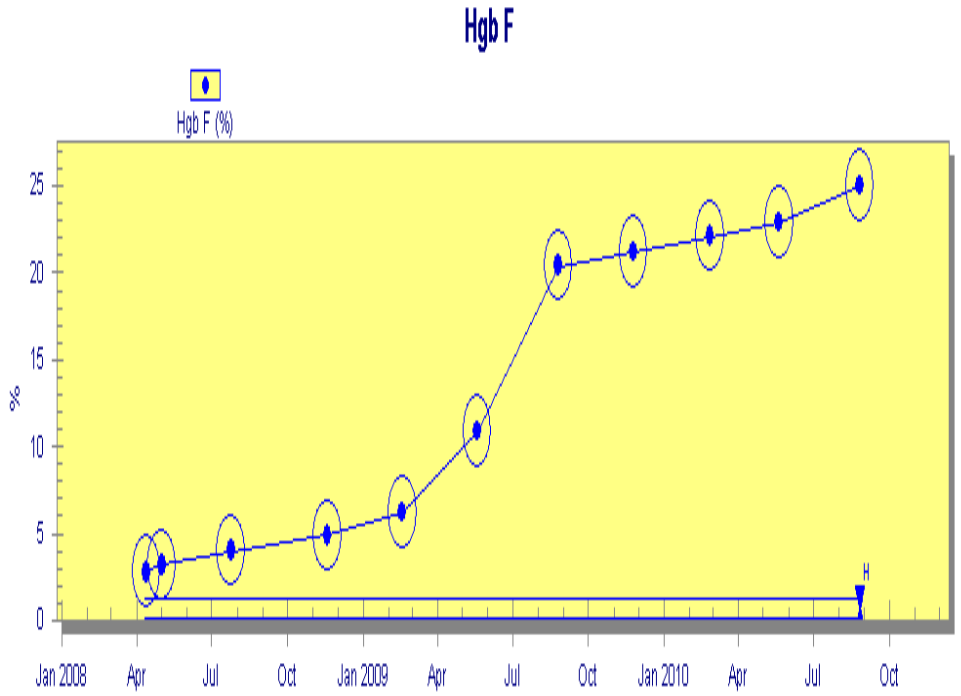
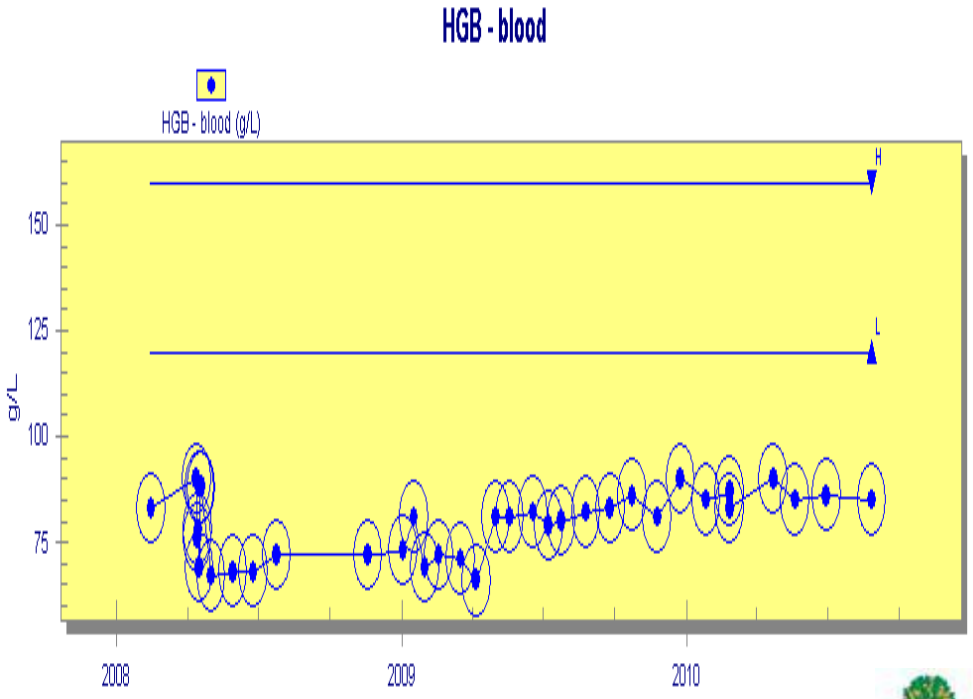


Benefits for SCD

Fetal hemoglobin induction and altered red cell kinetics





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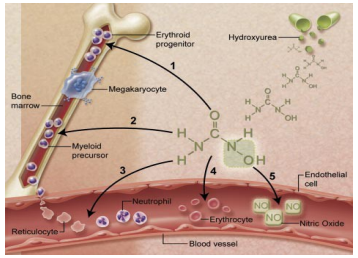
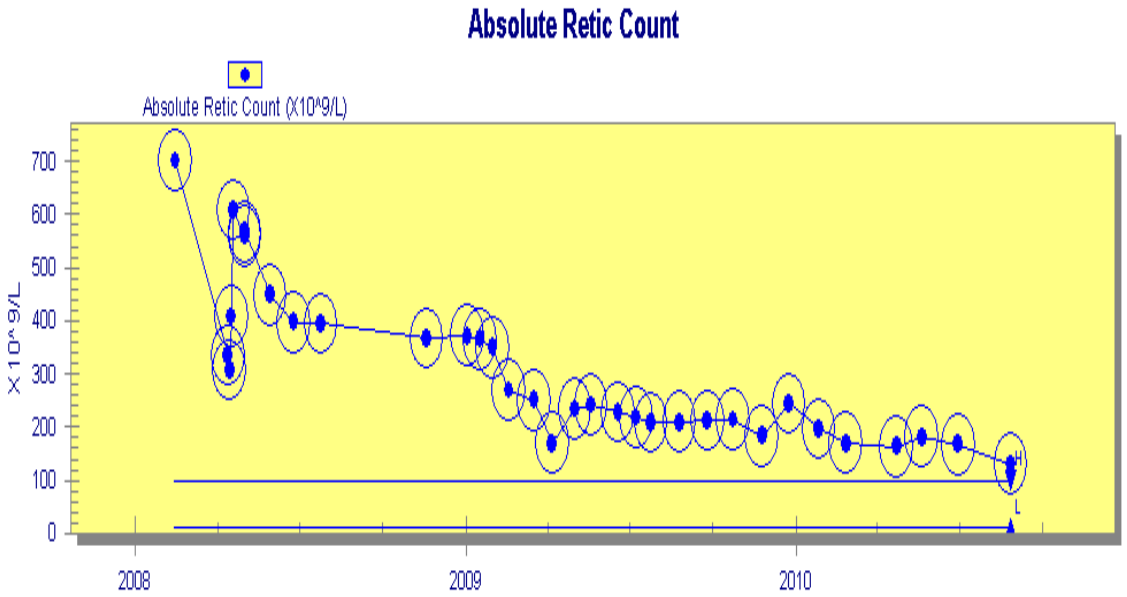
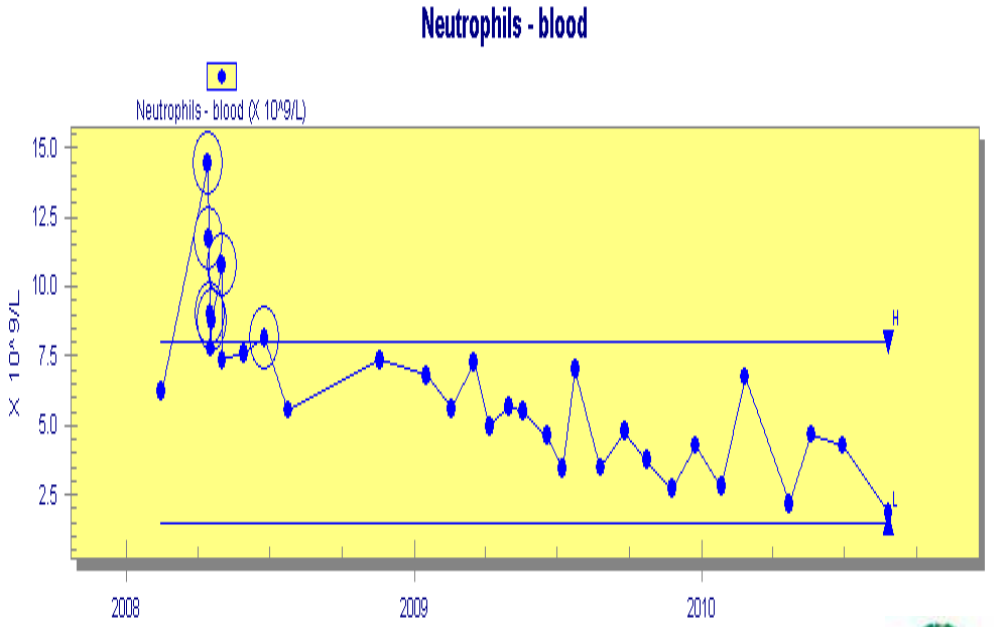


Benefits for SCD

Lower neutrophil and reticulocyte counts from ribonuclease reductase inhibition and marrow cytotoxicity





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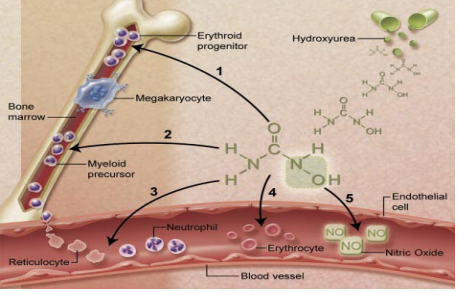
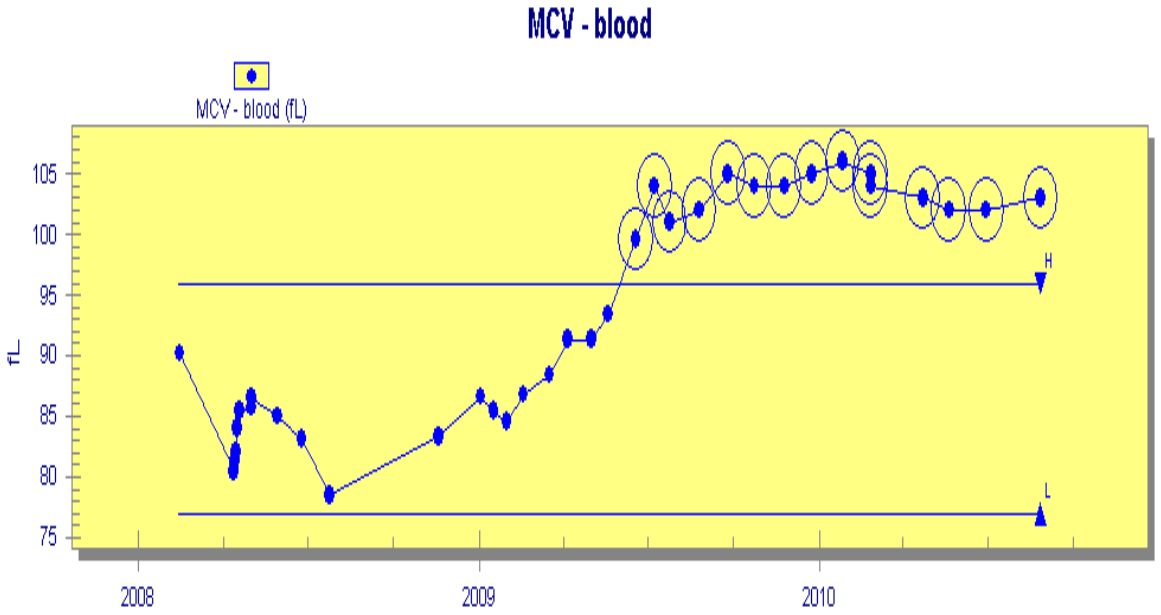


Benefits for SCD

Decreased adhesiveness and improved rheology of circulating neutrophils and reticulocytes



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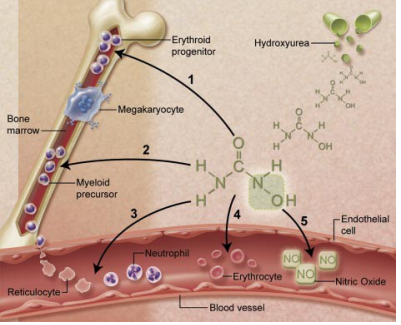
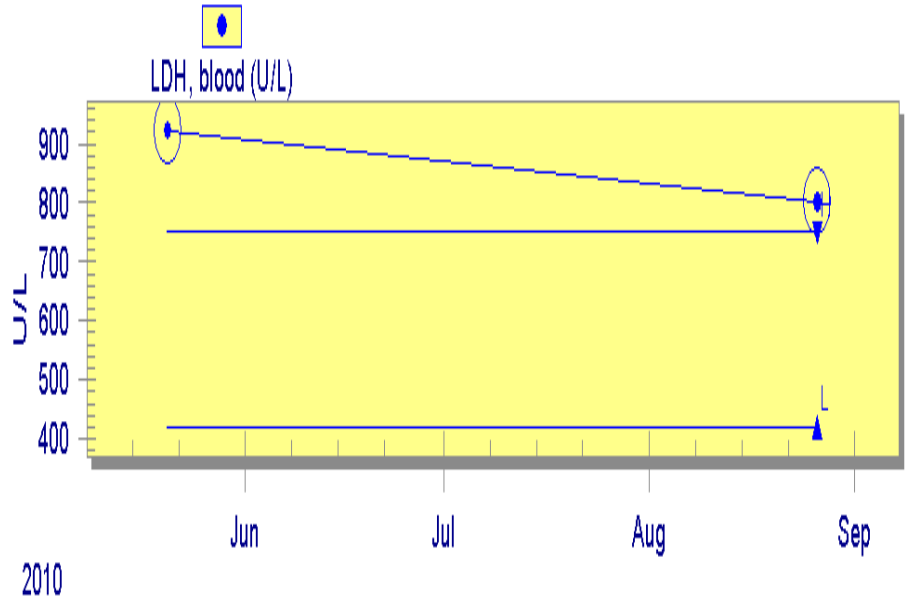
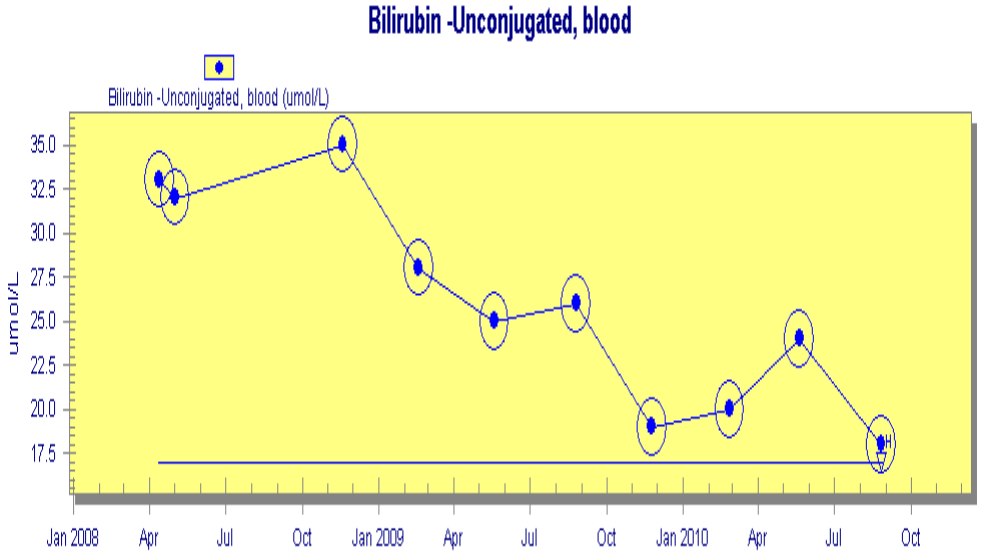


Benefits for SCD

Reduced hemolysis through improved RBC hydration, macrocytosis and reduced sickling of cells.

LDH, blood





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Clinical Response in this Case

- April 2008 - August 2012
- No hospital admissions
- No VOCs requiring intensive management

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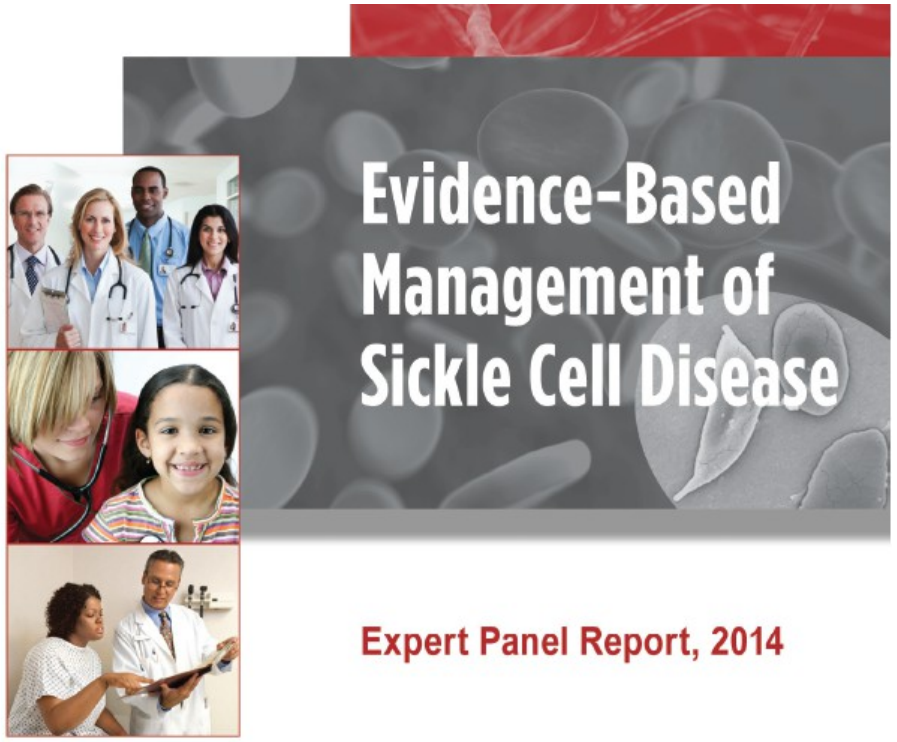
Hydroxyurea Clinical Trials in Africa

- NOHARM
- NOHARM-MTD
- SPIN
- REACH
- SPRING
- SPRINT

Standard of Care



"In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea **regardless of clinical severity** to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia)."

http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/[nhlbi.nih.gov]

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U.S. Department of Health and Human Services
National Institutes of Health

NIH National Heart, Lung, and Blood Institute

JAMA 2014;312(10):1033-1048

Evidence-based recommendations for us of hydroxyurea therapy	Strength of Recommendation	Quality of Evidence
Adults with SCA with ≥ 3 moderate to severe pain crisis during 12 months	Strong	High
Adults with SCA with sickle cell-associated pain that interferes with daily activities and QoL	Strong	Moderate
Adults with SCA who have severe symptomatic anemia that interferes with daily activities and QoL	Strong	Moderate
Infants ≥ 9 mo age, children and adolescents with SCA to be offered HU regardless of clinical severity to reduce complications related to SCD	Strong and moderate	High and moderate
Discontinue HU therapy in women who are pregnant or breastfeeding	Moderate	Low
Use established prescribing and monitoring protocol to ensure proper use of HU and maximize benefits and safety	Strong	High
In persons with SCD-SC or SCD-Sβ+-thalassemia who have recurrent SCD-associated pain that interferes with daily activities and QoL, consult SCD expert for consideration of HU therapy	Moderate	Low
In persons not demonstrating a clinical response to appropriated doses and duration of HU therapy, consult an SCD expert	Moderate	Very low

Hydroxyurea for Sickle Cell Disease

Treatment Information from the
American Society of Hematology

Back to Case

- April 2008 to Aug 2012
  - No hospitalization for VOC
- Aug 2012
  - 2 admissions with VOC
- Why?

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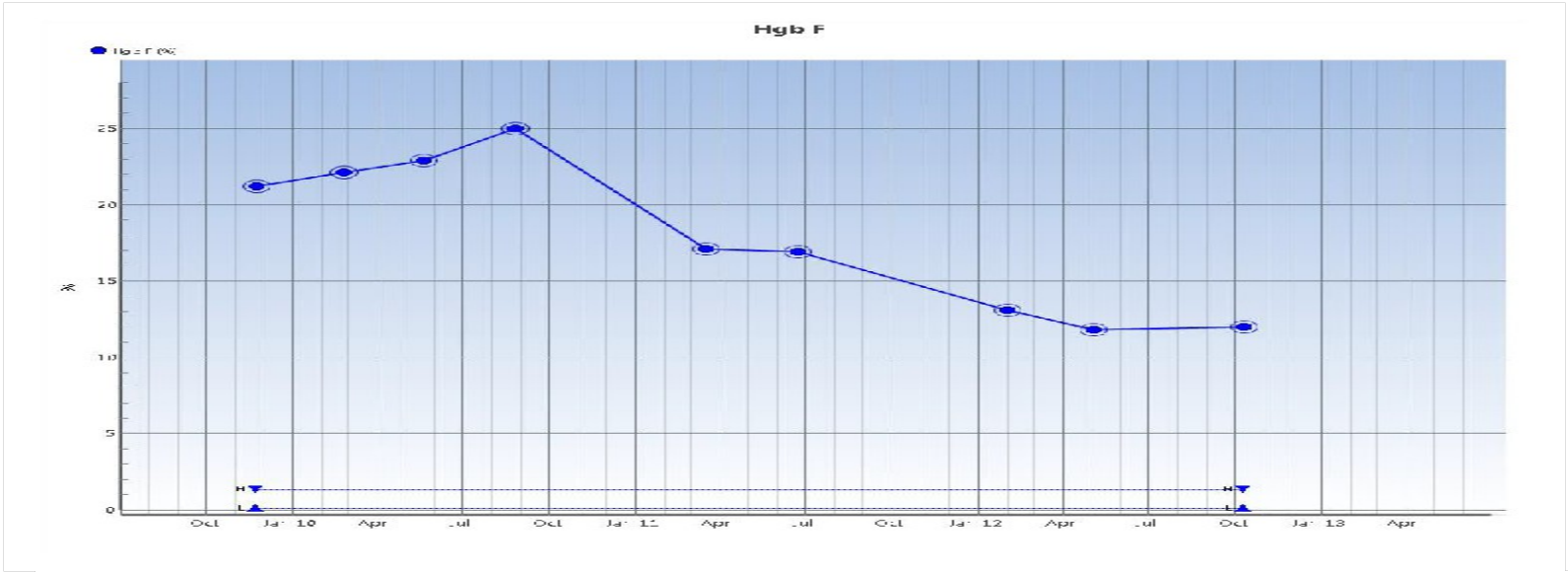
Hgb F
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MCV - blood
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75
80
85
90
95
100
105
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Jan 13
Apr

The Big Questions

- If HU therapy is
  - Clinically efficacious – strong evidence
  - Minimally harmful- moderately strong evidence
  - Easily administered: once a day by oral route
  - Relatively affordable
- Why then
  - Do a significant number of patients refuse it?
  - Do some patients fail to adhere to therapy?

t should we be doing to promote

eatment uptake?

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Adherence

- Caregivers
  - Show patients the favourable hematological profile while adhering to HU- Hb , MCV, WBC, Hb F and blood smears
  - Show loss of response when not adherent. Cumulative graphs of parameters has potent visual effect
  - Emphasize the desirable targets of HU response
  - Present data on impact of HU on survival
  - Social support crucial
  - Drug plans to ensure access

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Adherence

- Patients/Parents
  - Keep records of events and hematological parameters
  - Both parents should be involved with the child's HU therapy if possible
  - Encourage electronic alarm systems as reminders for HU intake
  - Non-adherence could be signs of social/emotional upheavals. Social workers input critical

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How do we combat ignorance about HU therapy?

- Caregivers
  - Educate, educate, educate! Why not hydroxyurea?
  - NIH Guidelines are out
  - Canadian guidelines have been developed
- Patients/Families
  - Educate using culturally-appropriate medium and language
  - Combat the fears about cancer, infertility etc
- Providers/Health system
  - Make the cost-effectiveness and health economics case
  - Successful HU therapy saves money, improves patient QoL and survival
  - No brainer! Providers should be canvassing for HU uptake and adherence to therapy

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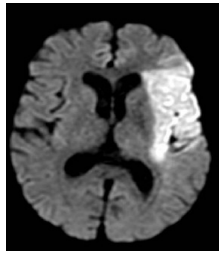
Neurological complications of SCD

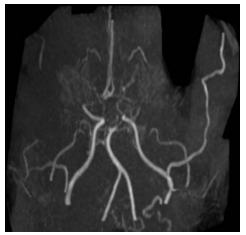
- **Overt stroke**: 1.02/100 pt-years between

  2 and 5 yrs *(Ohene-Frempong K, 1998)*

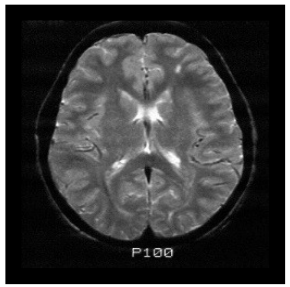


- **Moya-Moya** (progressive stenosis of distal ICA + abnormal network of collaterals) :

  20% in children with strokes *(Moritani T, 2004)*

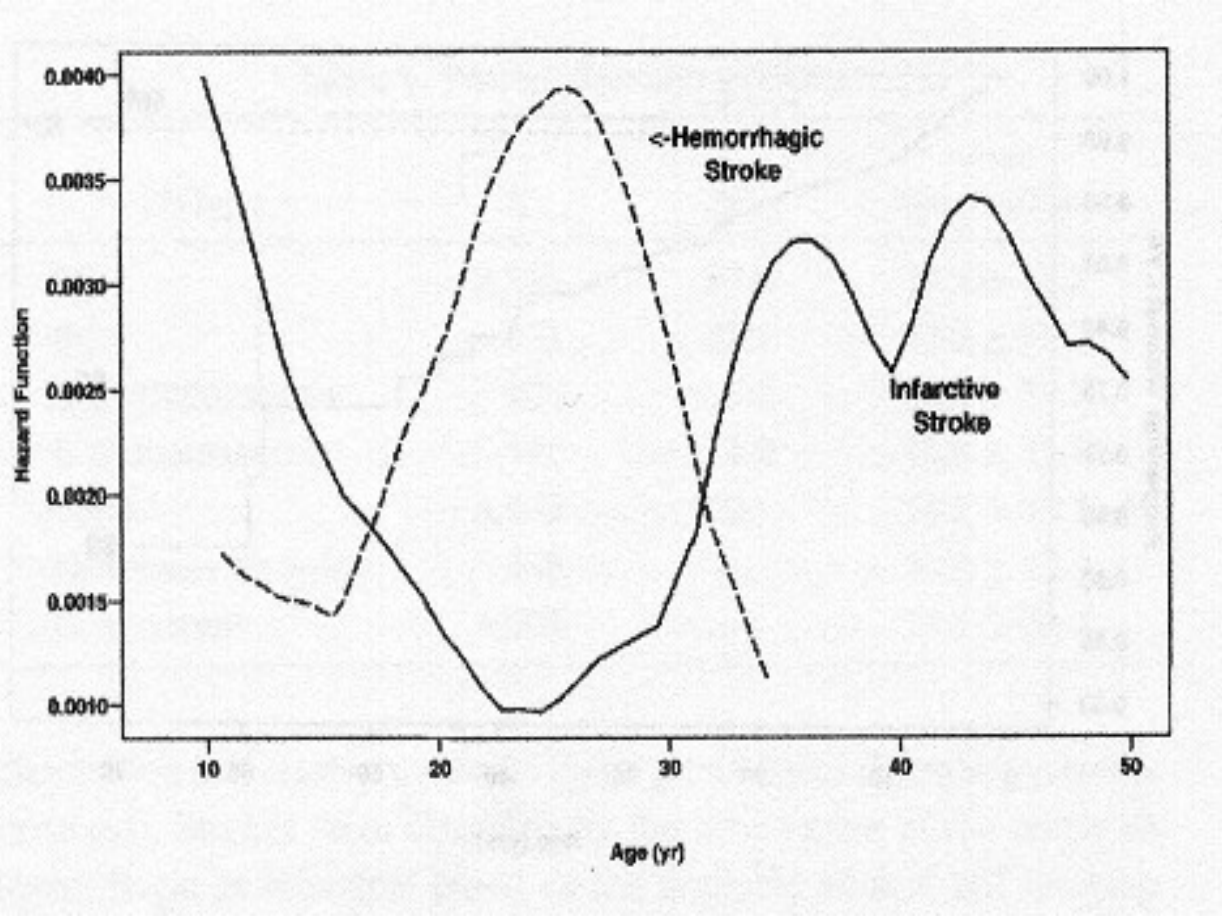


- **Silent cerebral infarcts**
  - 21.8% SS children aged 6 to 19 yrs *(Pegelow CH, 2002)*
  - 37% SS children by their 14th birthday *(Bernaudin F, 2011)*



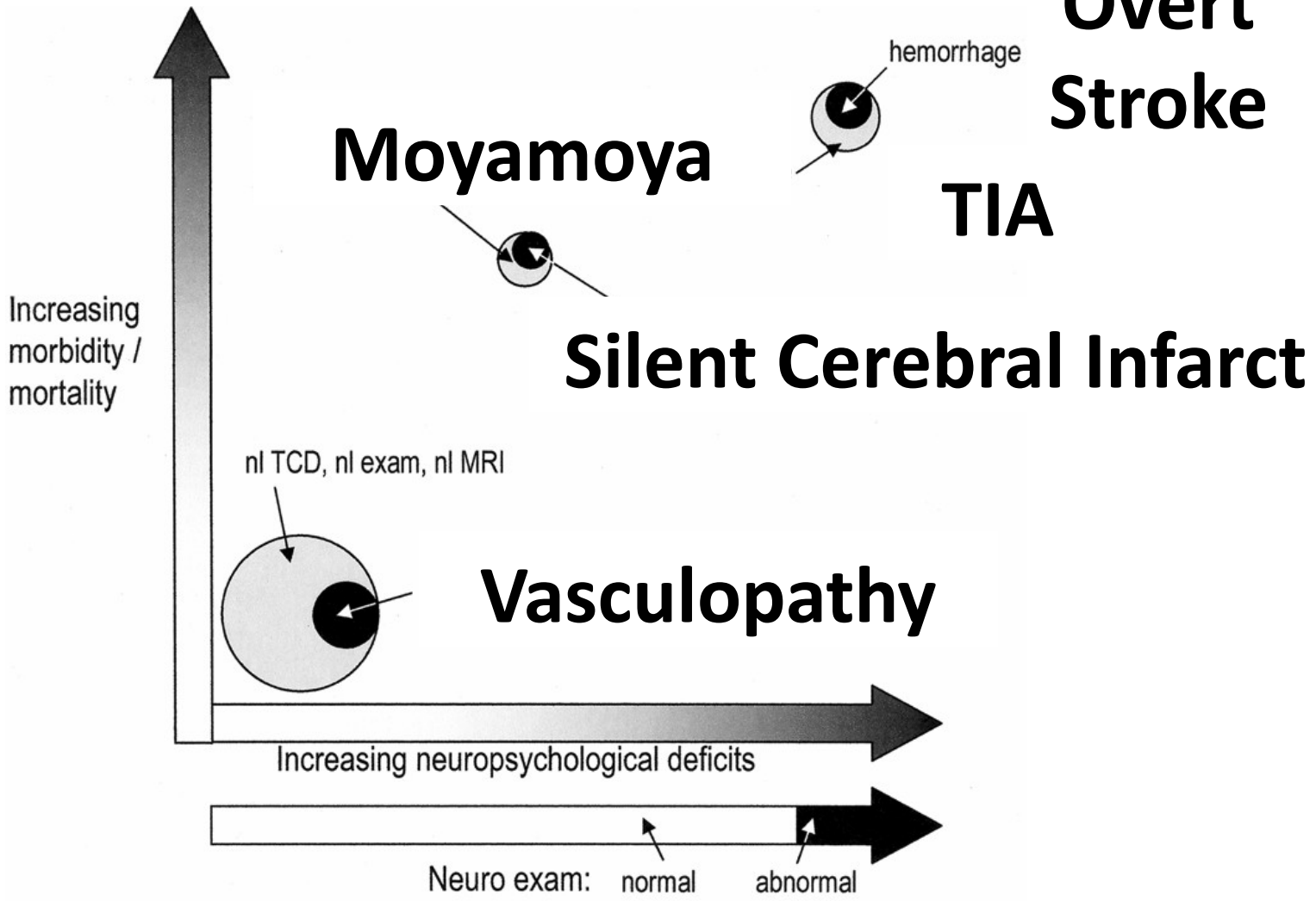
Related with cognitive impairments *(DeBaun MR, 2012)*

Stroke Incidence



Ohene-Frempong et al. **Blood** 1998;91:288-294

Stroke and Other Neurological Events in Sickle Cell



Stroke Prevention - STOP trial

- Adams et al. NEJM 1998; 339: 5-11
  - Blood transfusions used to prevent recurrent stroke in SCD patients
  - High blood-flow velocity on transcranial Doppler (TCD) ultrasonography are correlated with stenosis on angiography
  - Study design:
    - Using TCD, identify SCD children at risk for stroke
    - Randomize between standard care or transfusions to prevent a first stroke

Stroke Prevention

- ***Annual TCD starting from 2 years old (SS/Sβ°thal)***

Velocity (cm/sec)	Interpretation	Follow up
< 170	Normal	TCD q 1 yr
170-200	Conditional	TCD q 4-6 months
> 200	Abnormal	TCD q 1month

If TCD is abnormal, packed red blood cells transfusions to maintain % Hb S < 30% are recommended.

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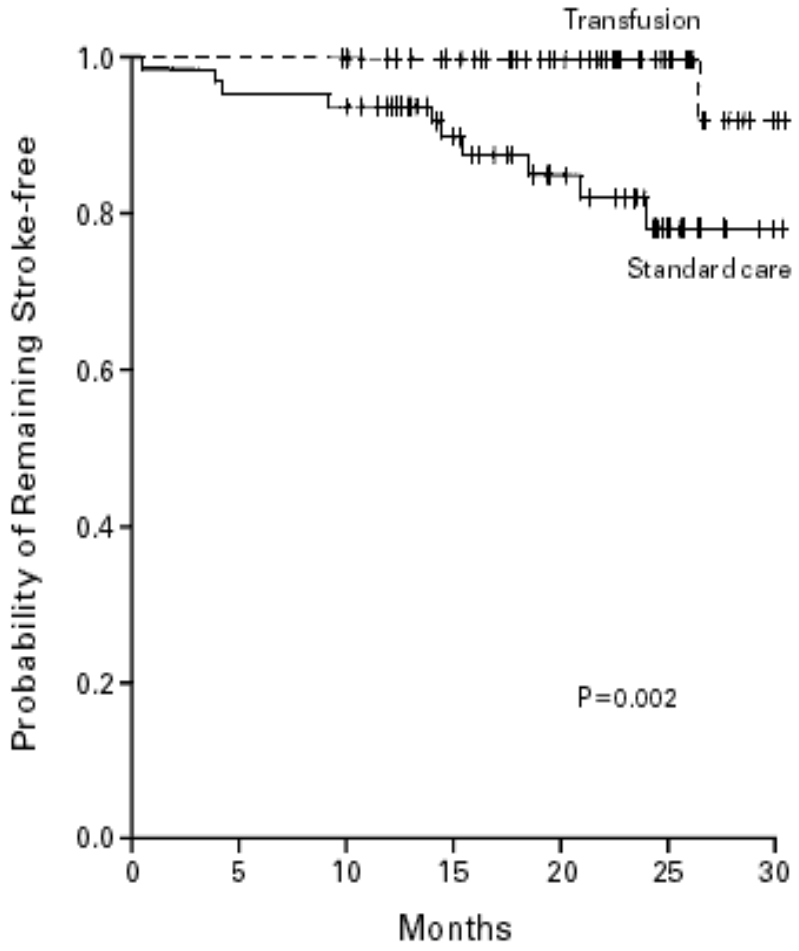
STOP Trial

TABLE 2. LENGTH OF FOLLOW-UP AND NUMBER OF PRIMARY EVENTS.

VARIABLE	TOTAL (N=130)	TRANSFUSION (N=63)	STANDARD CARE (N=67)
Follow-up (mo)			
Total	2550	1321	1229
Median	21.1	22.2	18.3
Mean ±SD	19.6±6.5	21.0±5.7	18.3±7.0
No. of strokes	12	1	11
Cerebral infarction	11	1	10
Intracerebral hematoma	1	0	1



Age: 2 to 16 years old

Genotype: SS and Sβ°thal

Adams et al. NEJM 1998; 339: 5-11

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STOP II trial

- How long should transfusions be continued?

- Transfusion-halted group:
  - 2 strokes
  - 14 abnormal TCD
- Tranfusion continued group:
  - No event

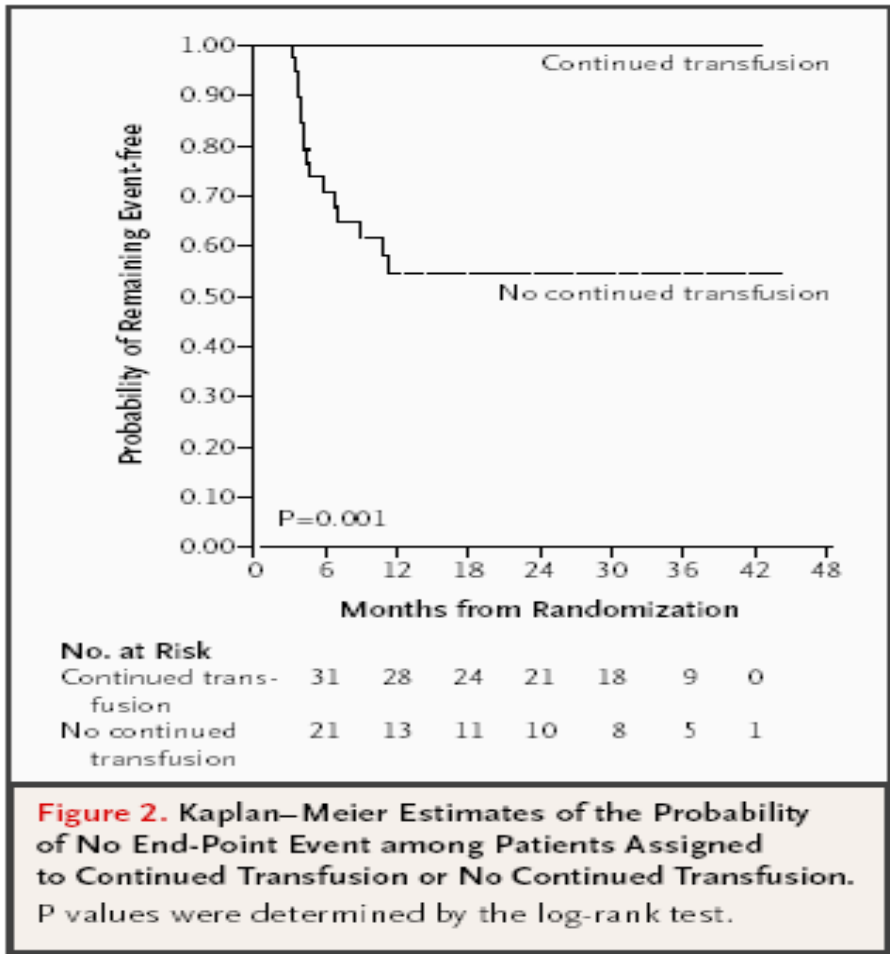
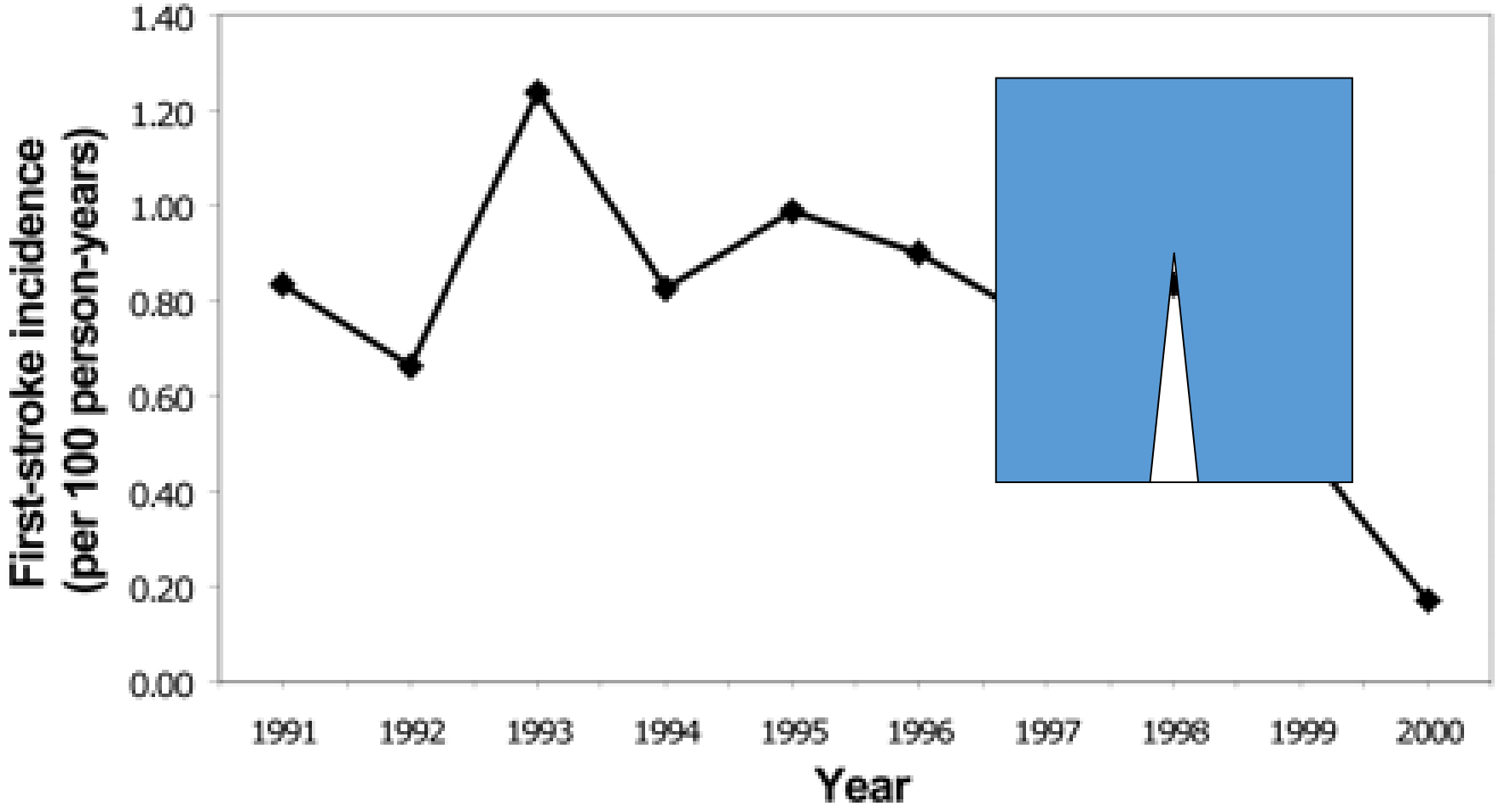


Figure 2. Kaplan–Meier Estimates of the Probability of No End-Point Event among Patients Assigned to Continued Transfusion or No Continued Transfusion.
P values were determined by the log-rank test.

STOP II Trial Investigators. NEJM, 2005.

TCD and Incidence of Stroke



Fullerton et al. Blood. 2004; 104:336-339

Preventing Stroke

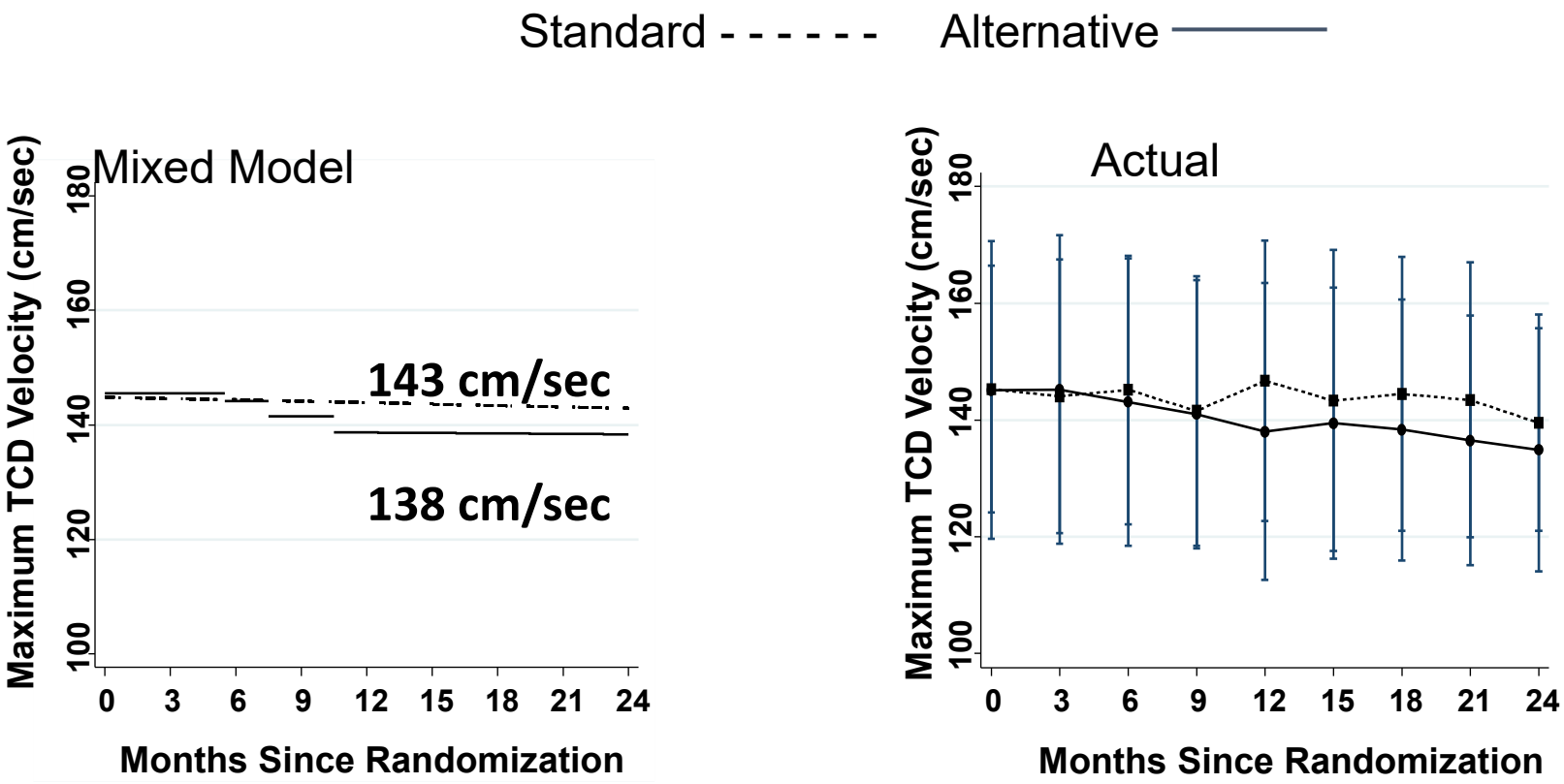
Secondary Stroke Prevention

- Alternative to chronic blood transfusions
- Better management of iron overload using phlebotomy

Primary Stroke Prevention

- Attractive alternative to transfusions or observation
- Fewer complications, less cost, better compliance
- Compelling option for low-resource countries

TWiTCH Study: Primary Endpoint

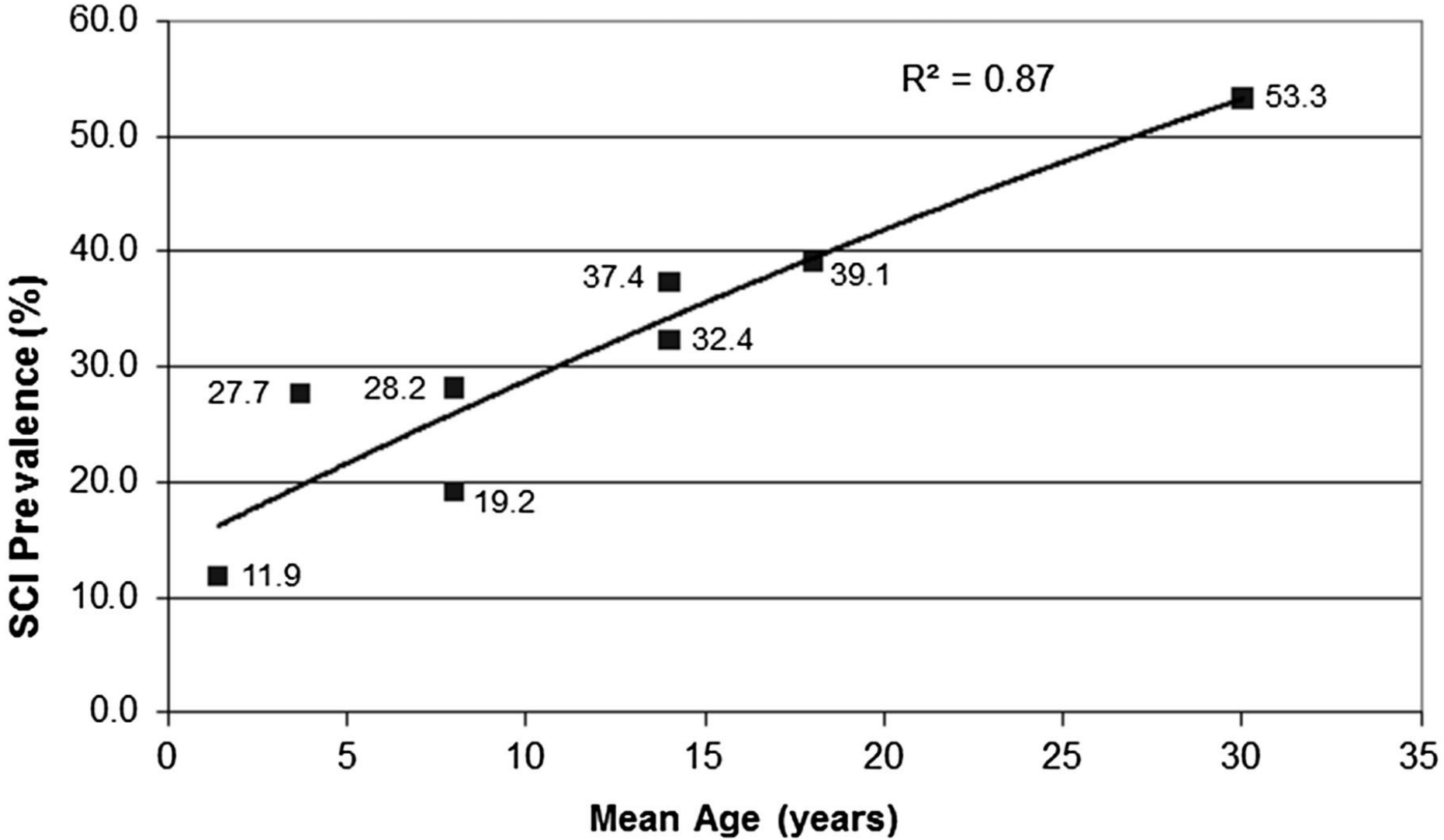


ITT per-protocol non-inferiority comparison (p=8.82 x 10-16) Additional post-hoc analysis for superiority (p=0.023)

Prevention of First & Recurrent Strokes

- Hydroxyurea vs Chronic Transfusion for Maintenance of TCD Velocities in Children with SCA- TWiTCH trial
  - Hydroxyurea can substitute for chronic blood transfusions to maintain TCD velocities and help prevent strokes
    - **Ware et al. The Lancet 2016;387(10019):661-670**
- Incidence rates of stroke recurrence
  - Meta-analysis of several studies
    - Regular transfusions 1.9 (CI 0.1-2.9)/100 patient yrs
    - Hydroxurea therapy 3.8 (CI 1.9-5.7)/100 patient yrs
    - No therapy 29.1 (CI 19.2-38.9)/100 patient yrs

or patients who have had a 1st stroke, HU and chronic blood transfus



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Kassim AA et al. Blood 2016;127(16):2038-40

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Evidence-Based Recommendations for Use of Transfusion Therapy	Strength of Recommendation	Quality of Evidence
Adults and children with SCA , transfuse RBC to bring Hb to 10 g/dL prior to surgical procedure under GA	Strong	Moderate
In persons with SCD-SS and who already have Hb > 8.5 g/dL without transfusion, are receiving long-term HU therapy or who require high-risk surgery, consult with SCD expert for guidance as to the appropriate transfusion method.	Strong	Low
RBC units transfused in persons with SCD should include matching C, E and Kell antigens	Moderate	Low
In persons with SCA who do not receive long-term transfusions, avoid transfusing to target Hb > 10 g/dL	Moderate	Low
In children with SCA who receive long-term transfusion, the goal should be to maintain pre-transfusion Hb S level < 30%	Moderate	Moderate
Consult blood bank for workup of a possible delayed transfusion reaction in a patient with acute anemia, pain or jaundice 3 weeks after transfusion	Strong	Moderate
In persons on long-term transfusion therapy, perform serial assessments for iron overload	Strong	Moderate
Administer Fe-chelation therapy (in consultation with a hematologist) to persons with SCD and document transfusional iron overload	Moderate	Moderate

Complication	Transfusion Method	Strength of Recommendation	Quality of Evidence
Symptomatic severe acute chest syndrome (O2 sats < 90% despite supplemental O2)	Exchange	Strong	Low
Acute splenic sequestration with severe anemia	Simple	Strong	Low
In children and adults with acute stroke, initiate monthly transfusions	Simple or exchange	Moderate	Low
Hepatic sequestration	Exchange or simple	Consensus	Panel
Intrahepatic cholestasis	Exchange or simple	Consensus	Panel
Multisystem organ failure	Exchange or simple	Consensus	Panel
Aplastic crisis	Simple	Consensus	Panel
Symptomatic anemia	Simple	Consensus	Panel
Child with TCD reading > 200 cm/s	Exchange or simple	Strong	High
Adults and children with previous clinically over stroke	Exchange or simple	Moderate	Low

Summary

- Evidence-based therapies for SCD have emerged and many more underway
- Their proven efficacy need to be translated into effectiveness for patients
- Patients/families, provider and systems barriers need to be overcome to bridge the gap between efficacy and effectiveness
- Better outcomes for patients must be the ultimate goal

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Thank You

Questions?

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