DEFERIPRONE EVALUATION IN PAEDIATRICS

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 261483

Barts Health NHS Trust

The emerging issue of SCD

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Overview

- Epidemiology of SCD in UK and Europe
- Indications for chronic transfusion
- Iron overload in SCD- pathological effects and monitoring
- Management of iron overload
- Implications for DEEP trial

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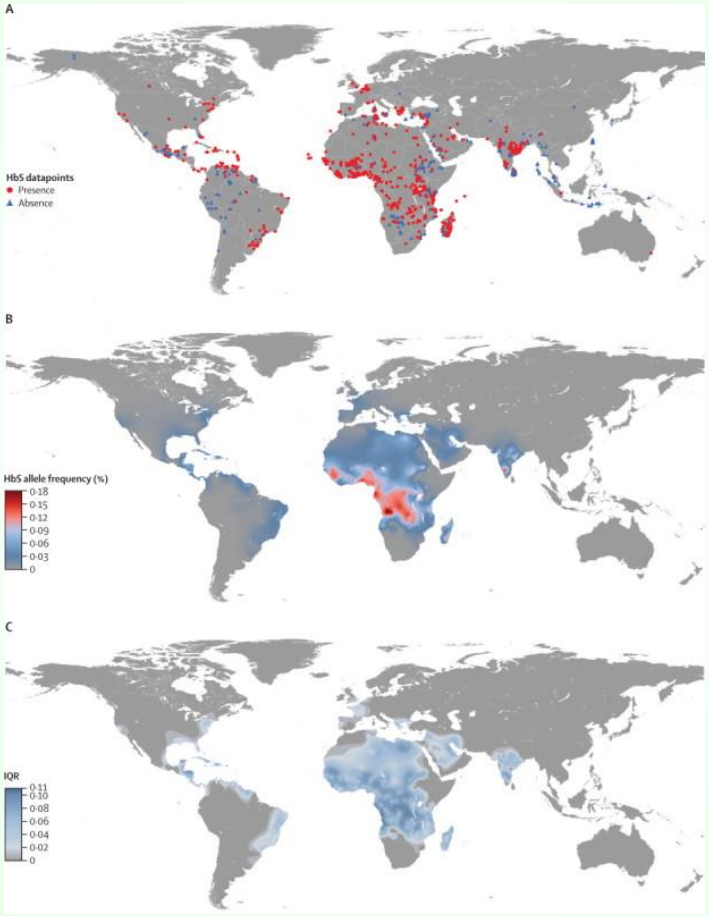
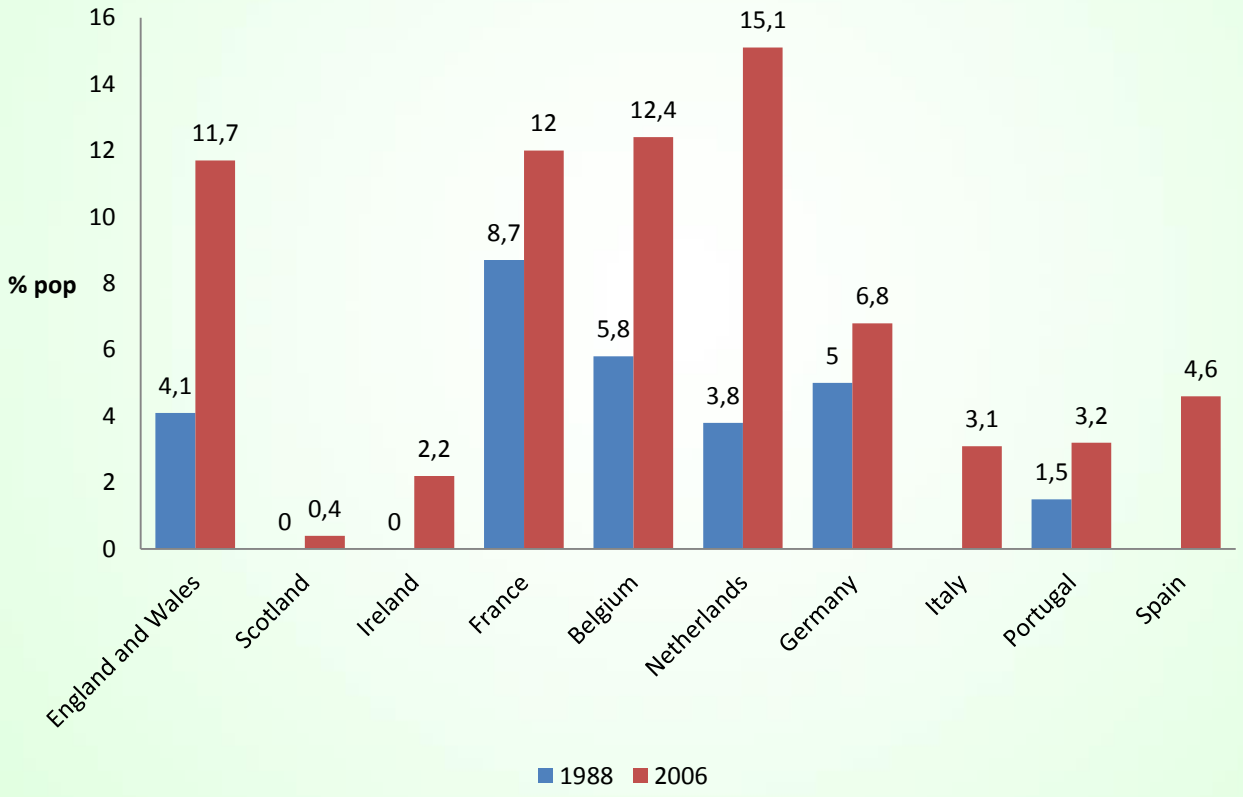
Epidemiology

Predicted HbS allele frequency

Piel et al, Lancet 2013

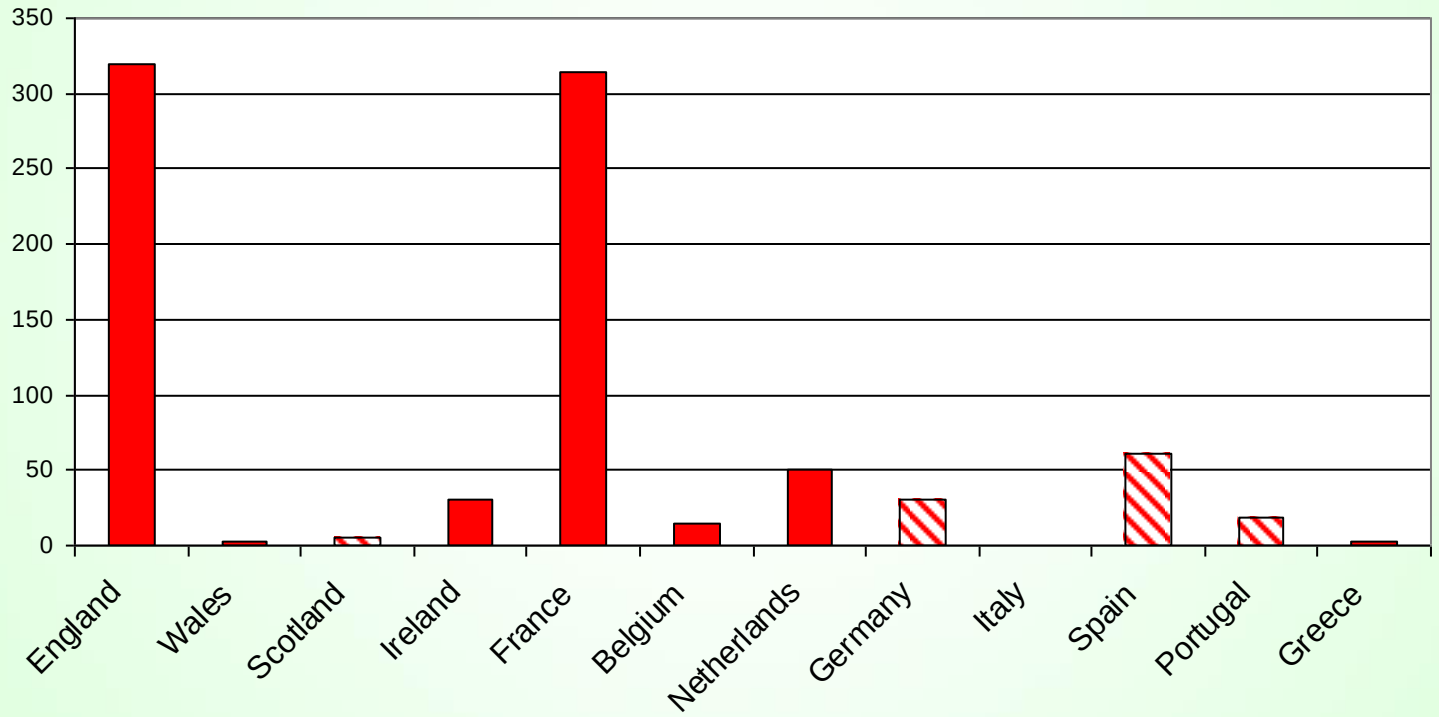


Trends in at-risk populations 1988 and 2006



Adapted from Modell et al, Scan J Clin Lab Invest 2007; 67: 39-70

Estimated annual birth rate with SCD



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Transfusion in SCD

RATIONALE FOR TRANSFUSION

- Increase total Hb
- Dilute with HbAA RBC's
- Suppress endogenous HbS production

↓

- Improve blood flow
- Improve tissue oxygen delivery
- Inhibit vaso-occlusion
- Prevent vasculopathy
- Prevent tissue damage

TRANSFUSION OPTIONS

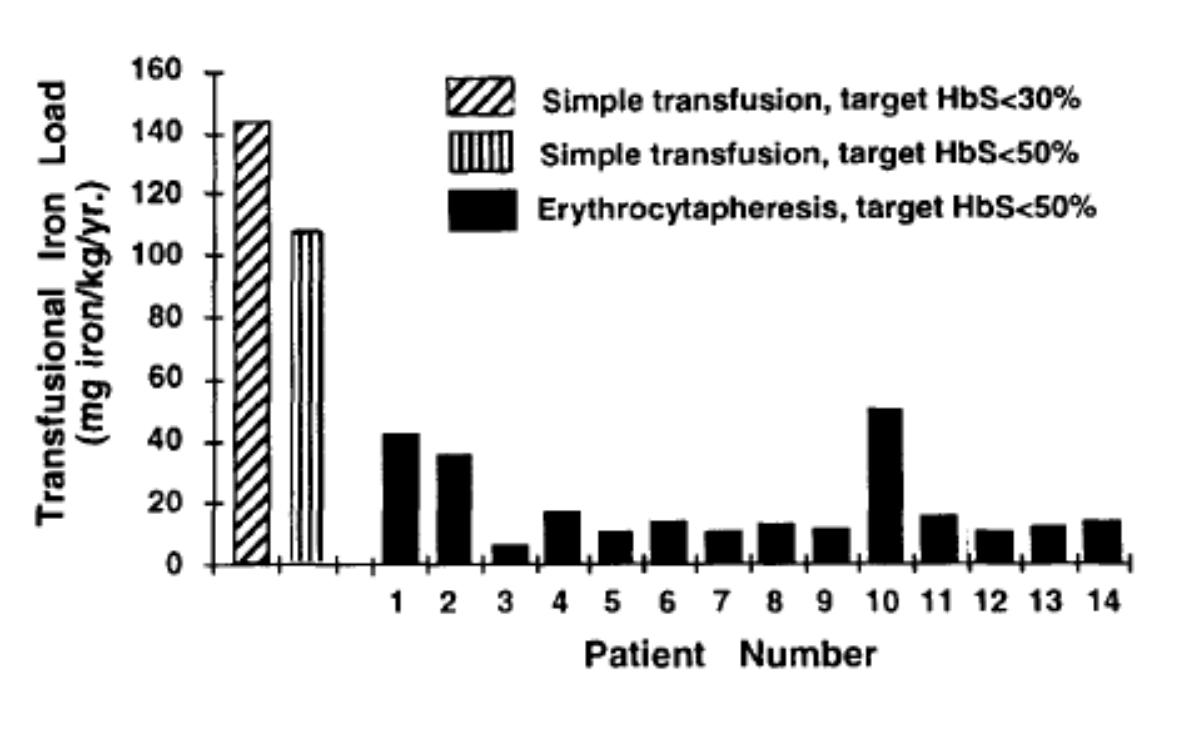
- Acute transfusion
- Chronic transfusion programme

- Simple or exchange transfusion

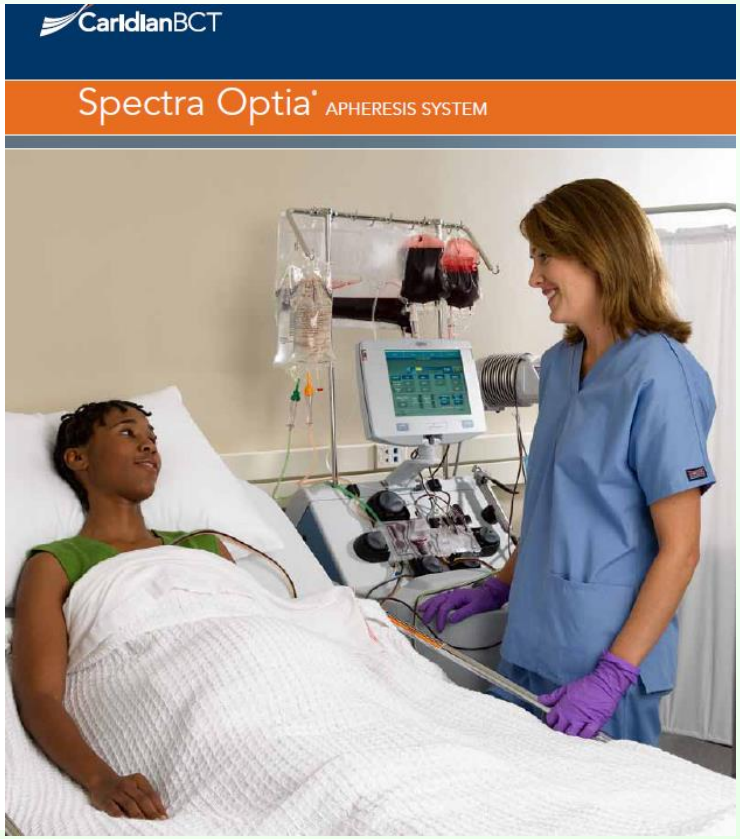
- Exchange
  - Partial or full volume
  - Manual or automated

Erythrocytapheresis therapy to reduce iron overload

Kim et al, Blood 1994




Optia


CaridianBCT
Spectra Optia® APHERESIS SYSTEM

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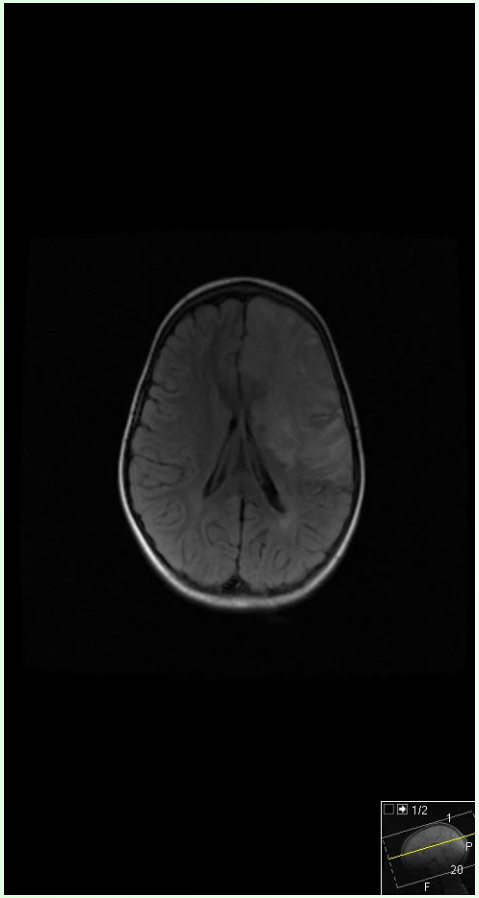
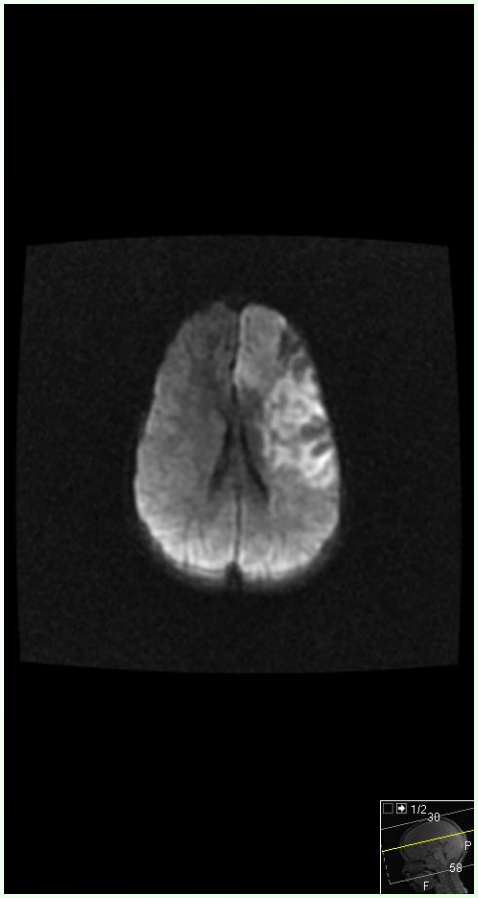
Indications for transfusion

Acute ischaemic stroke

L internal carotid artery occlusion





SECONDARY STROKE PREVENTION

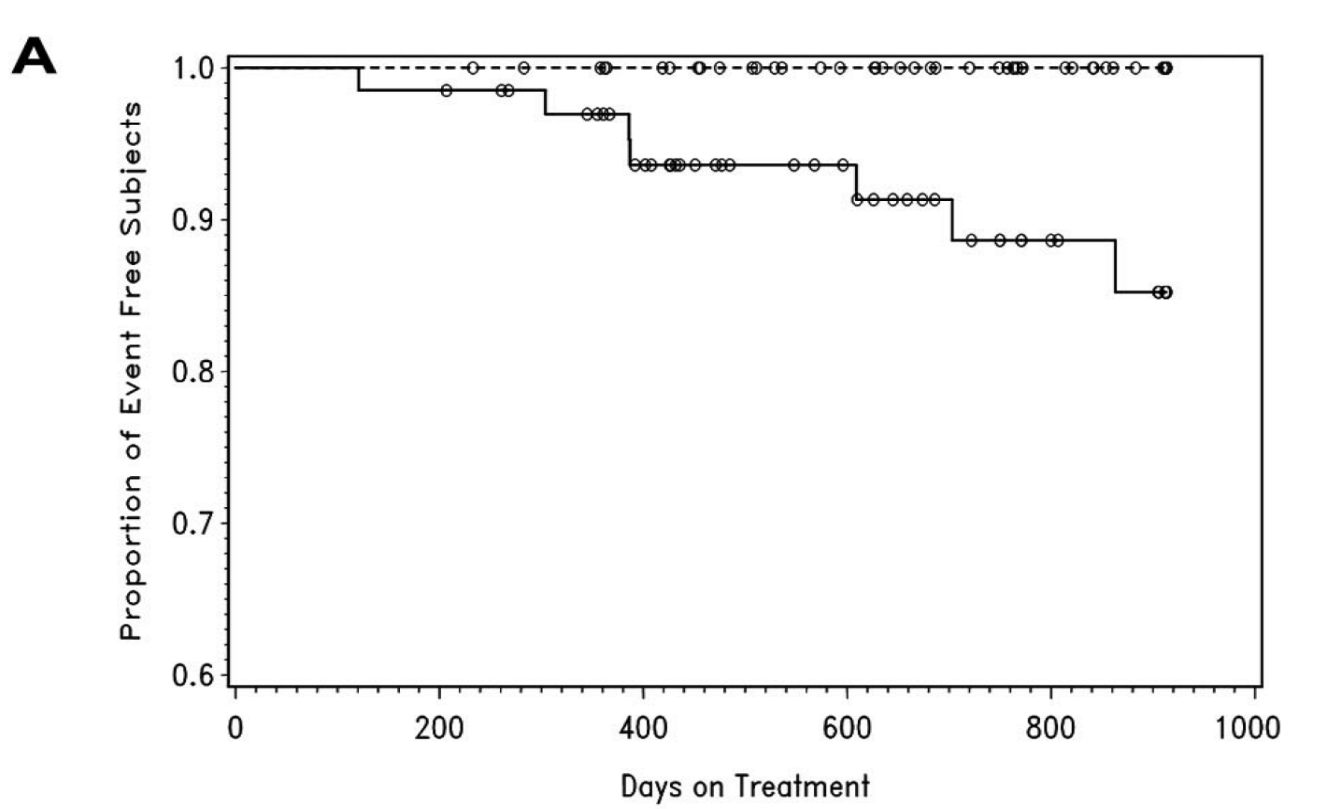
- No transfusion
  - recurrence rate 30-70%
- Long-term transfusion HbS 30%
  - recurrence 14-23%
  - 2.2-6.4 episodes per 100 patient years

Pegelow et al, J Pediatr 1995

Scothorn et al, J Pediatr 2002

Stroke recurrence in SWiTCH

Ware et al, Blood e-pub Feb 2012



All patients enrolled, 78% of pt years achieved

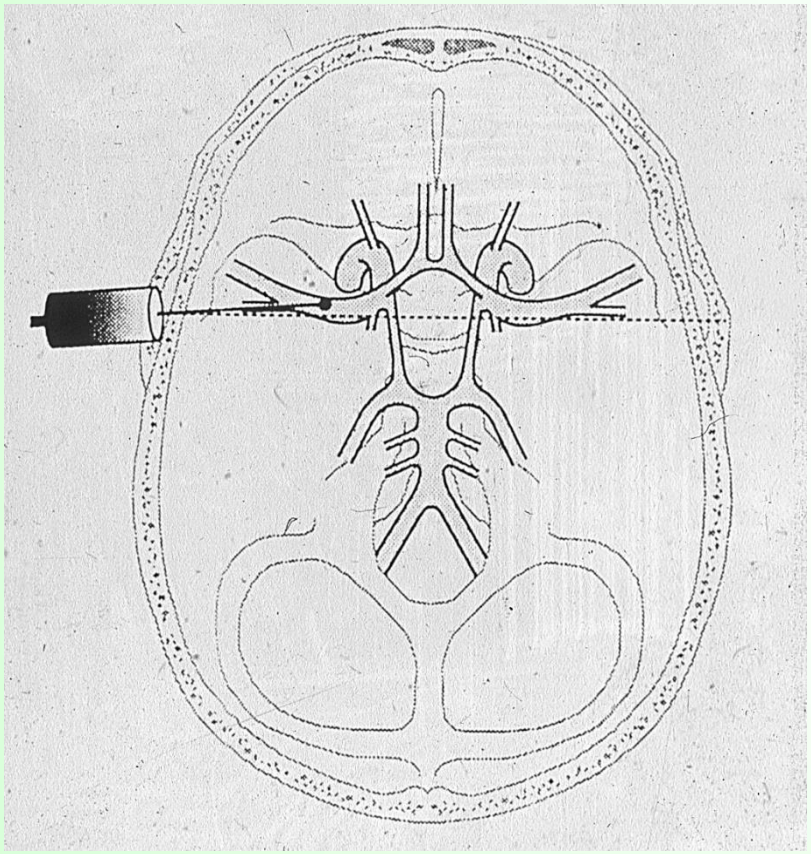
7 episodes of ischaemic stroke in Hydroxyurea/venesection (10%, 5.6 per 100 pt yrs)

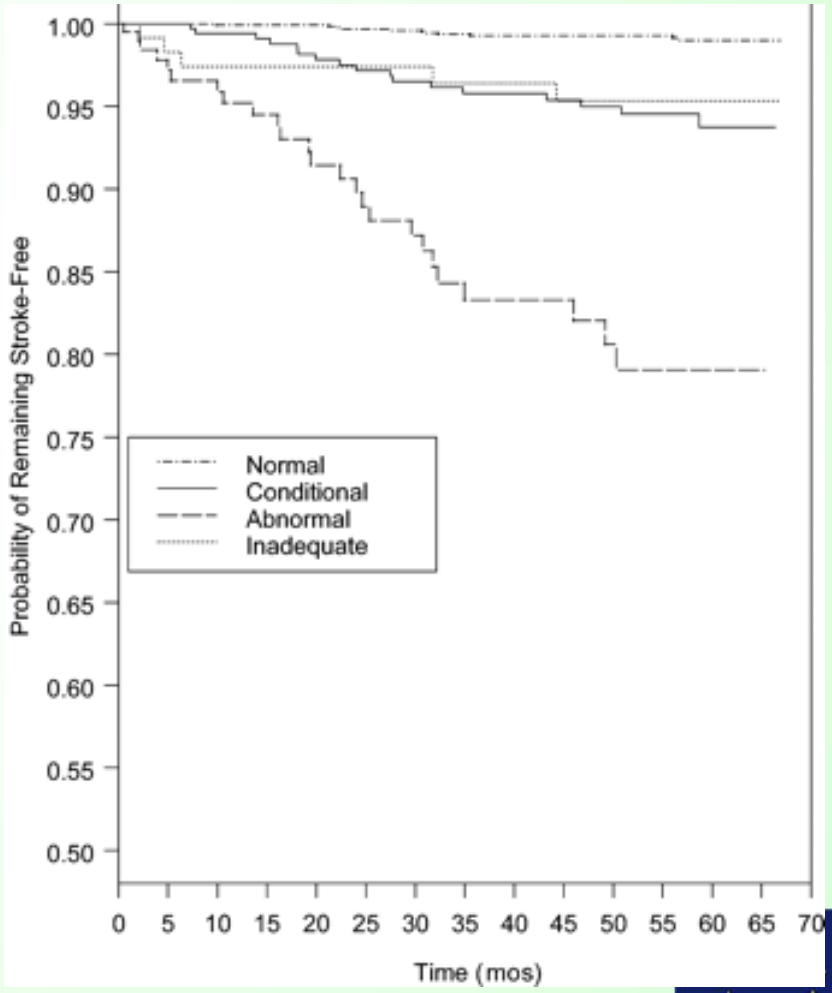
None in transfusion/chelation arm

Still within margin of non- inferiority

- No difference in LIC between two arms at first interim analysis at 30 months
- Study terminated on grounds of futility for composite primary end point
- *'Based on the SWiTCH trial results, transfusion and chelation remain the better way to manage children with SCA, stroke and iron overload..'*

Transcranial Doppler Scanning in children with SCD: Risk classification

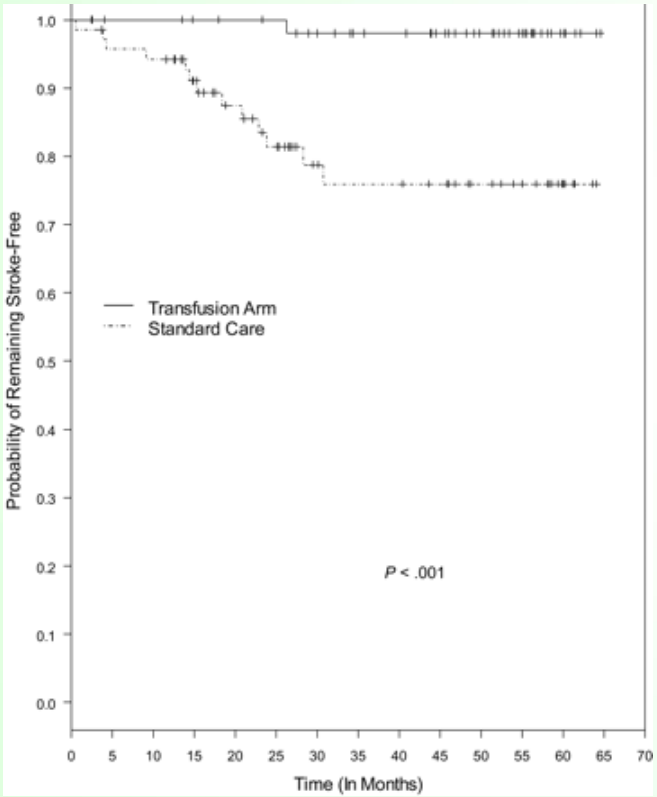




From Adams et al, Blood 2004; 103: 3689

Primary prevention of ischaemic stroke in children with abnormal TCD scan

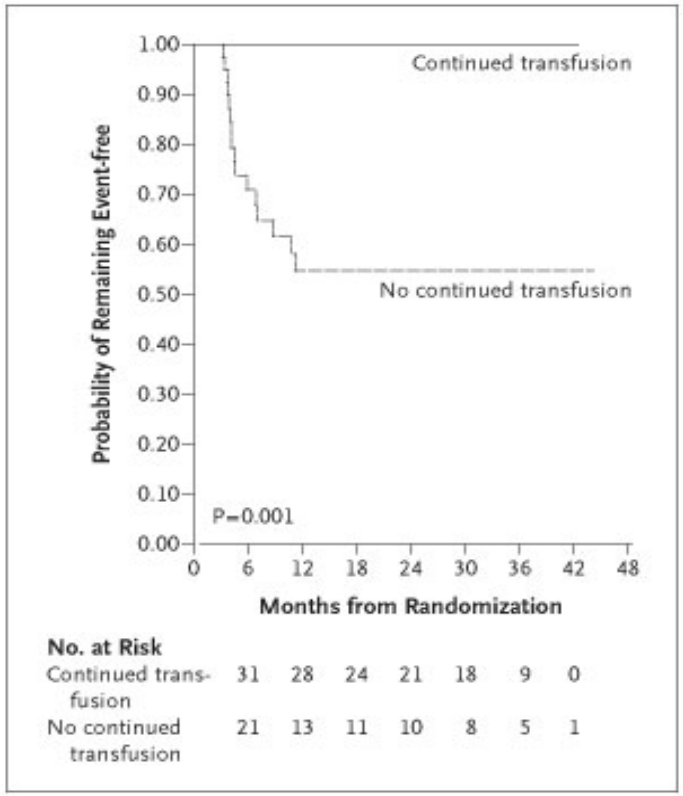
STOP Study. Adams et al, N Engl J Med 1998.



- 130 randomised, 63 transfusions, 67 standard care
- 11 CVA (10 ischaemic) in standard care, 1 (1 ischaemic) in transfusion arm
- 92% difference in stroke risk
- Early termination of trial
- Recommendation of TCD screening and transfusion of children with abnormal TCD

Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease: STOP 2

N Eng J Med 2005; 353: 2769

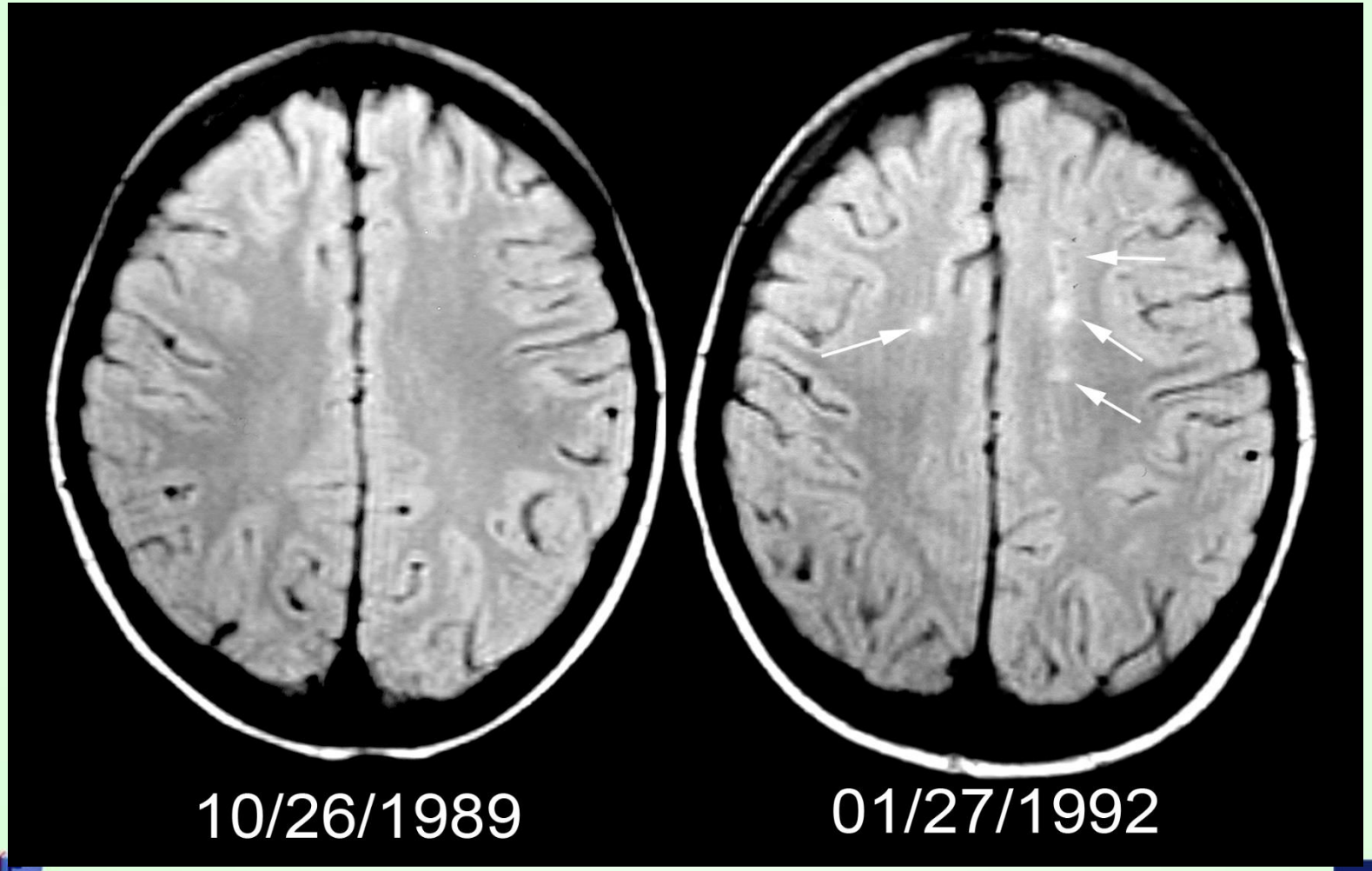


- Children with abnormal TCD, on transfusions >30 months with normalization of TCD and no severe stenotic lesion on Cerebral MRA
- Composite primary end-point of stroke or reversion to abnormal TCD
- 71 out of planned 100 enrolled
- 41 stop, 38 continue
- 14 reverted to abnormal TCD, 2 had CVA vs none in transfusion arm
- Early termination of trial
- Transfusions cannot be safely stopped even in children considered at low risk

Results with implementation of TCD screening programme

	Setting	Time period	Number pts/pt yrs fu	Rate of abnormal TCD	Rate of Stroke per 100 pt yrs (95%CI)
Bernaudin et al, Blood, e-pub 2010	Paris, regional centre	1998-2008	217/ 1609	30%	0.19 (0.04-0.5)
Enninful-Eghan et al, Journal of Pediatrics 2010	Philadelphia, regional centre	1998-2006	530 /3578	12.4 %	0.06 (0.01-0.2)
Telfer et al, 2011	E. London and Essex, Regional centre	2001-2010	451/ 4673	13.9 %	0.13 (0.05-0.2)

Silent cerebral infarction



Official Report-Normal

Official Report No- Change

Silent Cerebral Infarct Transfusion Trial:
Multi-Center Clinical Trial

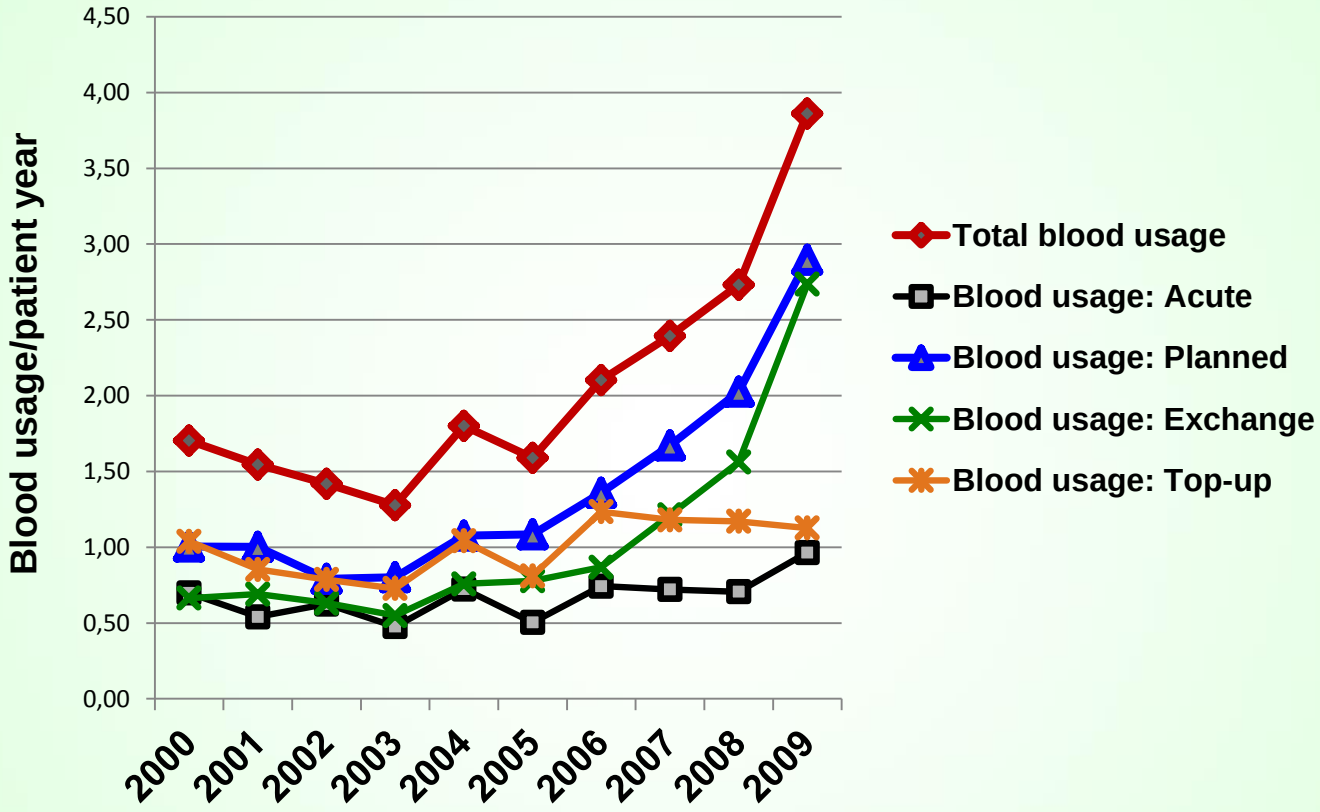
- Primary Hypothesis:

*Prophylactic blood transfusion therapy in children with silent cerebral infarcts will result in at least **86%** reduction in the proportion of patients with clinically evident strokes, new or progressive silent cerebral infarcts*

Other indications for regular transfusion

- Prevention of acute painful crisis and ACS (Grade B)
- Severe anaemia and renal dysfunction (Grade C)
- Maintenance of transplant renal function post-allograft (Grade C)
- Recurrent lower limb ulceration (Grade C)
- Recurrent priapism (Grade C)
- Avascular necrosis of hips in childhood (Grade C)

Increasing use of blood transfusions in adult patients



- 41% of all patients received ≥ 1 unit blood in 10 years
- Significant increase in blood usage both for planned and acute sickle-related complications
- More “indications”: renal failure, ulcers, lung disease, priapism

Drasar E et al. Br J Haematol. 2011;152:766-70.

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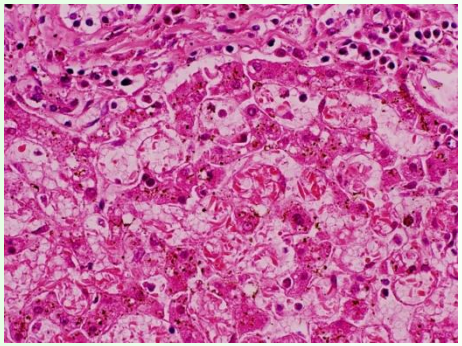
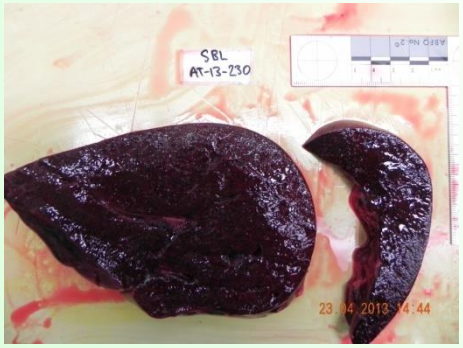
Iron overload in SCD

Iron overload in SCD

- Reduced incidence of cardiac and endocrine complications compared to TM
- These complications may become more common in heavily transfused older patients
- Liver damage is multifactorial

Chronic liver disease in HbSS, ‘hepatopathy’





Pathophysiology

- Sequestration
- Vaso-occlusion
- Iron overload
- Viral hepatitis

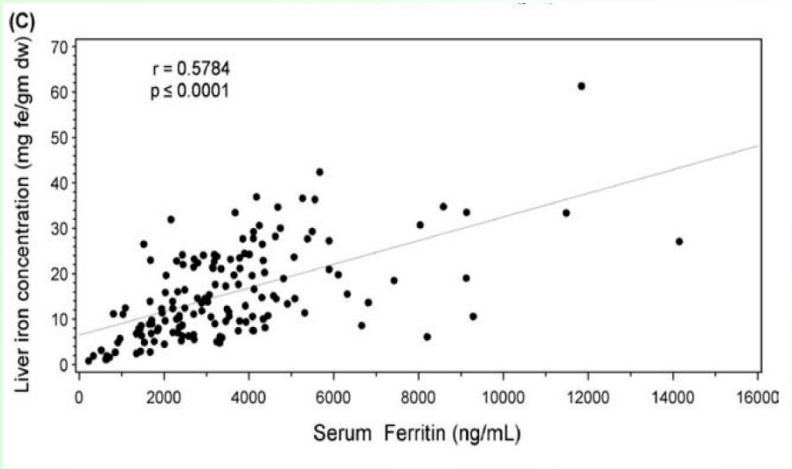
Measuring iron overload in SCD

- Liver iron validated against R2* (Hankin et al, Blood 2009)
- R2 (Ferriscan) generally used in UK for LIC
- Poor correlation of SF with LIC
- Annual trends in SF and LIC more important
- Cardiac iron loading is less common than in TM

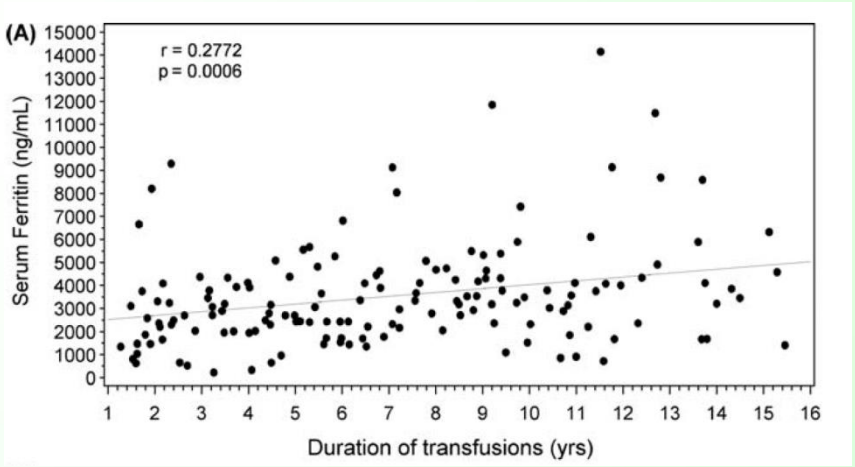
Problems with serum ferritin

Kwiatkowski et al, Am J Haematol. 2011

Correlation with liver iron



Correlation with duration of transfusions



Iron chelation- licensing in SCD

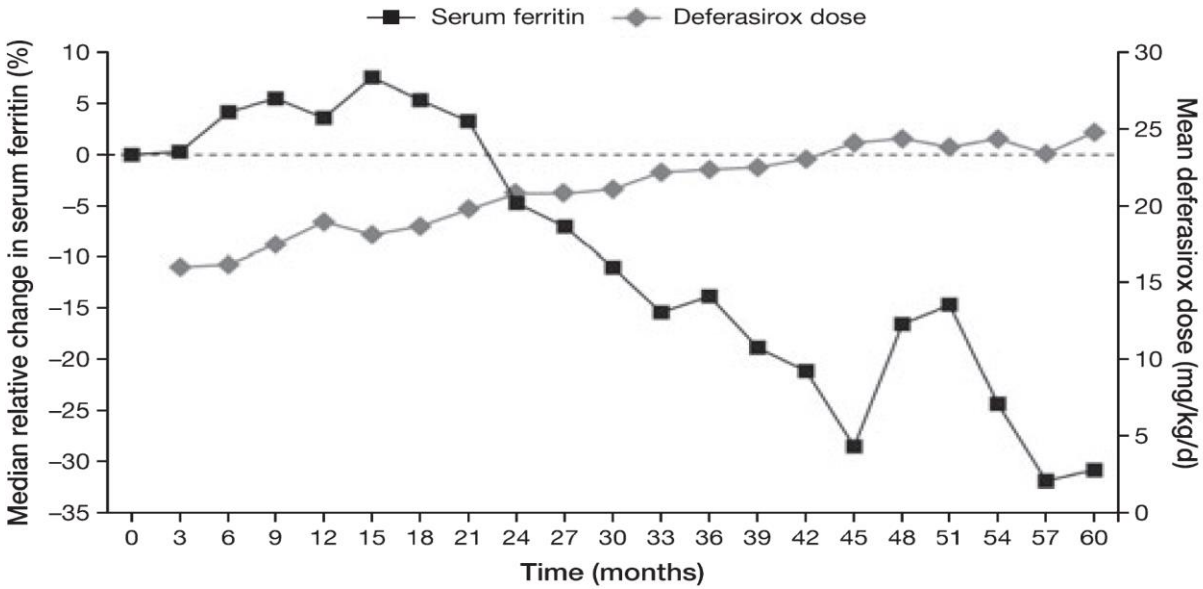
- **Deferiprone**: Not licensed
- **Desferrioxamine**: Iron overload ...primary and secondary haemochromatosis including thalassaemia and transfusional haemosiderosis; in patients in whom concomitant disorders (e.g. severe anaemia, hypoproteinaemia, renal or cardiac failure) preclude phlebotomy.....

Iron chelation - licensing in SCD

- Deferasirox (EXJADE) .... the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:
- - in patients with other anaemias aged 2 years and older.

Results with deferasirox- long-term follow up of Phase II trial patients

Vichinsky et al, B J Haem. 2011; 154: 387-397



Patients, *N*	185			177			168			141			135			114			99			93			77			70			47
Iron intake				Year 1						Year 2						Year 3						Year 4						Year 5			
Mean ± SD (mg/kg/d)				0·23 ± 0·13						0·22 ± 0·13						0·21 ± 0·12						0·22 ± 0·17						0·22 ± 0·12			

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

Deferiprone versus Deferoxamine in Sickle Cell Disease: Results from a 5-year long-term Italian multi-center randomized clinical trial

Giusi Calvaruso [a], Angela Vitrano [b], Rosario Di Maggio [a], Samir Ballas [c], Martin H. Steinberg [d], Paolo Rigano [a], Massimiliano Sacco [a], Paul Telfer [e], Disma Renda [a], Rita Barone [a], Aurelio Maggio [a,*], The Investigators of the Multicenter Randomized Clinical Trial of Deferiprone versus Deferoxamine in Sickle-Cell-Disease

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[b] Dipartimento di Scienze Economiche, Aziendali e Statistiche, Università di Palermo, Palermo, Italy
[c] Division of Hematology/Cardeza Foundation, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA
[d] Center of Excellence in Sickle Cell Disease, Department of Pediatrics, Pathology and Laboratory Medicine, Boston Medical Center, Boston, MA, USA
[e] Department of Hematology, The Royal London Hospital, London, United Kingdom

Means of serum ferritin levels (μg/l) during a 5-year multi-center randomized clinical trial comparing Deferiprone (DFP) versus Deferoxamine (DFO) treatment in Sickle-Cell-Disease.

Years	DFP mean ± sd (n)	DFO mean ± sd (n)
Baseline	1440.13 ± 712.80 (29)	1726.03 ± 694.01 (29)
1	1033.00 ± 737.41 (19)	1522.64 ± 954.98 (22)
2	1076.80 ± 897.51 (15)	1100.05 ± 798.61 (19)
3	580.10 ± 581.56 (10)	1127.68 ± 516.42 (16)
4	438.22 ± 320.81 (9)	1078.26 ± 356.31 (15)
5	695.00 ± 597.74 (7)	1333.85 ± 871.74 (14)

Conclusions for DEEP trial

- Increasing numbers of children with SCD on regular transfusion
- Additional chelation options are needed in addition to deferasirox
- Licensing of deferiprone for children with SCD would enhance options
- End points of SF and cardiac iron are unlikely to be as sensitive in SCD as in TM
- There are likely to be more SAE's reported in SCD children