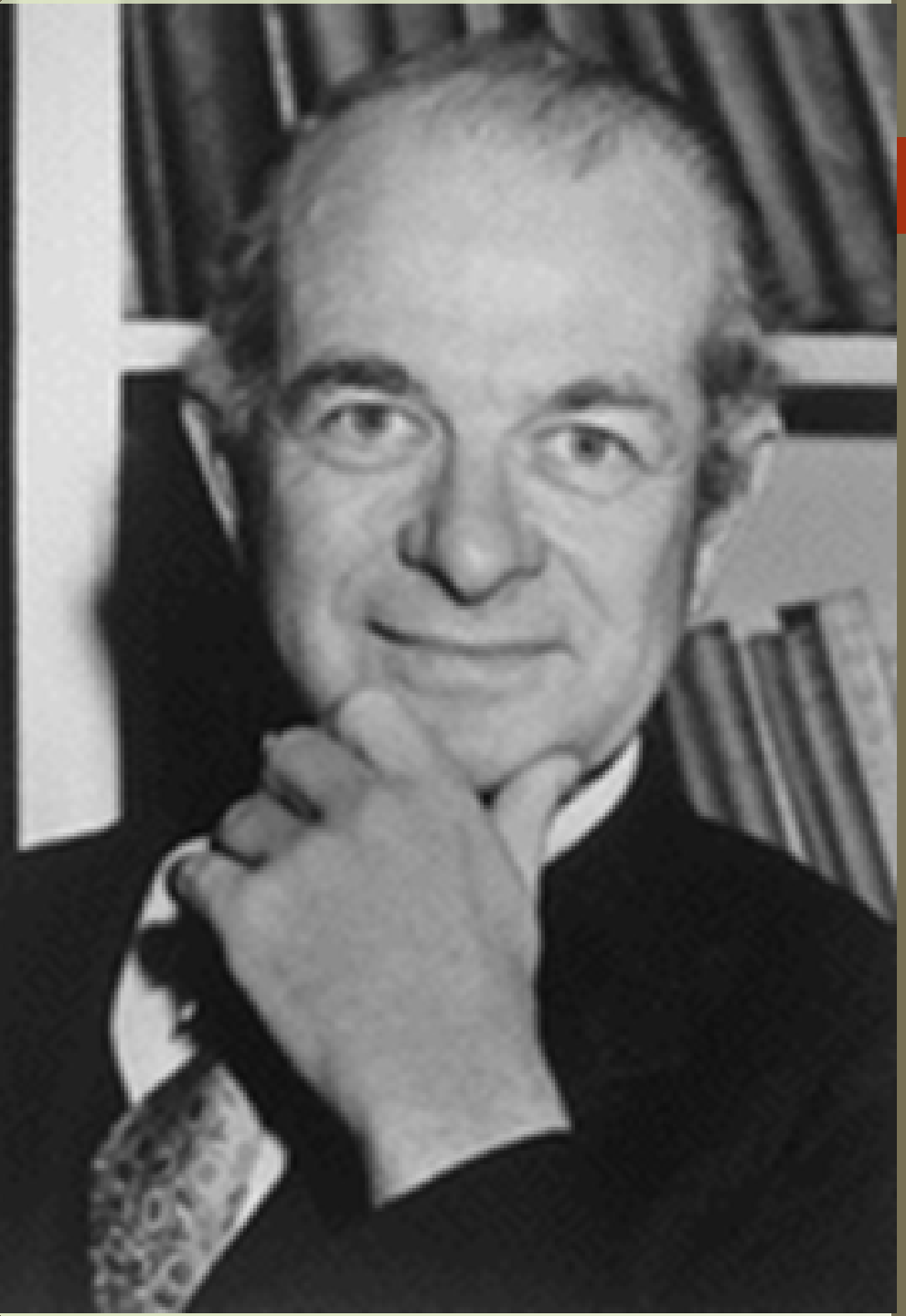
"Sickle cell disease: from diagnosis to cure!”

Dr. Ricardo Helman

Hospital Israelita Albert Einstein

São Paulo - Brazil



Sickle cell disease - history

1910 - James Herrick

First report of the disease

1946 - Accioly, Neel e Beet

Definition of the genetic basis of the disease

1949 - Pauling

Discovery of the "molecular disease“

1957 – Ingram

Genetic replacement in the beta chain

Definition

Genetic disease, autosomal recessive, characterized by the presence of two abnormal hemoglobins, at least one of which is Hb S

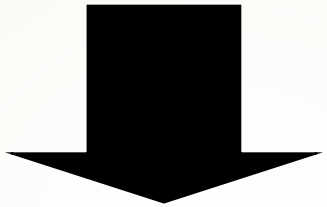
- Hb SS (Sickle Cell Anemia)
- Hb S / ß0 Thalassemia (S / ß0 Thalassemia)
- Hb SC (Hemoglobinopathy SC)
- Hb S / ß + Thalassemia (S / ß + Thalassemia)
- Other double heterozigoses with HbS

As Hemoglobinopatias

Hemoglobinopatia	No. RN/Ano
Anemia Falciforme (SS)	217.331
Doença SC	54.736
S β talassemia	11.074
β talassemia maior	22.989
HbE β talassemia	19.128
Doença HbH	9.568
Hb Barts	5.183

Weatherhall DJ Blood 2010
Modell B, Darlison M. Bull World Health Organ. 2008

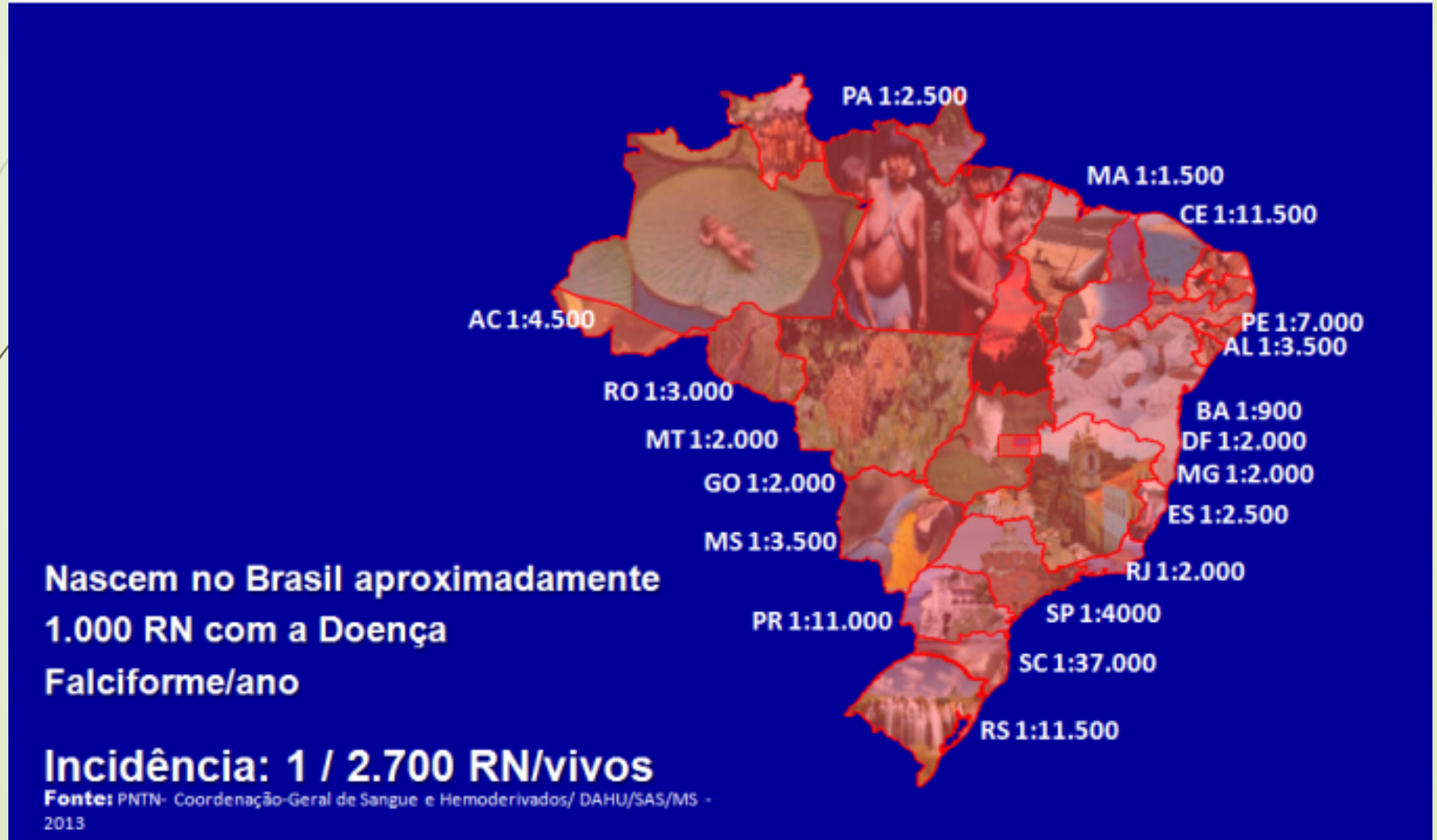
Monogenic Injury



- Chronic hemolytic anemia
- Vaso-occlusion
- Chronic inflammatory state
- Injury and bankruptcy of tissues and organs

Switzer et al., Lancet Neurol 2006

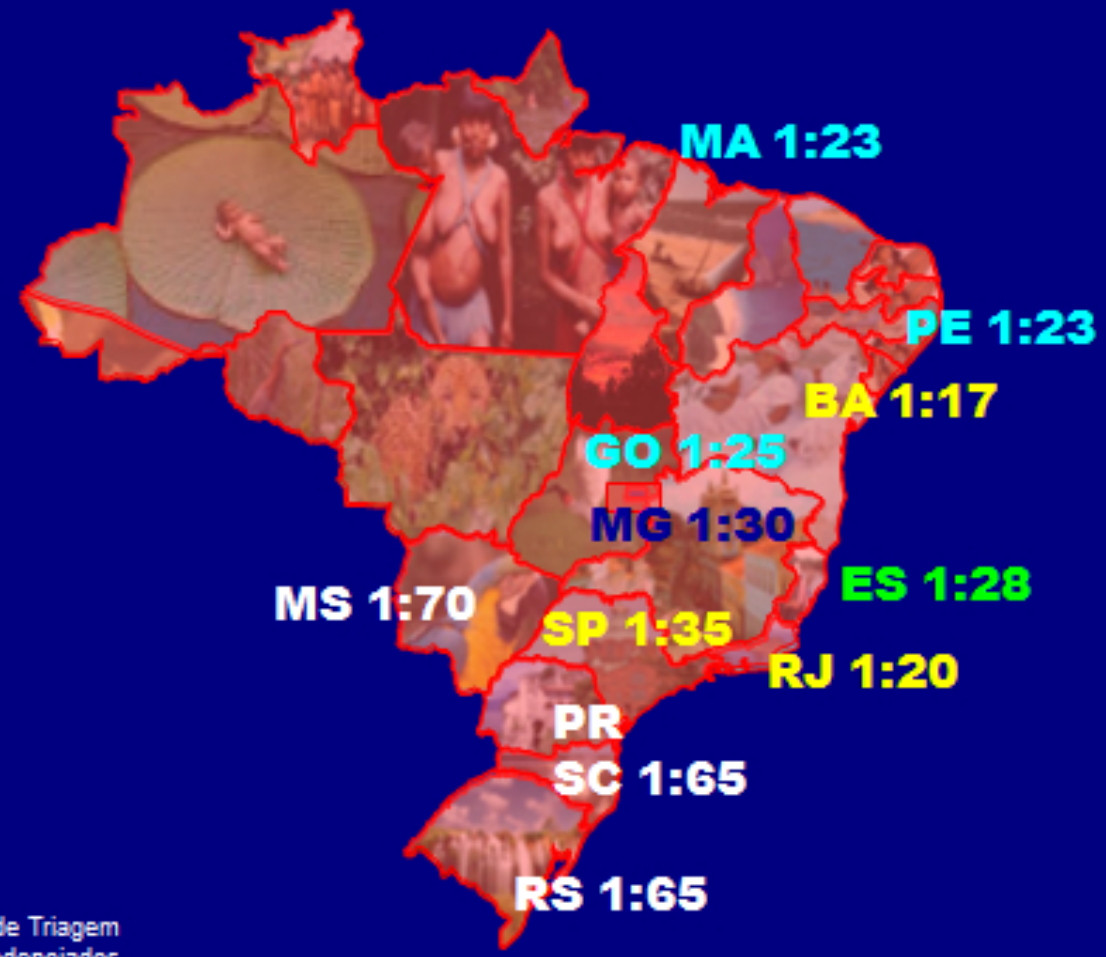
Incidência da Doença Falciforme



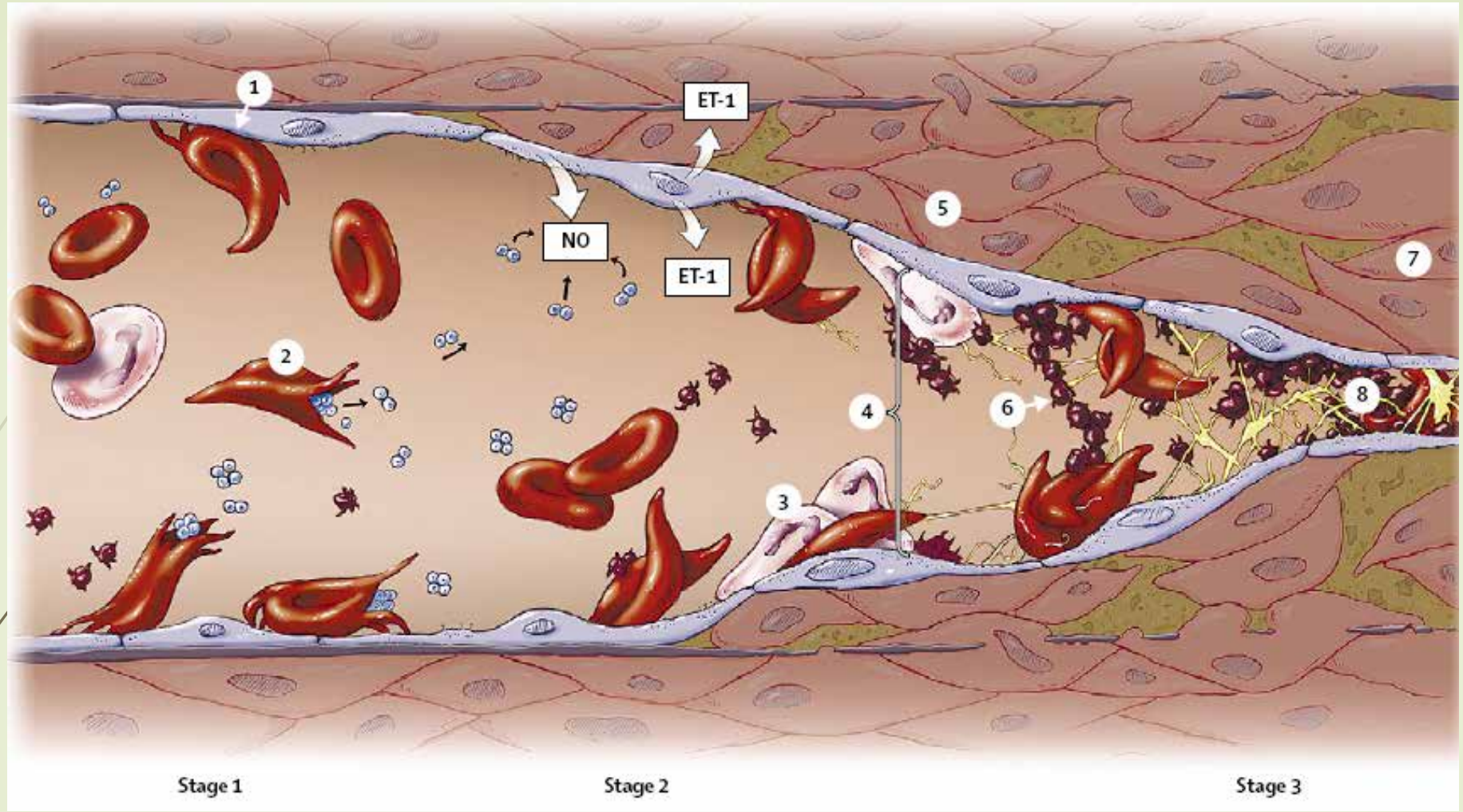
POLÍTICA NACIONAL DE SANGUE E HEMODERIVADOS

Incidência do Traço Falciforme

Nascem no Brasil cerca de 160.000 a 200.000 crianças / ano com traço falciforme



Fonte: PNTN/Ministério da Saúde, Programas Estaduais de Triagem Neonatal/Serviços de Referência em Triagem Neonatal Credenciados.



① **Aderência anormal ao endotélio vascular**

② **Hemólise intravascular**

③ **Aderência de leucócitos**

④ **- Tônus vasomotor**

⑤ **Proliferação de células musculares lisas e fibroblastos na íntima**

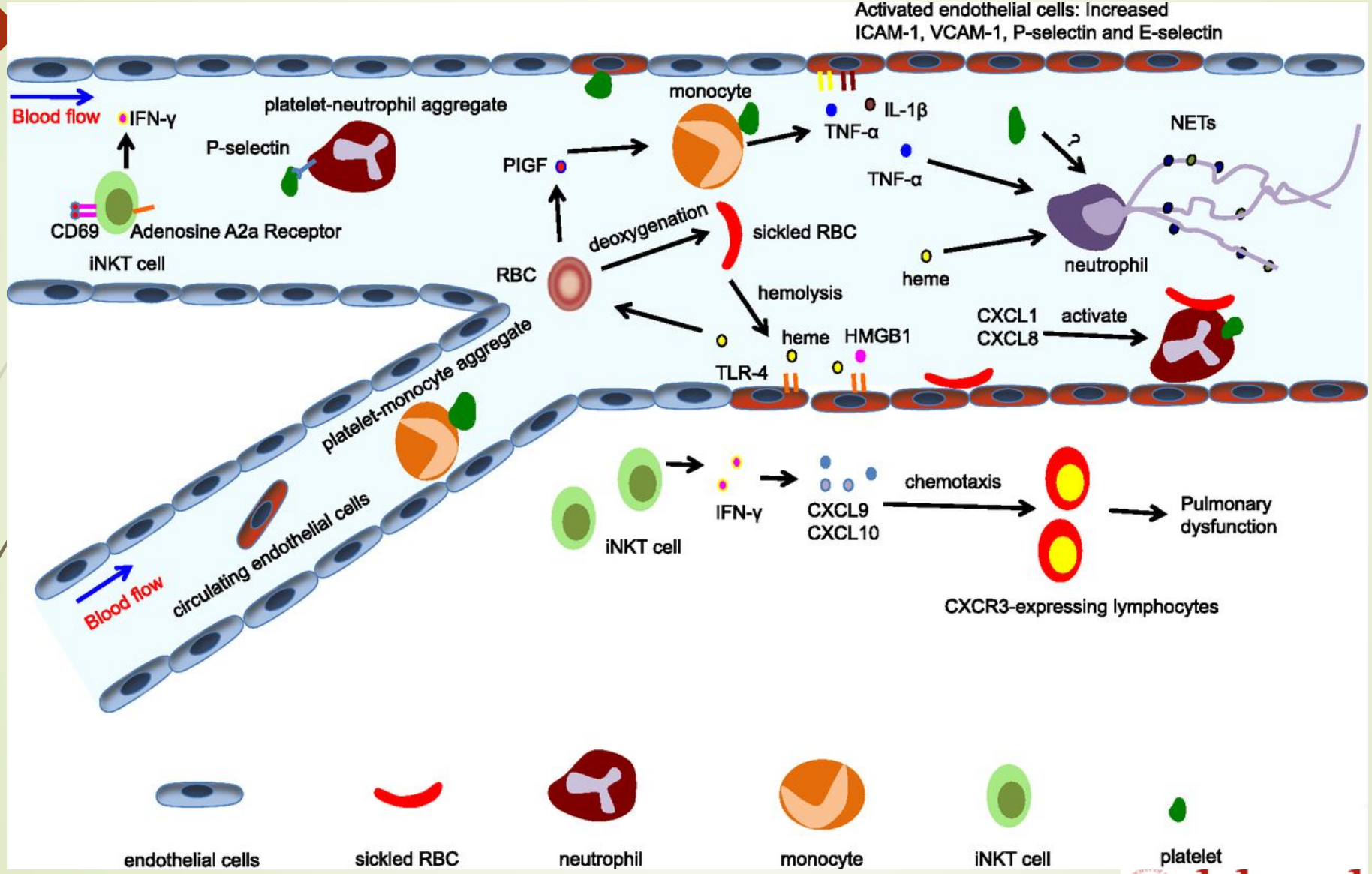
⑥ **Agregação plaquetária**

⑦ **Vasculopatia**

⑧ **Oclusão vascular**

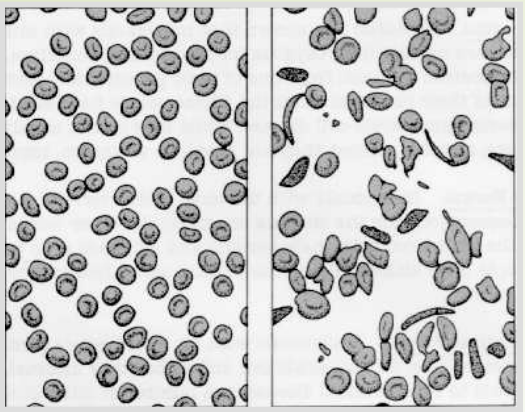
Switzer et al., Lancet Neurol 2006

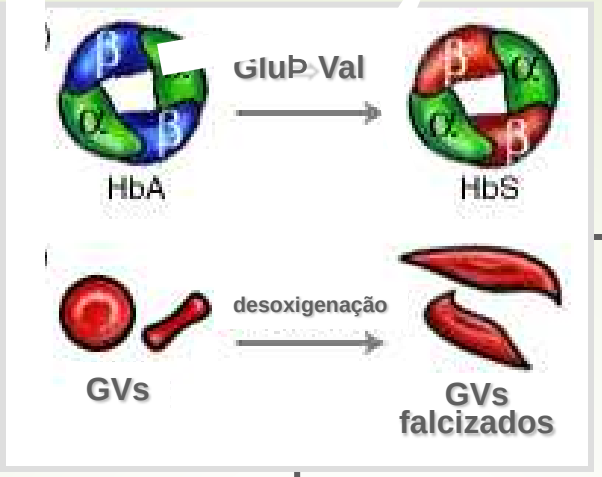
Inflammation in Sickle Cell Disease



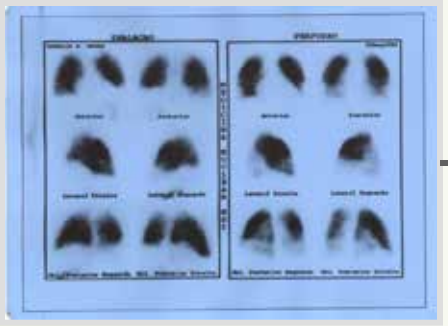
Dachuan Zhang et al. Blood 2016;127:801-809

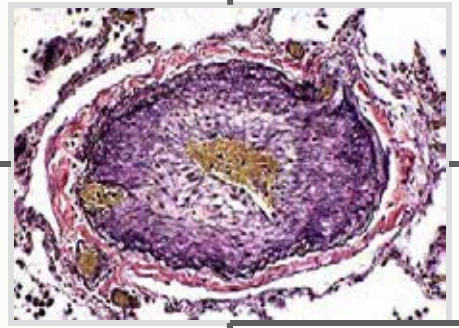
©2016 by American Society of Hematology




Glu Val
HbA
HbS
desoxigenação
GVs
GVs falcizados



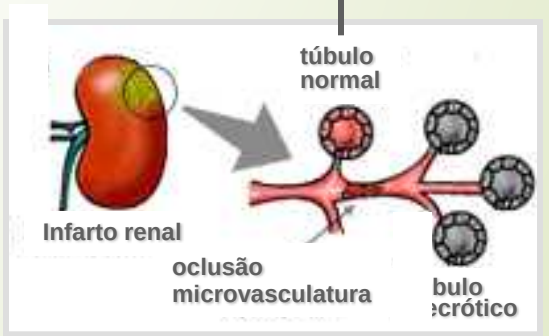








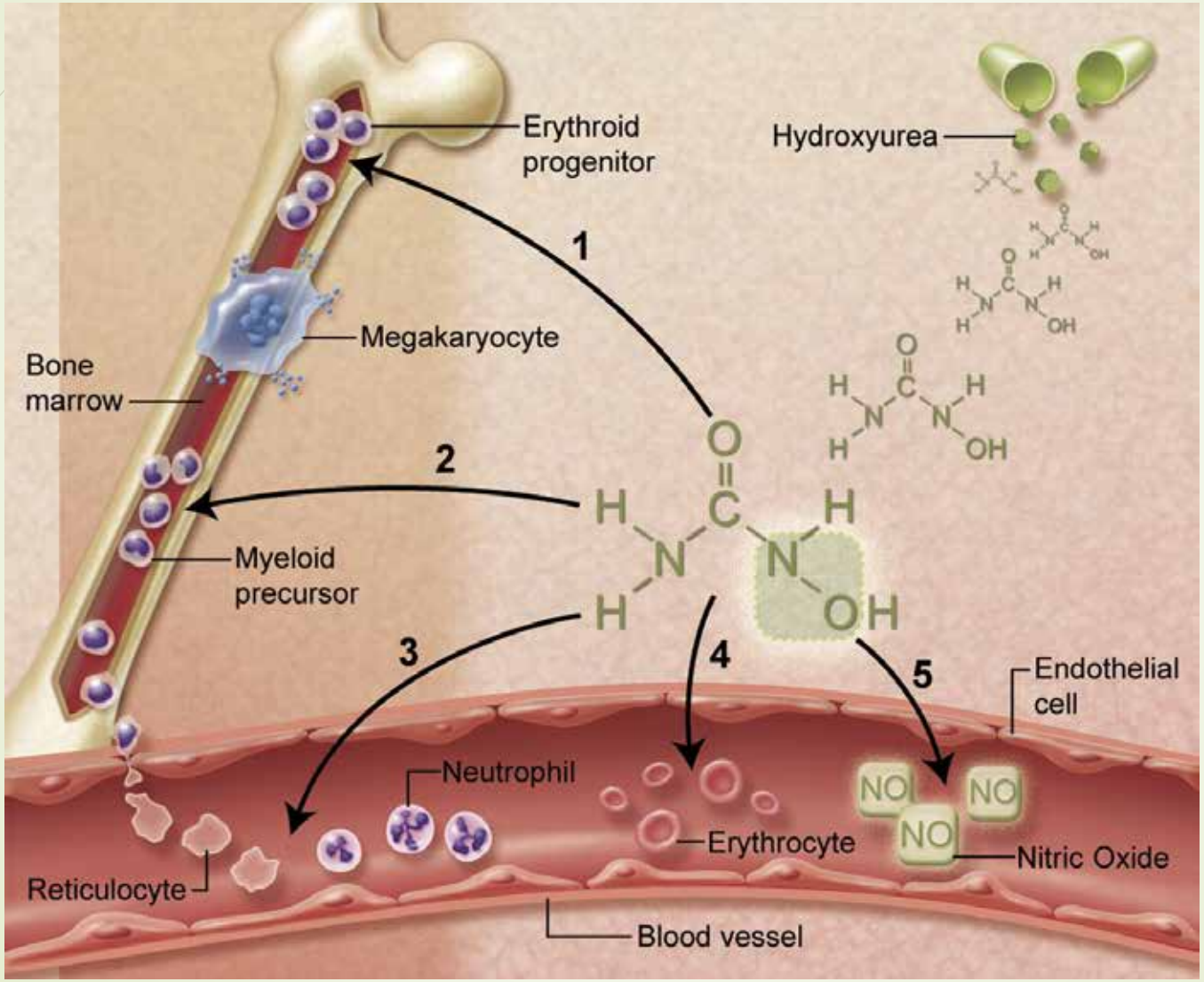



túbulo normal
Infarto renal
oclusão microvasculatura
bulo necrótico

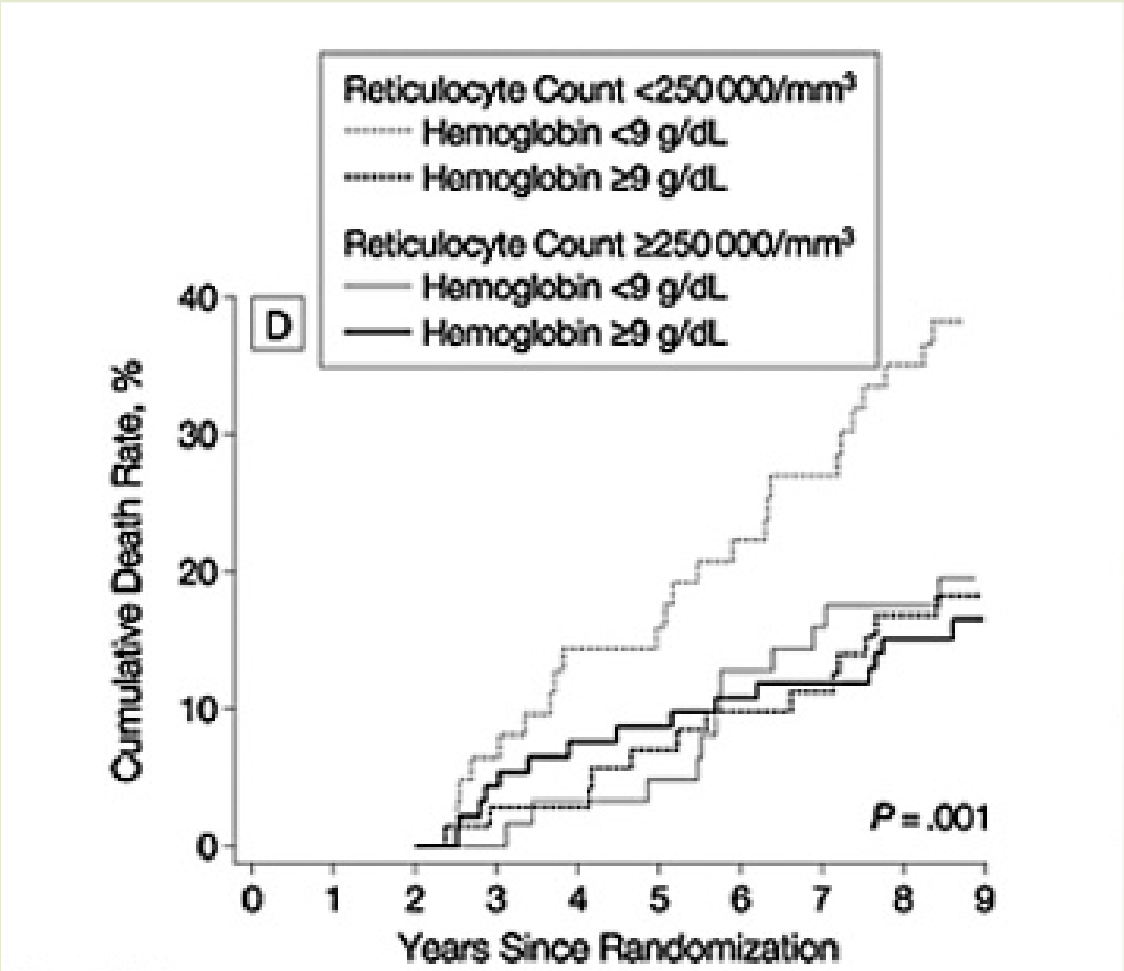
Complications

- Stroke
- Acute Thoracic Syndrome
- Chronic pain
- Infections

Painful crises



Hidroxiuréia

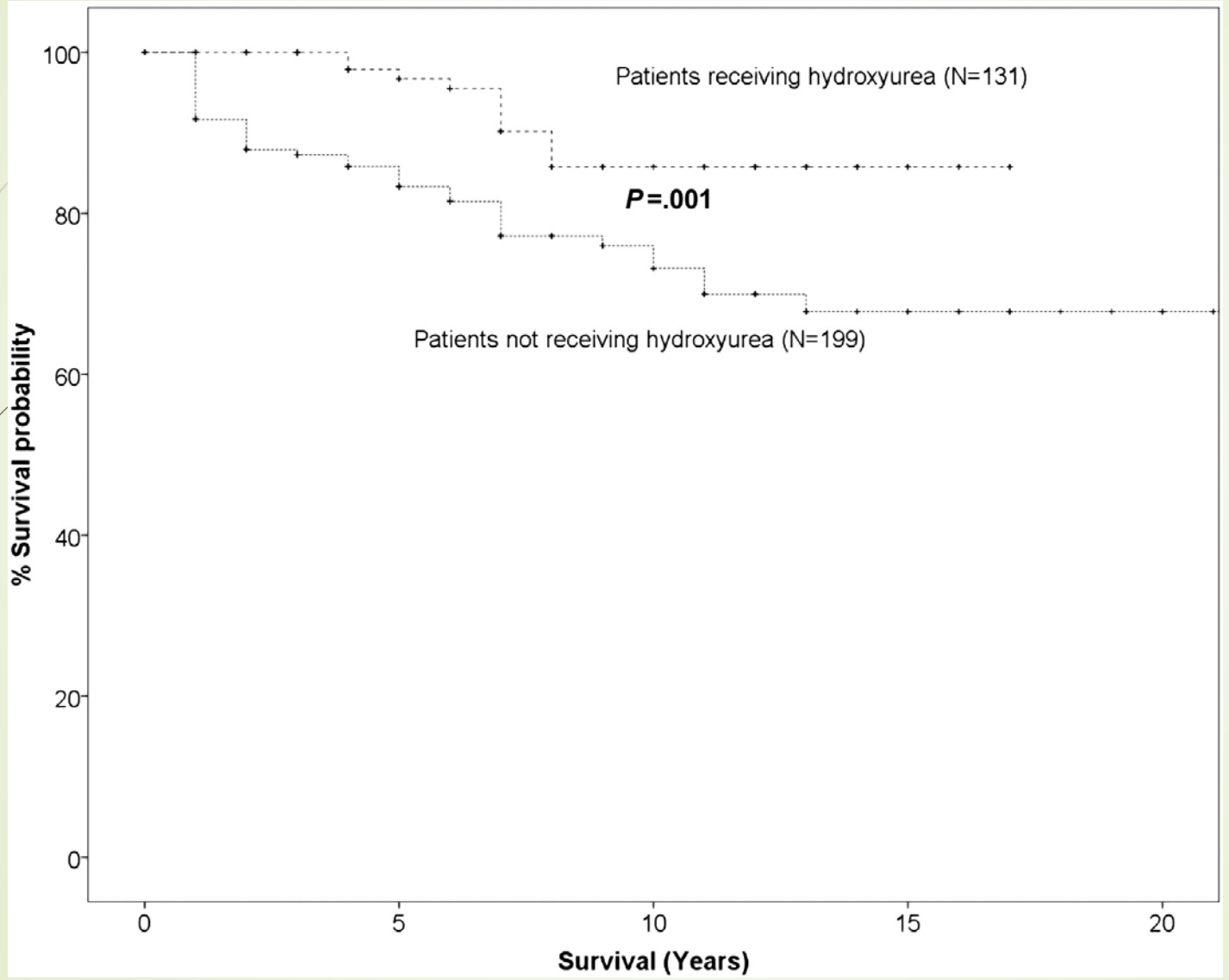


Reduced Episodes of acute chest pain,

Reduction of 40% in mortality

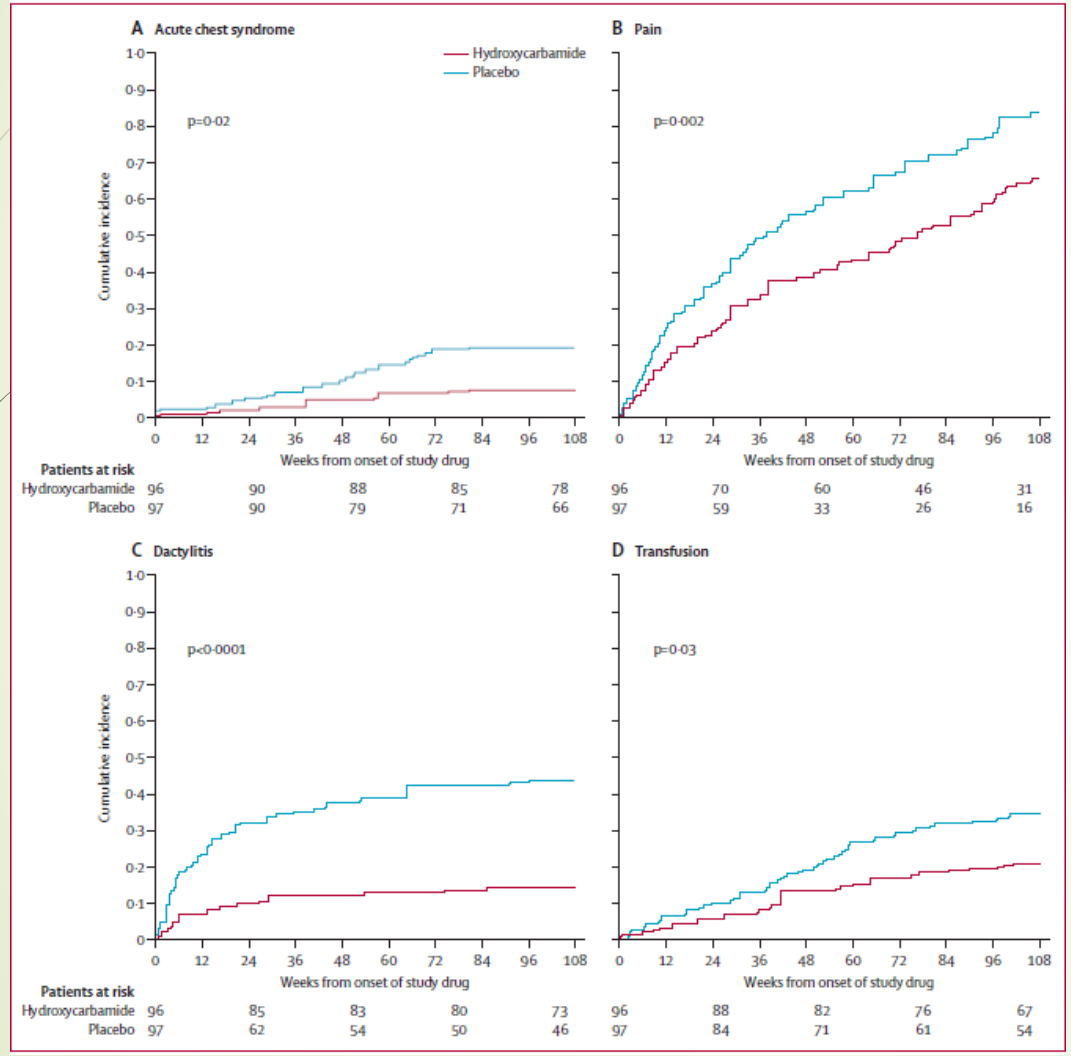
Steinberg et al. 2003

Hidroxiuréia



Voskaridou e col, blood 2010; Vol 115

Hidroxiureia childhood



Hydrea is safe and should be used on children> 8m

Wang c e cols, Lancet 2011: 377: 1663-72

Stroke

- Incidence: 8 to 10% (3 to 10 years)

Ischemic: children

Hemorrhagic: adults

- Location

Internal carotid (distal segment)

Middle and anterior cerebral artery

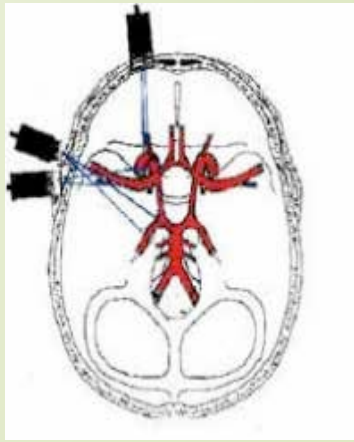
(Proximal segment)

Transcranial Doppler Ultrasound

Normal: < 170 cm/sec
"Suspeito": > 170 e < 200 cm/sec
Anormal: ≥ 200 cm/sec

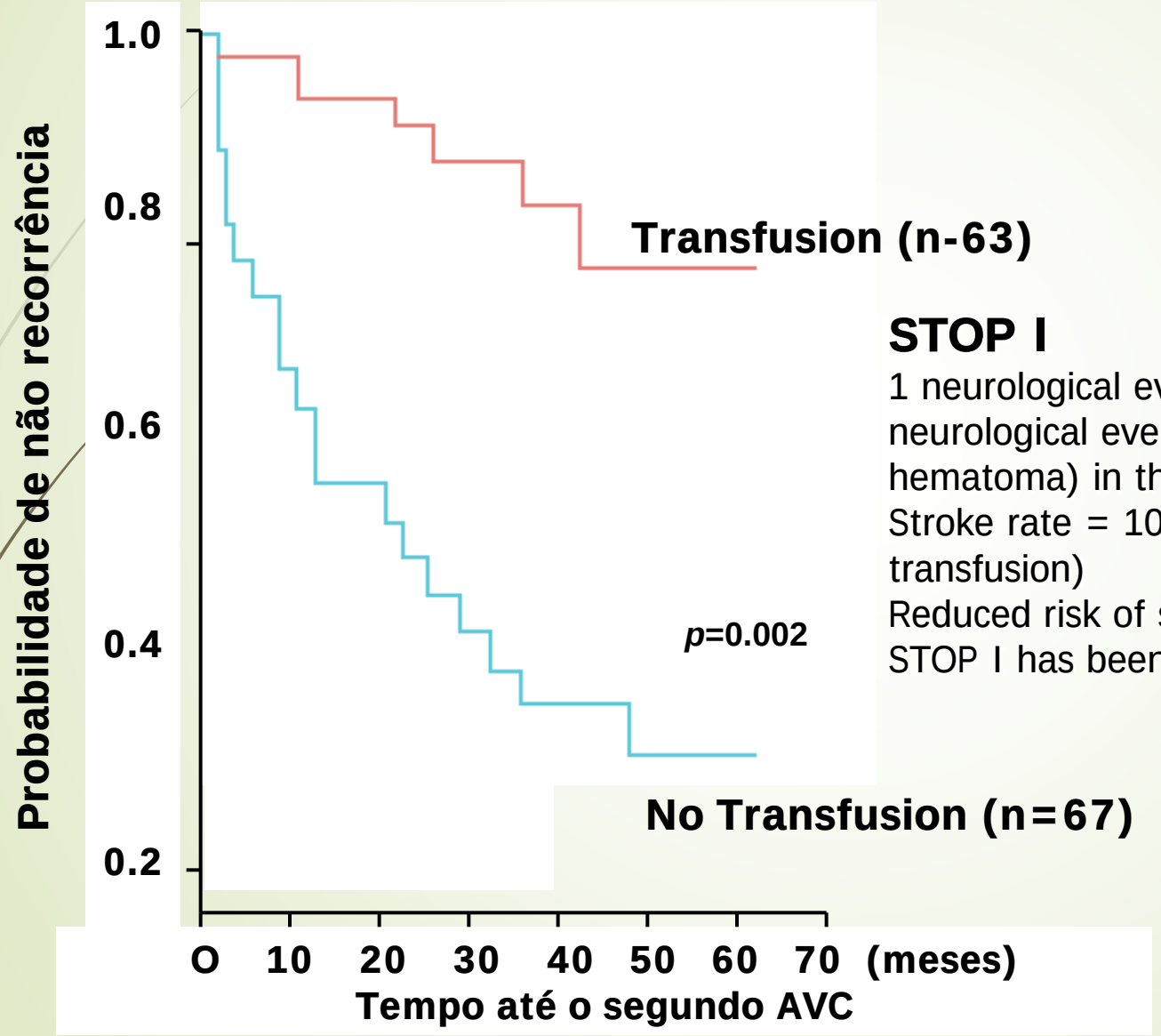






Adams et al, NEJM 1992; 326:605-10

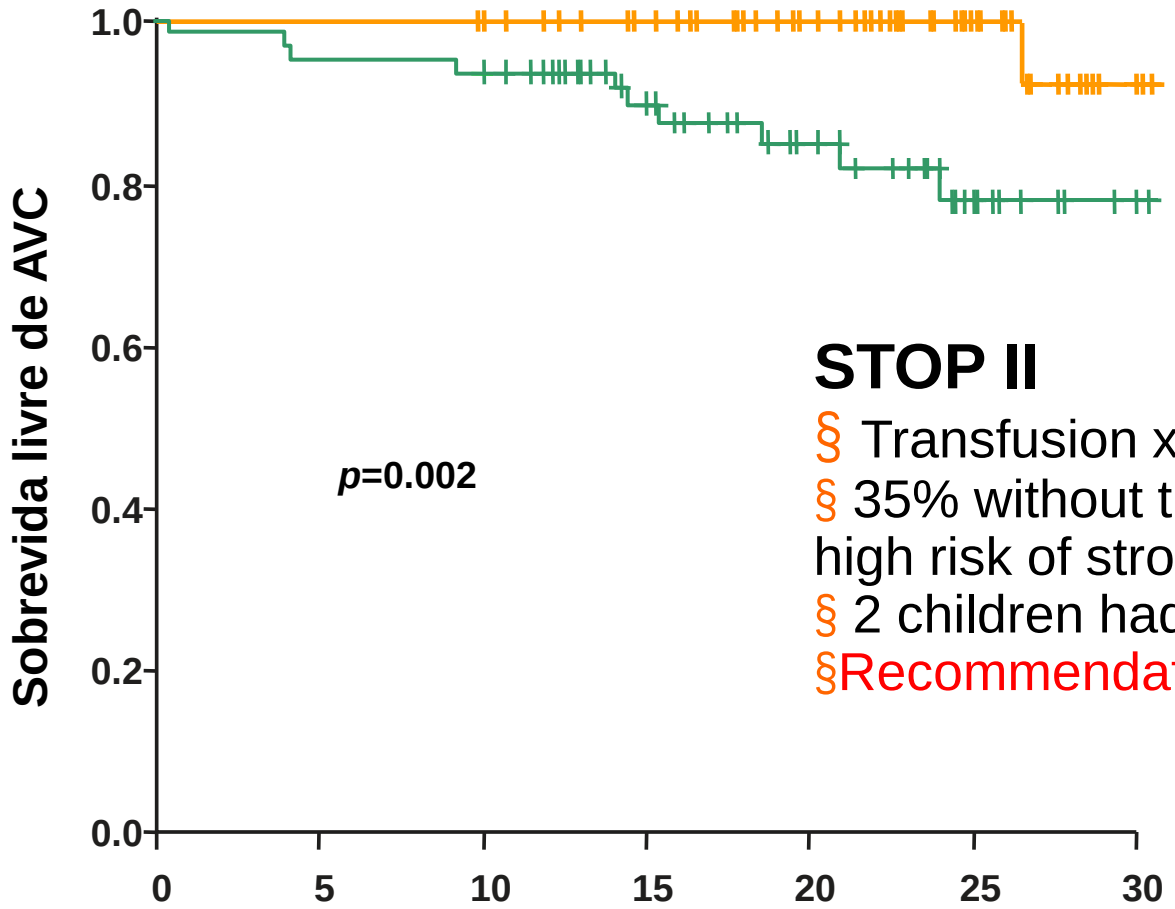
Effect of Regular Red Blood Transfusion On Recurrence of Stroke



STOP I

1 neurological event (stroke) versus 11 neurological events (10 strokes and 1 hematoma) in the non-transfusion group,
Stroke rate = 10% per year (arm without transfusion)
Reduced risk of stroke by 92% (p <0.001)
STOP I has been discontinued.

Stroke OS



STOP II

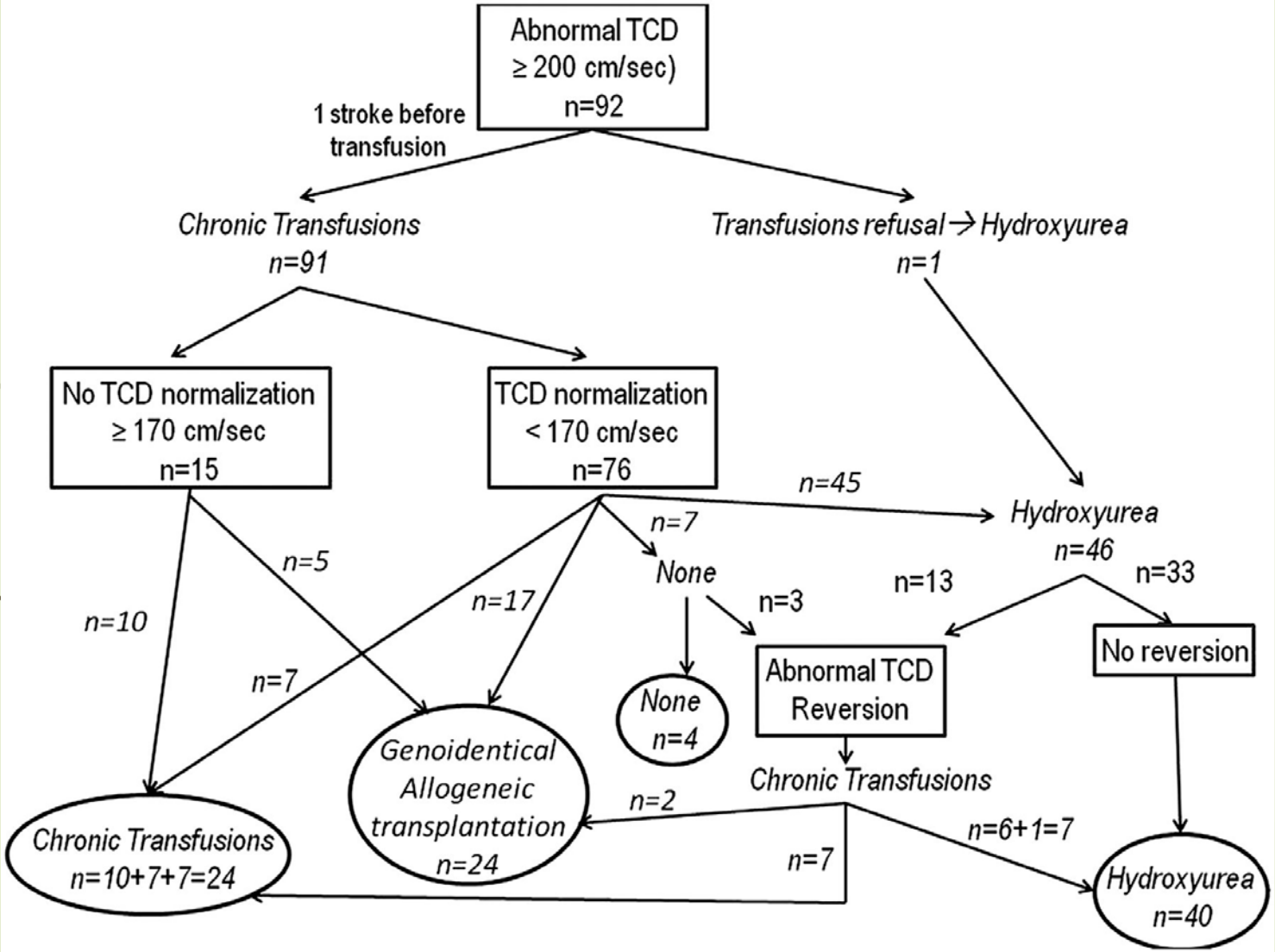
§ Transfusion x No Transfusion

§ 35% without transfusion returned to high risk of stroke

§ 2 children had stroke (± 5m)

§Recommendation: Do not stop Transfusions

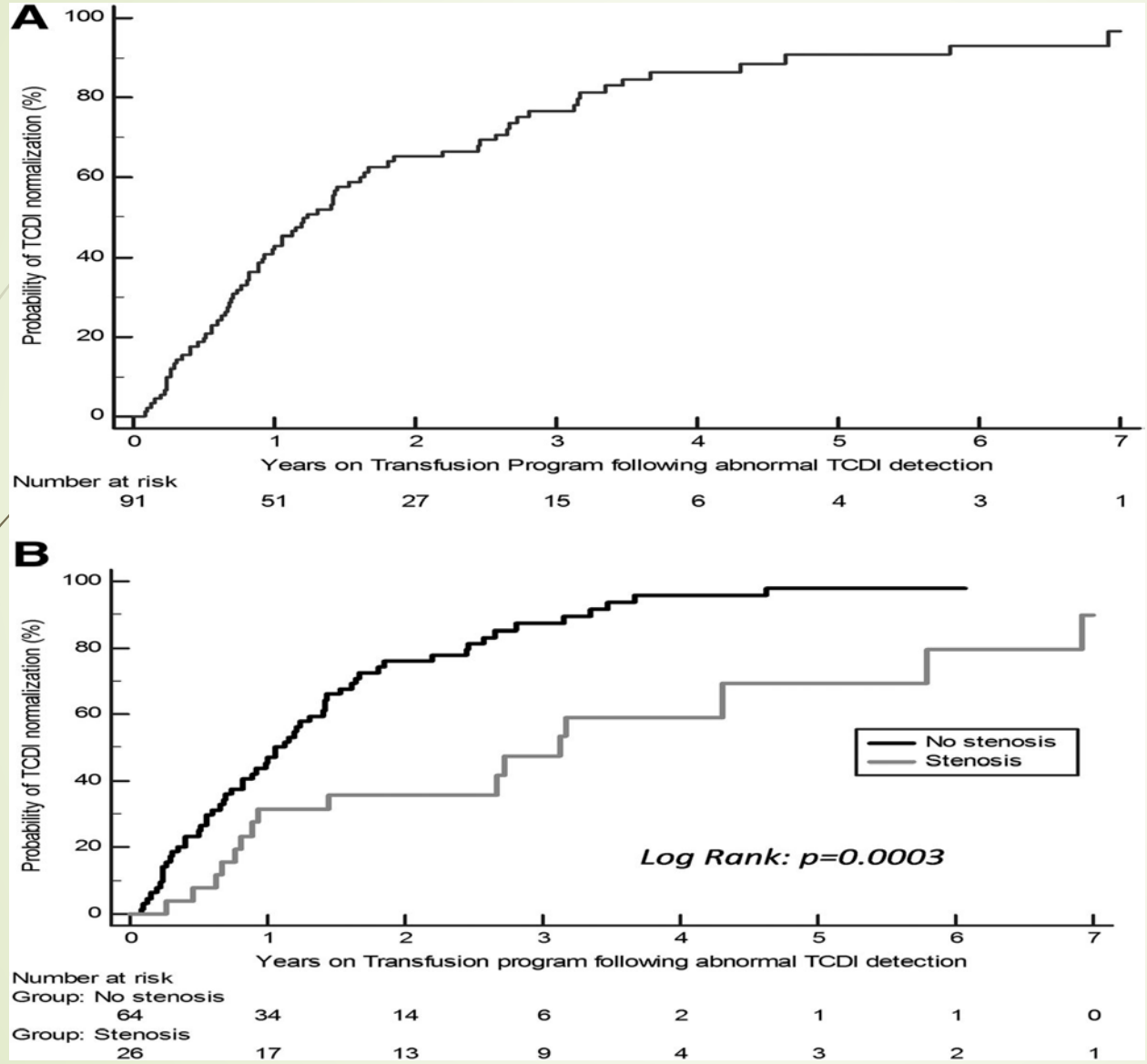
Adams RJ et al. (STOP II) N Engl J Med, 2005; 353:2769-2778



Françoise Bernaudin et al. Blood 2016;127:1814-1822

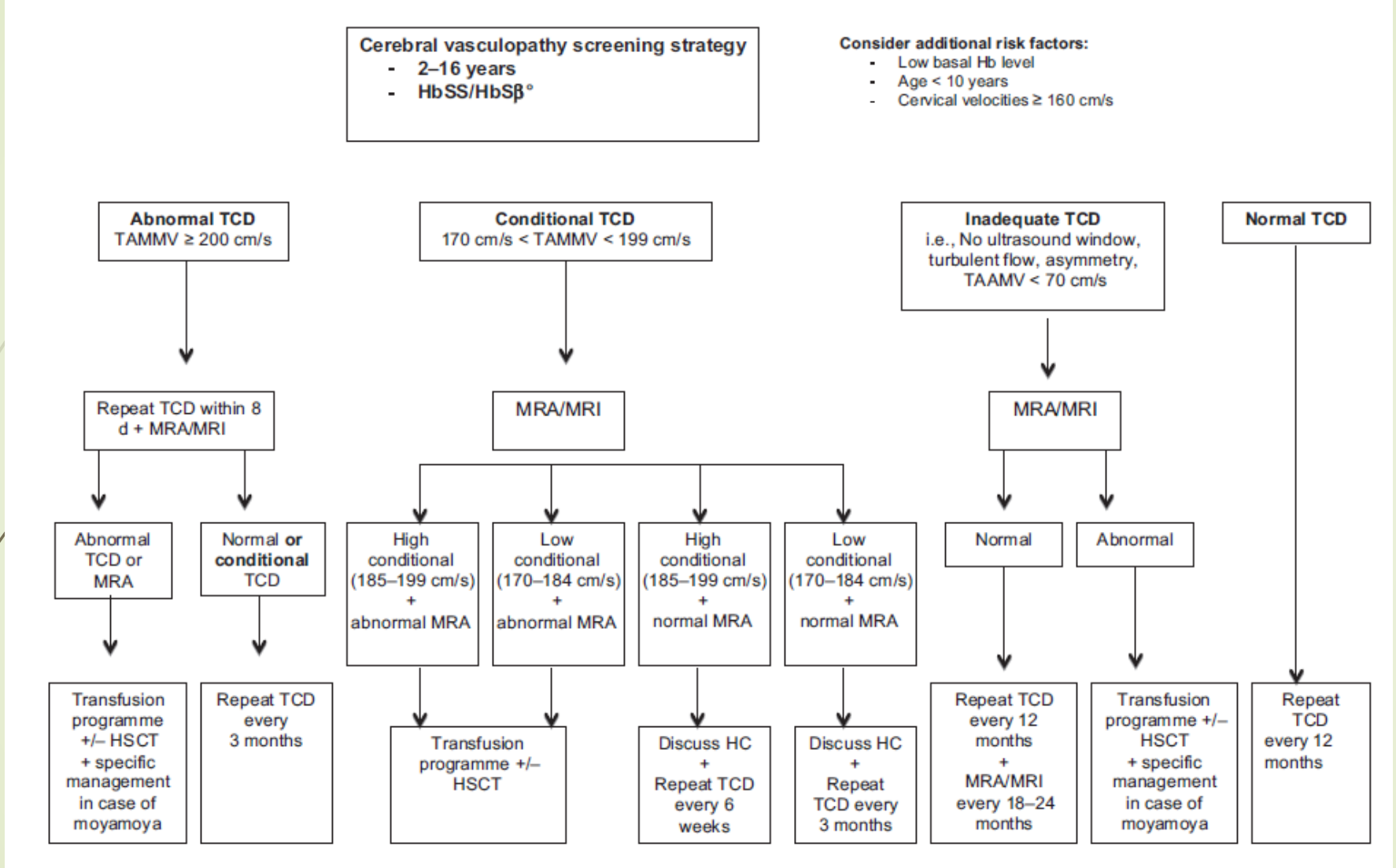
©2016 by American Society of Hematology

Patients with abnormal velocities.



Françoise Bernaudin et al. Blood 2016;127:1814-1822

©2016 by American Society of Hematology



British Journal of Haematology, 2015, **170**, 615–625

New Treatments

Table 1. Recently completed and ongoing studies targeting adhesion

Study title	Clinical trials #/Phase	Intervention	Status	Primary sponsor
Selectin inhibitors				
Study of GMI-1070 for the Treatment of Sickle Cell Pain Crisis	NCT01119833 Phase 2	GMI-1070 (rivipansel)	Complete	GlycoMimetics
Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-Occlusive Crisis in Hospitalized Subjects With Sickle Cell Disease	NCT02187003 Phase 3	GMI-1070 (rivipansel)	Ongoing	Pfizer
Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises	NCT01895361 Phase 2	SelG1	Ongoing	Selexys
Sevuparin Infusion for the Management of Acute VOC in Subjects With SCD	NCT02515838 Phase 2	Sevuparin	Ongoing	Dilaforette
β blockers				
Study of Propranolol as Anti-Adhesive Therapy in Sickle Cell Disease (SCD)	NCT01077921 Phase 2	Propranolol	Complete	Duke Univ.
Propranolol and Red Cell Adhesion in Non-asthmatic Children with Sickle Cell Disease	NCT02012777 Phase 1	Propranolol	Ongoing	Univ. of Miami
Other inhibitors of adhesion				
Phase III Randomized Study of Poloxamer 188 for Vaso-Occlusive Crisis of Sickle Cell Disease	NCT00004408 Phase 3	Poloxamer 188	Complete	Mast Therapeutics. CytRx
Evaluation of Purified Poloxamer 188 in Vaso-Occlusive Crisis of Sickle Cell Disease (EPIC)	NCT01737814 Phase 3	Poloxamer 188	Ongoing	Mast Therapeutics

BLOOD, 18 FEBRUARY 2016 x VOLUME 127, NUMBER 7

Table 2. Recently completed and ongoing studies targeting inflammation

Study title	Clinical trials #/Phase	Intervention	Status	Primary sponsor
Adenosine and invariant NK T (iNKT) cells				
Adenosine 2A Agonist Lexiscan in Children and Adults With Sickle Cell Disease	NCT01085201 Phase 1	Regadenoson	Complete	Dana-Farber Cancer Institute
A Phase II Trial of Regadenoson in Sickle Cell Anemia	NCT01788631 Phase 2	Regadenoson	Ongoing	Dana-Farber Cancer Institute
Safety, Pharmacokinetic, and Pharmacodynamic Study of NKTT120 in Adult Patients With Stable Sickle Cell Disease (SCD)	NCT01783691 Phase 1	NKTT120	Complete	NKT Therapeutics
Leukotrienes				
Phase 2 Study of Montelukast for the Treatment of Sickle Cell Anemia	NCT01960413 Phase 2	Montelukast	Ongoing	Vanderbilt Univ.
Trial of Zileuton CR in Children and Adults With Sickle Cell Disease	NCT01136941 Phase 1	Zileuton	Complete	Children's Hospital Medical Center, Cincinnati
Neutrophil adhesion and non-specific anti-inflammatory reagents				
Intravenous Gammaglobulin for Sickle Cell Pain Crises	NCT01757418 Phase 1/2	IVIg	Ongoing	A. Einstein College of Medicine, Yeshiva Univ.
Effect of Simvastatin Treatment on Vaso-occlusive Pain in Sickle Cell Disease	NCT01702246 Phase 2	Simvastatin	Ongoing	Children's Hospital & Research Center Oakland

Bone Marrow Transplantation

CONITEC Comissão Nacional de Incorporação de Tecnologias no SUS

6. RECOMENDAÇÃO DA CONITEC

Os membros da CONITEC presentes na 31ª reunião da CONITEC, realizada nos dias 3 e 4 de dezembro de 2014, por unanimidade, deliberaram por recomendar a incorporação da indicação de Transplante de Células-tronco Hematopoéticas em Doença Falciforme no Regulamento Técnico do Sistema Nacional de Transplantes.

BMO

Inclusion criteria:

Under 16 years and identical HLA donor

Have had one of the following events:

Stroke or acute neurological event lasting longer than 24 hours

Acute thoracic syndrome

No response to hydroxyurea

Dactilite < 1 y , leucocitose e Hb < 7 g/dL

Table 1. Transplantations for SCD by donor type and OS according to EBMT-Eurocord and CIBMTR

	EBMT-Eurocord (1986-2013)	CIBMTR (1986-2012)
Transplantations for SCD		
Total	611	627
Type of donor		
HLA-identical	487	430
CB related and unrelated	73	71
Haploidentical donor	34	61
Other unrelated donor	17	65
OS		
1 y	95% ± 1%	96% ± 2%
2 y	94% ± 1%	94% ± 1%

Eliane Gluckman Hematology 2013;2013:370-376

blood

2007 110: 2749-2756
Prepublished online July 2, 2007;
doi:10.1182/blood-2007-03-079665

Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease

- Condicionamento: Mieloablativo

1. Bussulfano 16mg/kg D-10 a -7
2. Ciclofosfamida 200mg/Kg D-5 a -2
3. ATG 20mg/Kg D-6 a -3

- Profilaxia GVHD

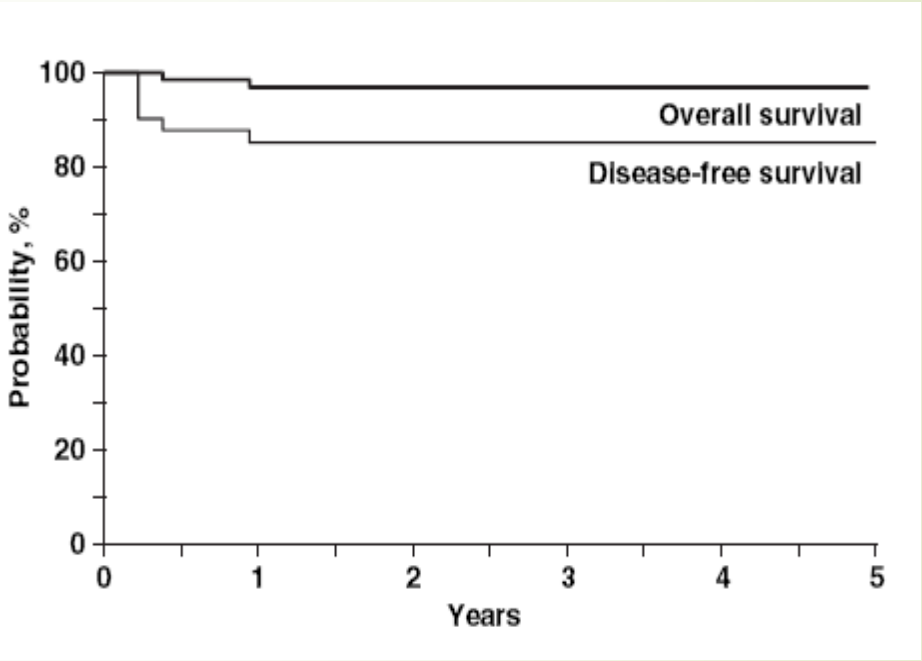
1. Mtx + Csa

- Cuidados:

1. Plaq> 50.000
2. Hb> 9,0g/L
3. Blood Pressure control

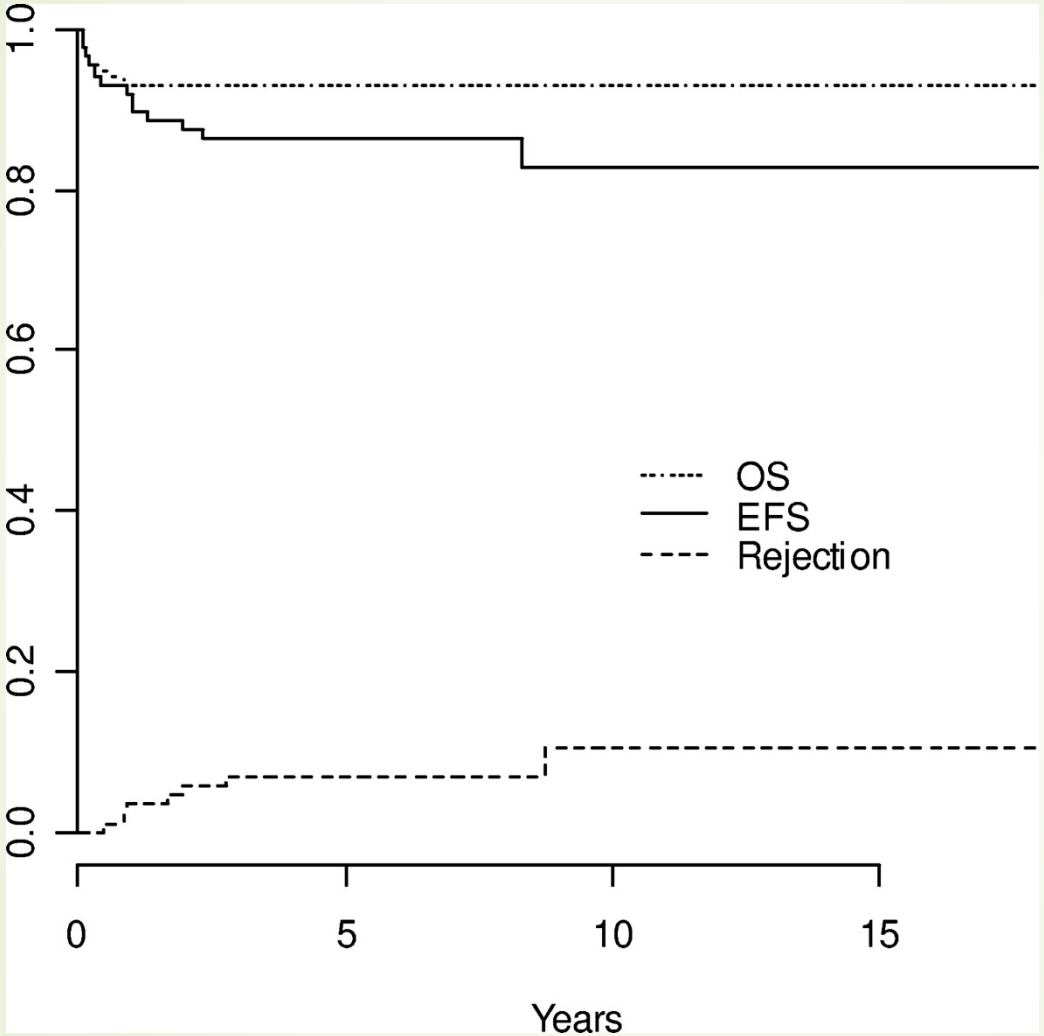
BMO

- N=67
- age – 10 (2 – 27)
- Main indications:
  - 42% stroke
  - 35% STA
  - 36% ≥ 3 CVO 12 m
- Avaliação pós- TMO
  - DECH aguda 10%
  - DECH cronica
- Death – 3 patients
  - 1 stroke – 5m after BMO
  - 1 falencia múltiplos órgãos – 1y
  - 1 cause unknown – 8y



Panepinto JA, Br Journal Haematology 2007

Estimated outcomes: OS, EFS, and cumulative incidence of rejection in the 87 patients.

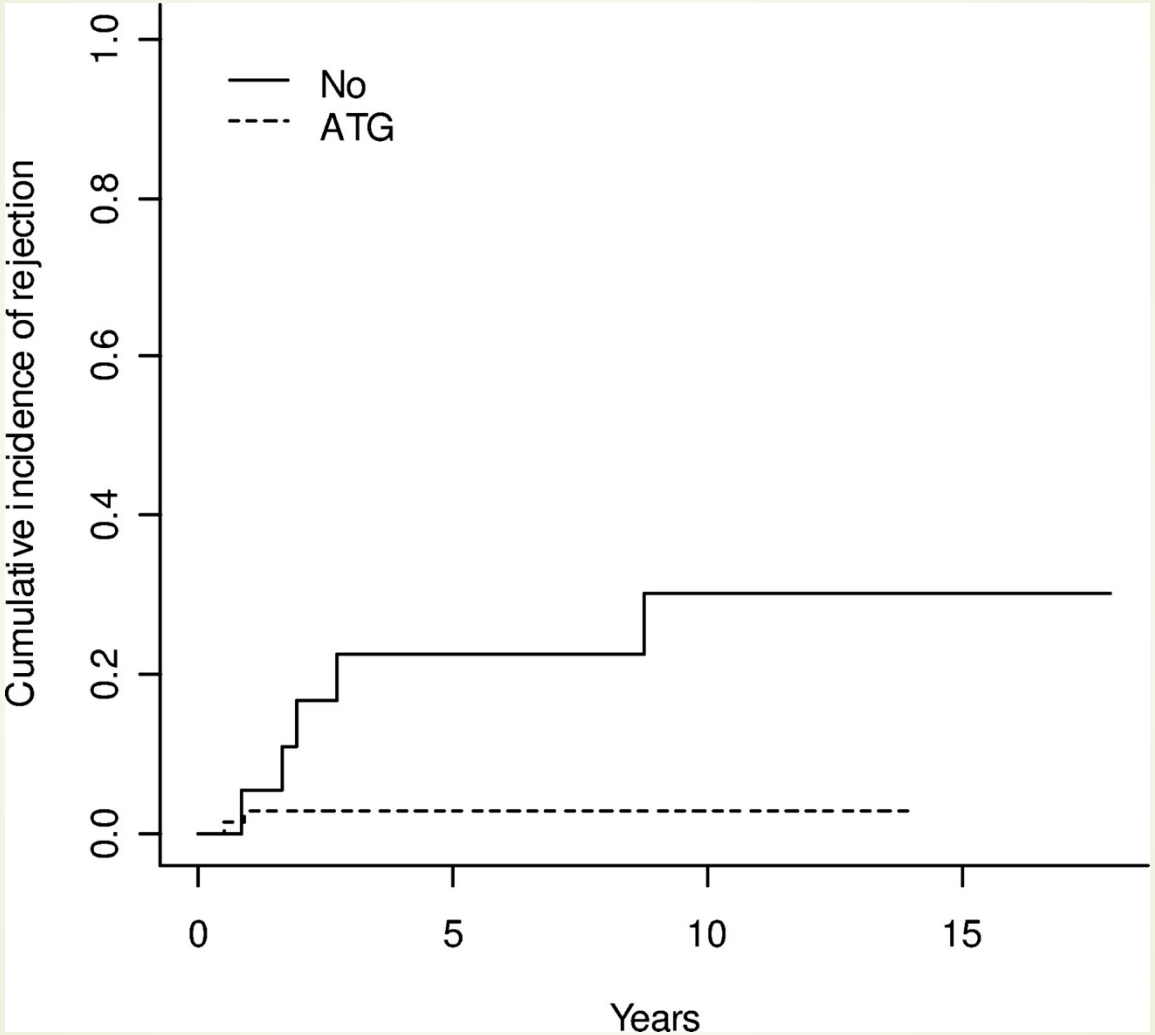


Françoise Bernaudin et al. Blood 2007;110:2749-2756

©2007 by American Society of Hematology

blood

Conditioning ATG X no ATG



Françoise Bernaudin et al. Blood 2007;110:2749-2756

©2007 by American Society of Hematology

Long-Term Outcome and Evaluation of Organ Function in Pediatric Patients Undergoing Haploidentical and Matched Related Hematopoietic Cell Transplantation for Sickle Cell Disease

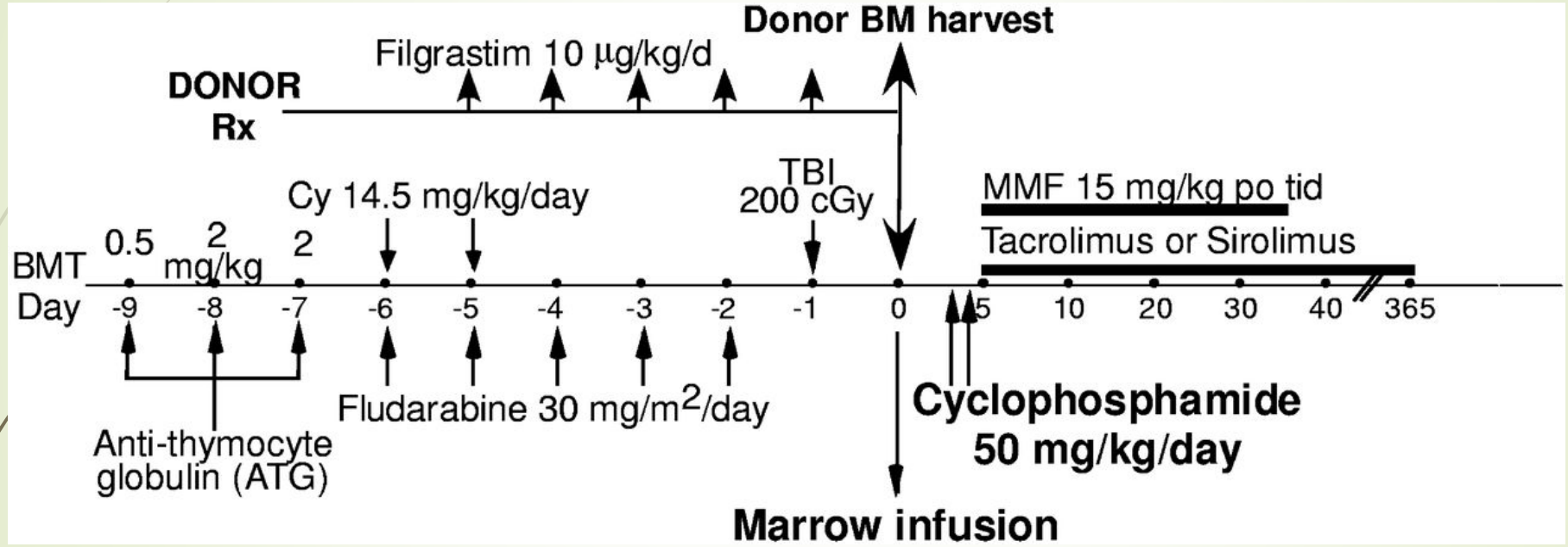
Mari H. Dallas, Brandon Triplett, David R. Shook, Christine Hartford, Ashok Srinivasan, Joseph Laver, Russell Ware, Wing Leung

Biology of Blood and Marrow Transplant
Volume 19, Issue 5, Pages 820-830 (May 2013)
DOI: 10.1016/j.bbmt.2013.02.010



Copyright © 2013 American Society for Blood and Marrow Transplantation Terms and Conditions

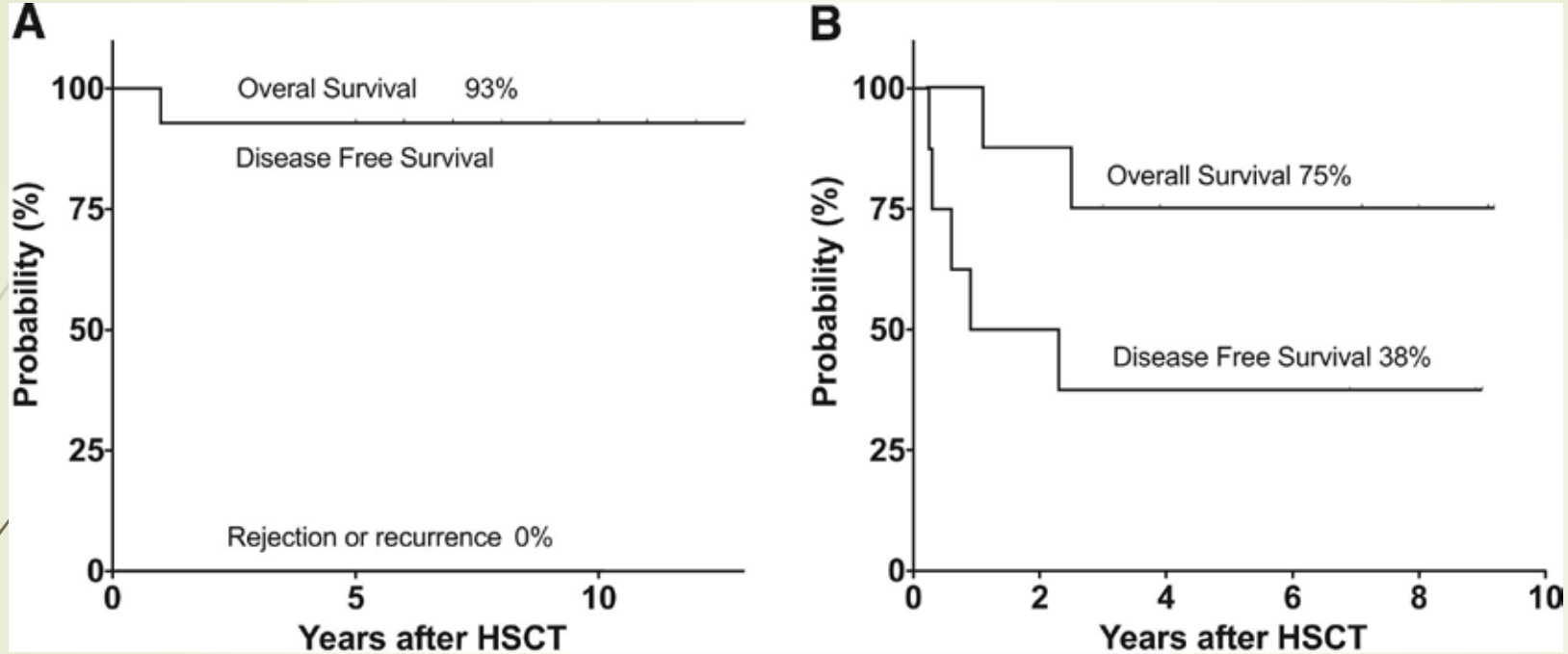
Haplo BMO



Javier Bolaños-Meade et al. Blood 2012;120:4285-4291

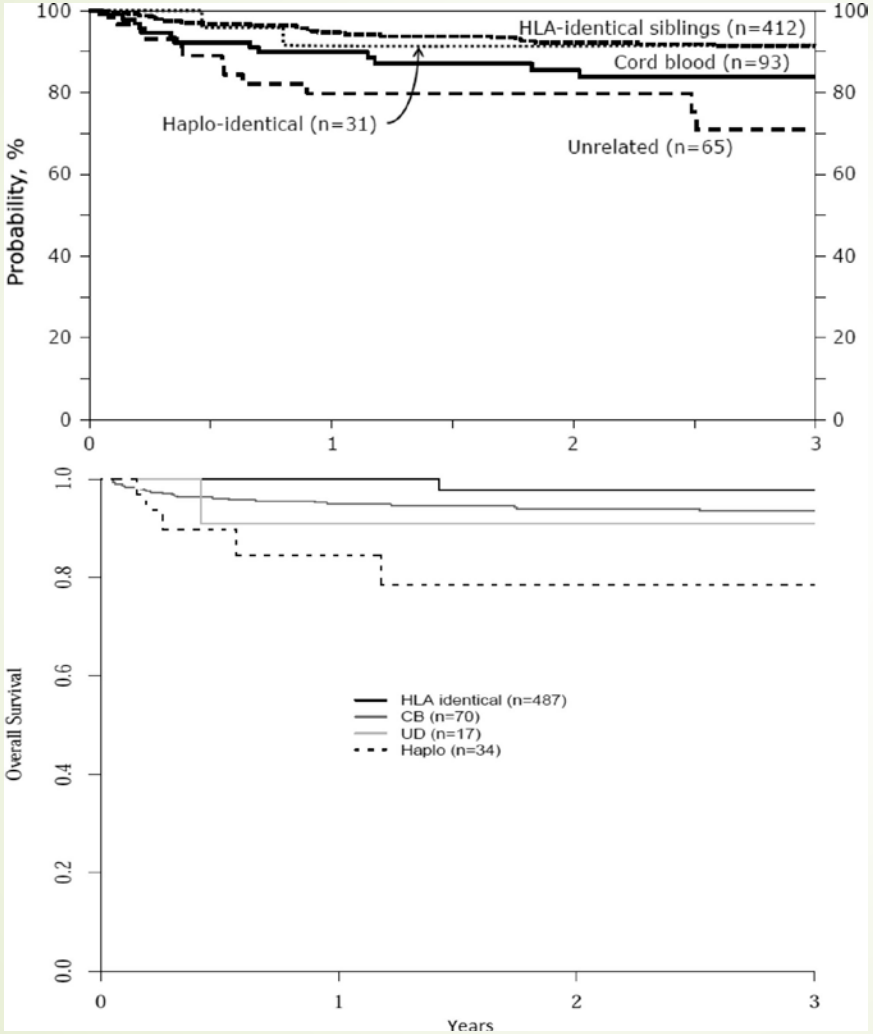
©2012 by American Society of Hematology

Figure 1



Biology of Blood and Marrow Transplant 2013 19, 820-830DOI: (10.1016/j.bbmt.2013.02.010)
Copyright © 2013 American Society for Blood and Marrow Transplantation Terms and Conditions

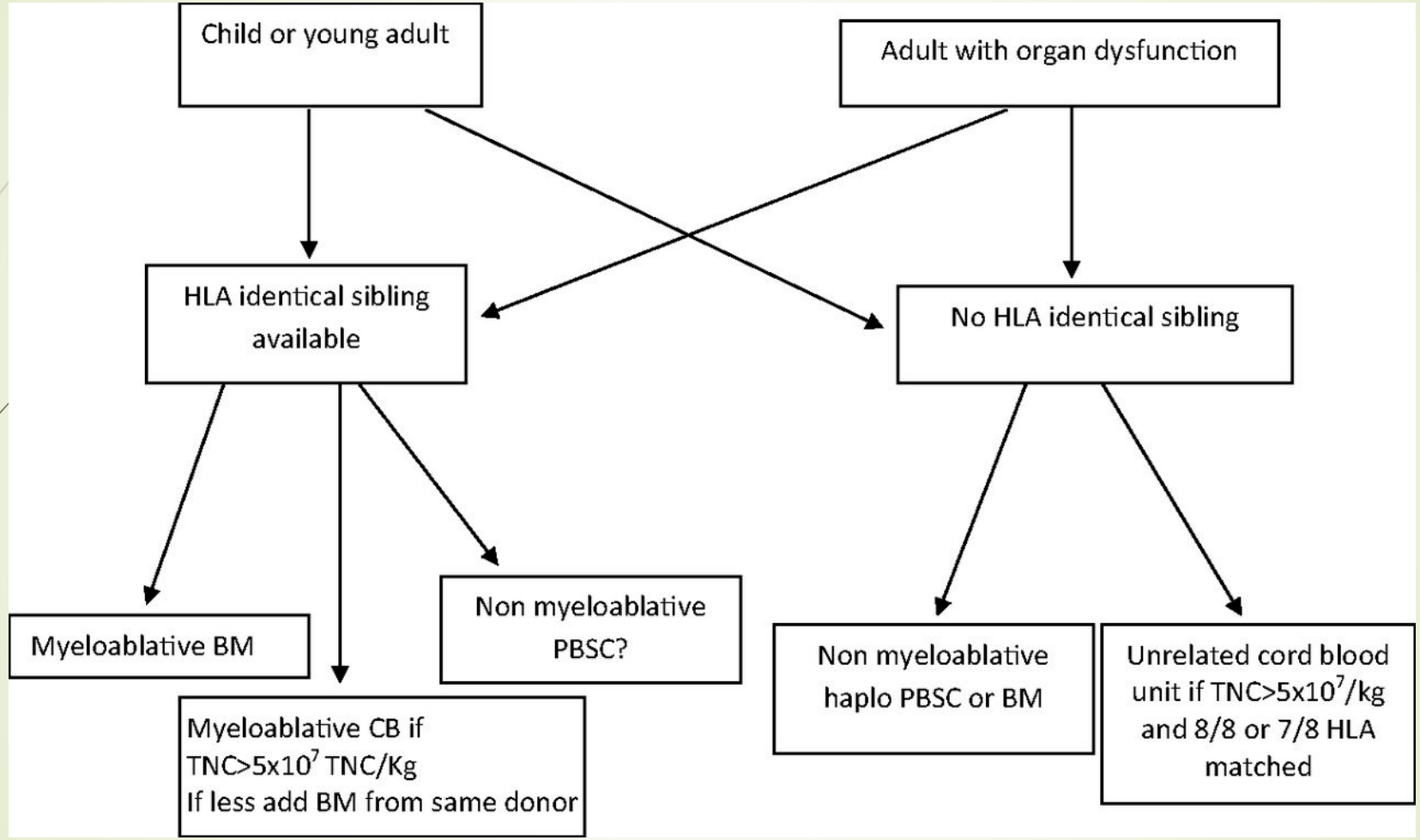
Overal Survival.



Eliane Gluckman Hematology 2013;2013:370-376

©2013 by American Society of Hematology

Choice of donors for patients with SCD.



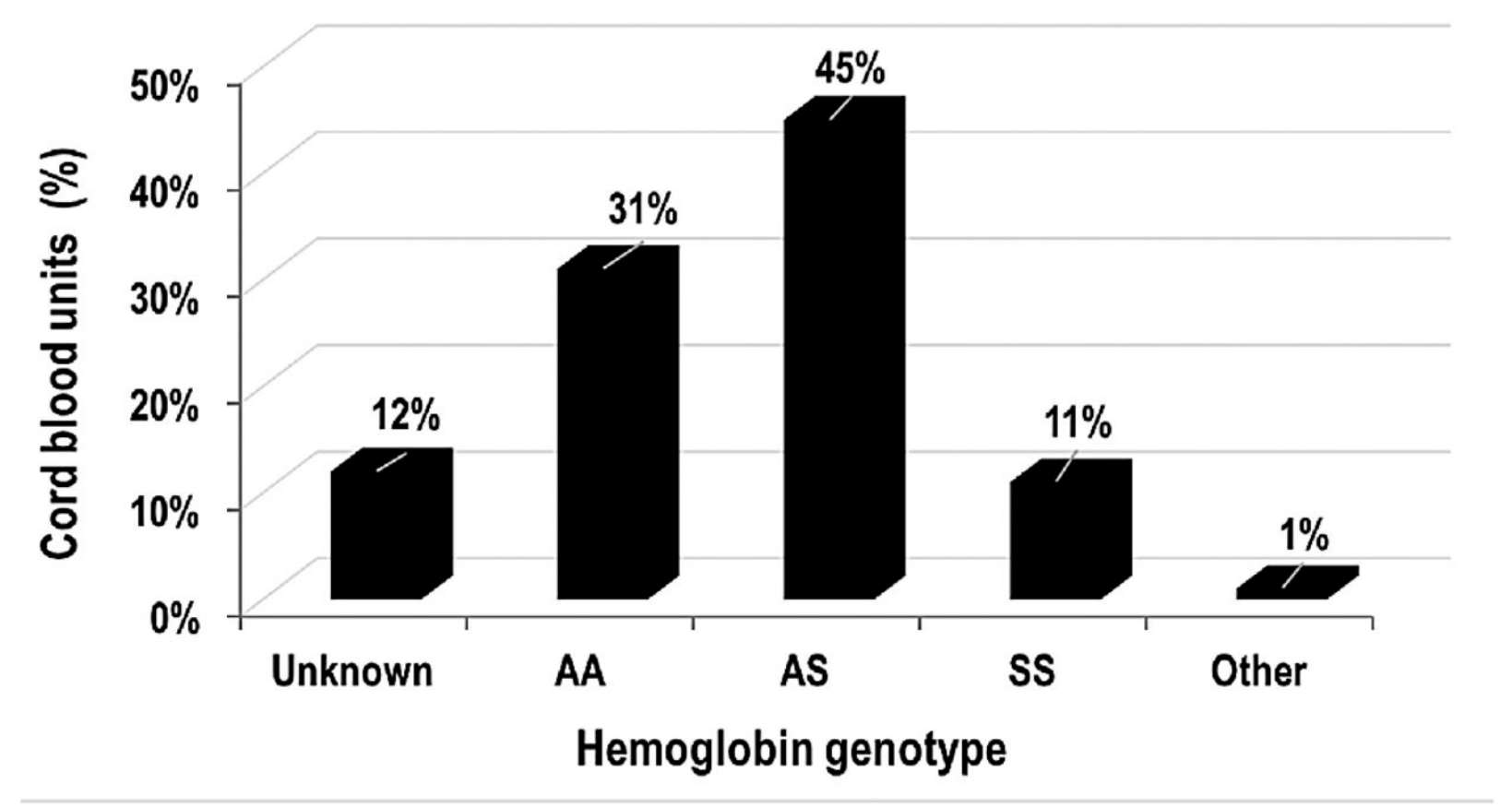
Eliane Gluckman Hematology 2013;2013:370-376

©2013 by American Society of Hematology

Albert Einstein experience

- 11 transplants were performed 2010-2017.
- The average age was 13 years old (7-24)
- Indications: Previous stroke (3), cerebral flow change (4), STA (3) and alo immunization (1).
- Conditioning: BuCy + ATG (3) and BuFlu + ATG (8)
- HLA 10/10 Source of Bone Marrow Cell
- 1 patient related cord
- The median of Neutrophilic grafting was D + 25
- Platelets D + 60
- 2 Deaths: GVHD Acute Hepatic and HCV
- 7 patients with 100% chimerism
- 2 patients Chimera <80%

Hemoglobin genotype of collected cord blood units.



Hanadi Rafii et al. Haematologica 2017;102:976-983

©2017 by Ferrata Storti Foundation

Characteristics of transplanted cord blood units.

	CBUs infused alone	CBUs infused with BM*	Total CBUs
CBUs transplanted, n (%)	23 (82%)	5 (18%)	28 (100%)
Median volume, mL (range)	109 (49 - 230)	55 (49 - 65)	99 (49 - 230)
Median recipient weight, kg	22 (14 - 45)	33 (14 - 56)	22 (14 - 56)
Collected cell dose, n (range)			
Median NC x10^7/kg	5.2 (2.9 - 13.1)	1.1 (0.5 - 1.7)	4.0 (0.5 - 13.1)
Median $CD34^+$ x10^5/kg	1.8 (0.6 - 14.8)	0.3 (0.2 - 0.4)	1.6 (0.2 - 14.8)
Median CFU x10^4/kg	1.6 (0.4 - 4.9)	0.3 (0.1 - 0.9)	1.1 (0.1 - 4.9)
Infused cell dose, n (range)			
Median NC x10^7/kg	3.7 (1.5 - 7.6)	1 (0.2 - 1.5)	3.1 (0.2 - 7.6)
Median $CD34^+$ x10^5/kg	2.1 (0.5 - 11.8)	0.3 (0.2 - 0.4)	1.4 (0.2 - 11.8)
Storage duration, years (range)	1.7 (0.4 - 8.1)	3.1 (2.6 - 4.0)	2.2 (0.4 - 8.1)

CBU: cord blood units; NC: nucleated cells; CFU: colony forming units; BM: bone marrow. *Characteristics of BM infused are reported in Table 5.

Hanadi Rafii et al. Haematologica 2017;102:976-983

©2017 by Ferrata Storti Foundation

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Cord blood transplantation

- HIAE Experience
- The girl 3 years - SS
- Indication - Splenic sequestration
- Conditioning: BuFLU + ATG
- Cord: TCN: 10.25x107 / Kg
- Prophylaxis DECH - Csa + MMF
- Neutrophilic Grafting: D + 23
- Chimera D + 60 - 70%

Hindawi

Go

Home Journals About Us

Case Reports in Hematology

Indexed in Web of Science

About this Journal Submit a Manuscript Table of Contents

Journal Menu

- About this Journal
- Abstracting and Indexing
- Aims and Scope
- Article Processing Charges
- Articles in Press
- Author Guidelines
- Bibliographic Information
- Citations to this Journal
- Contact Information
- Editorial Board
- Editorial Workflow
- Free eTOC Alerts
- Publication Ethics
- Reviewers Acknowledgment
- Submit a Manuscript
- Subscription Information
- Table of Contents

Case Reports in Hematology
Volume 2017 (2017), Article ID 8394732, 5 pages
https://doi.org/10.1155/2017/8394732

Case Report

A Child as a Donor for Hematopoietic Stem Cell Transplantation: Bioethical Justification—A Case Study on Sickle Cell Disease

Andrea Z. Pereira,[1] Ricardo Hellman,[2] Nelson Hamerschlak,[3] Andrea Kondo,[2] Polianna Mara Rodrigues de Souza,[1] Wilson Leite Pedreira Jr.,[2] Luiz Fernando Alves Lima Mantovani,[2] Eduardo Juan Troster,[4] Henrique Grunspun,[4] and Marco Aurélio Scarpinella Bueno[4]

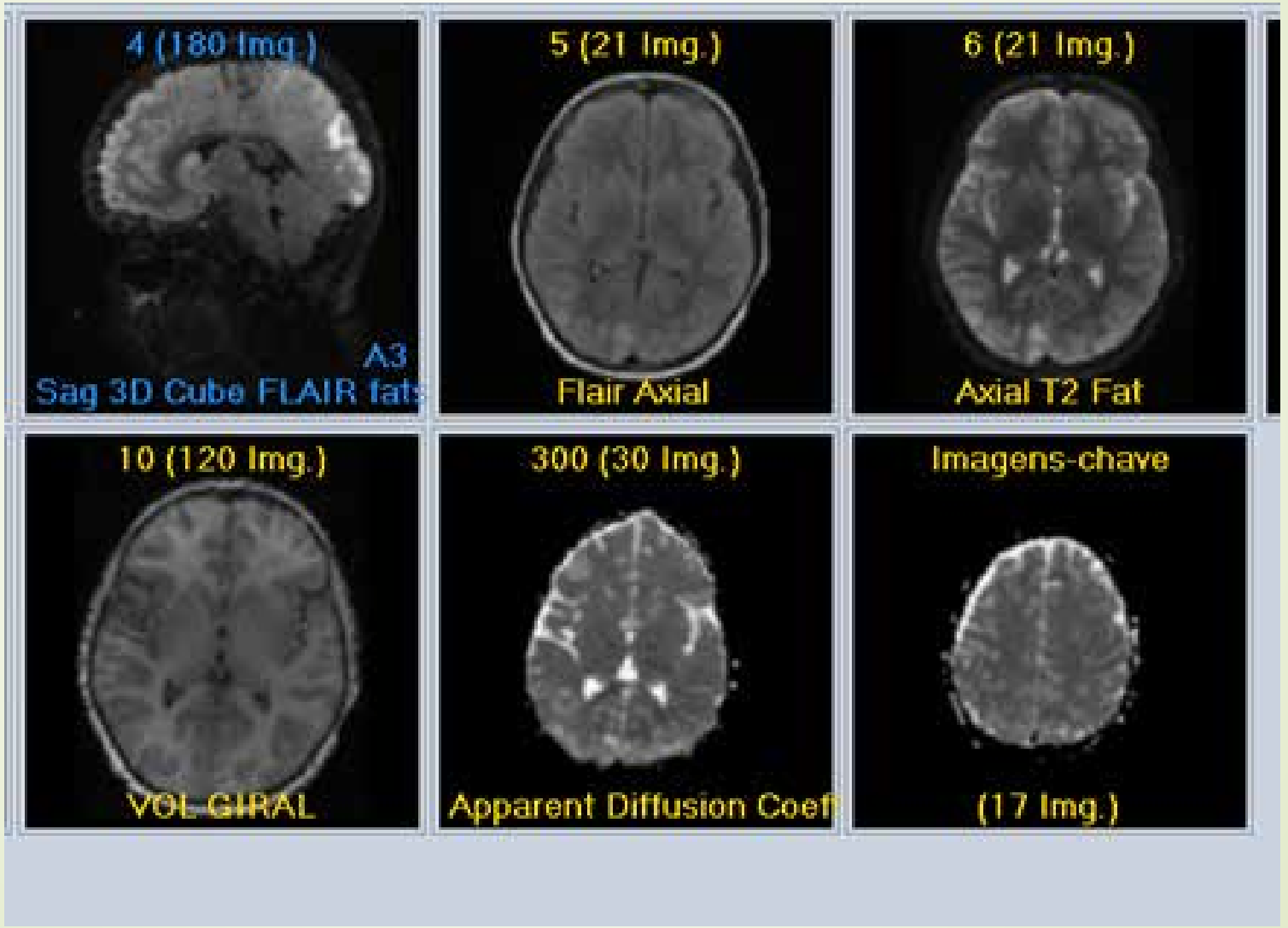
[1]Oncology, Hematology, and Bioethical Committee, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
[2]Oncology and Hematology, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
[3]Hematology and Bone Marrow Transplantation, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
[4]Bioethical Committee, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil

Correspondence should be addressed to Andrea Z. Pereira

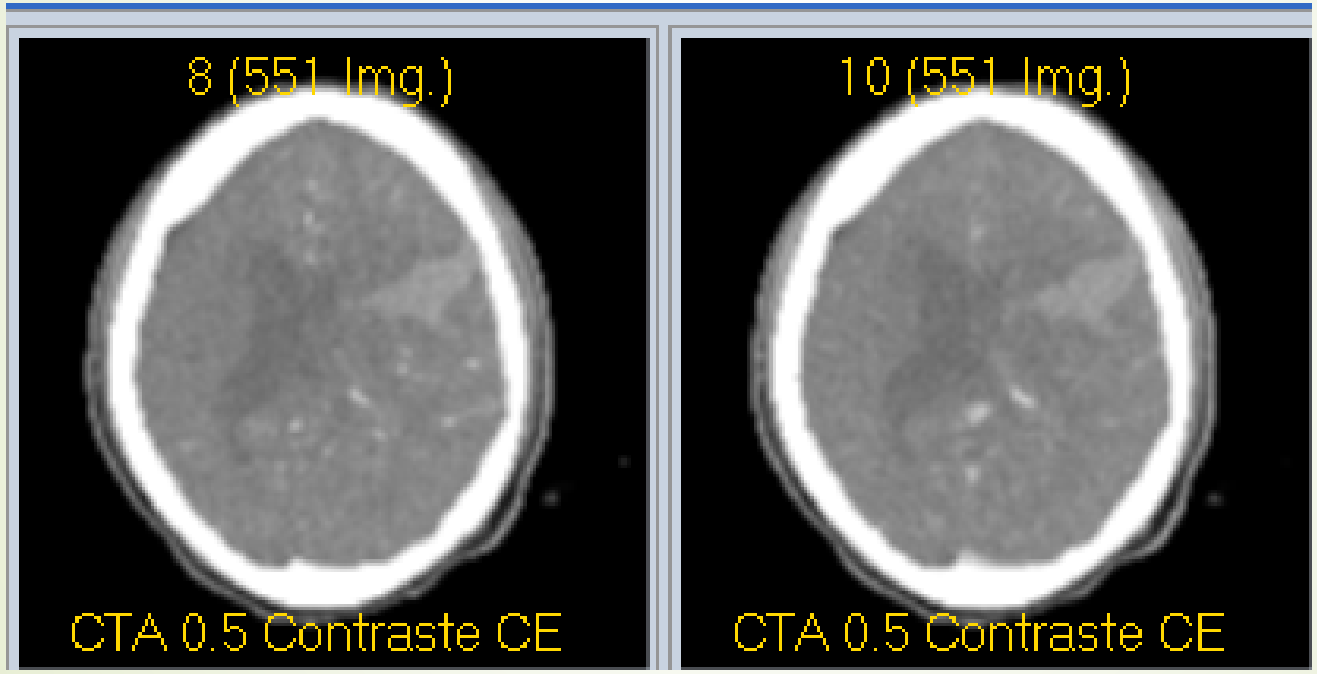
Abstract
Full-Text PDF
Full-Text HTML
Full-Text ePUB
Full-Text XML
Linked References
How to Cite this Article

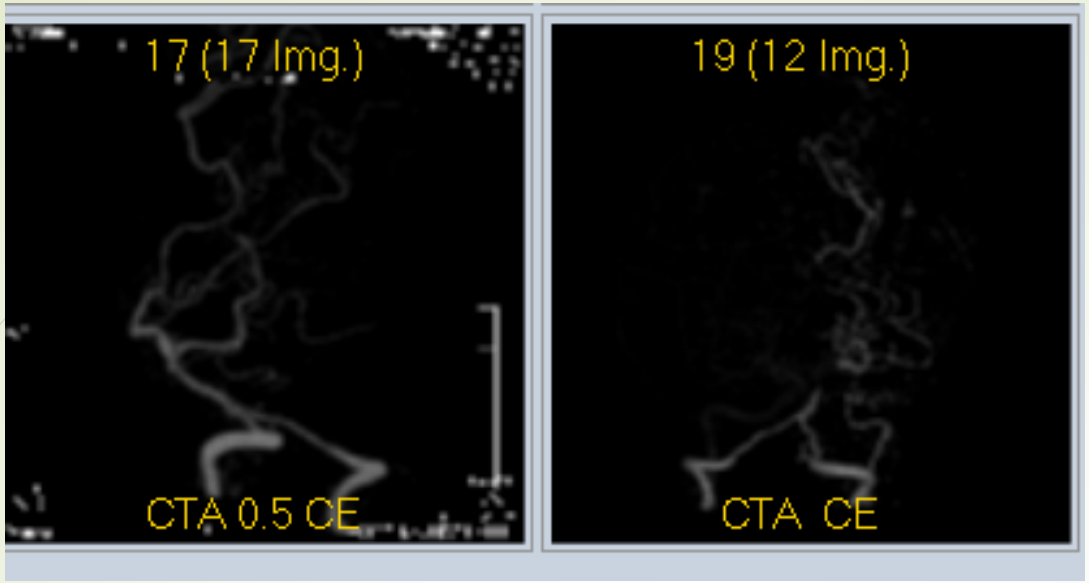
Views 396
Citations 0
ePub 2
PDF 162

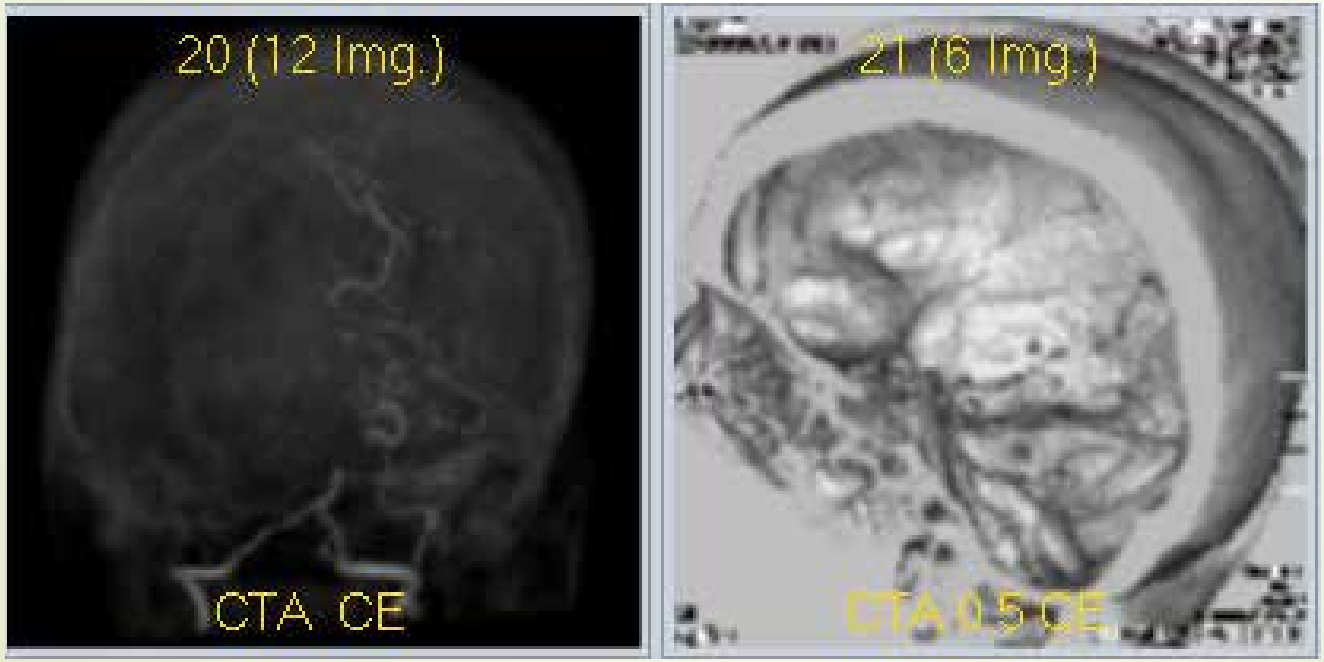
PRESS Syndrome



Hemorrhagic stroke




17 (17 Img.)
CTA 0.5 CE
19 (12 Img.)
CTA CE


20 (12 Img.)
CTA CE
21 (6 Img.)
CTA 0.5 CE

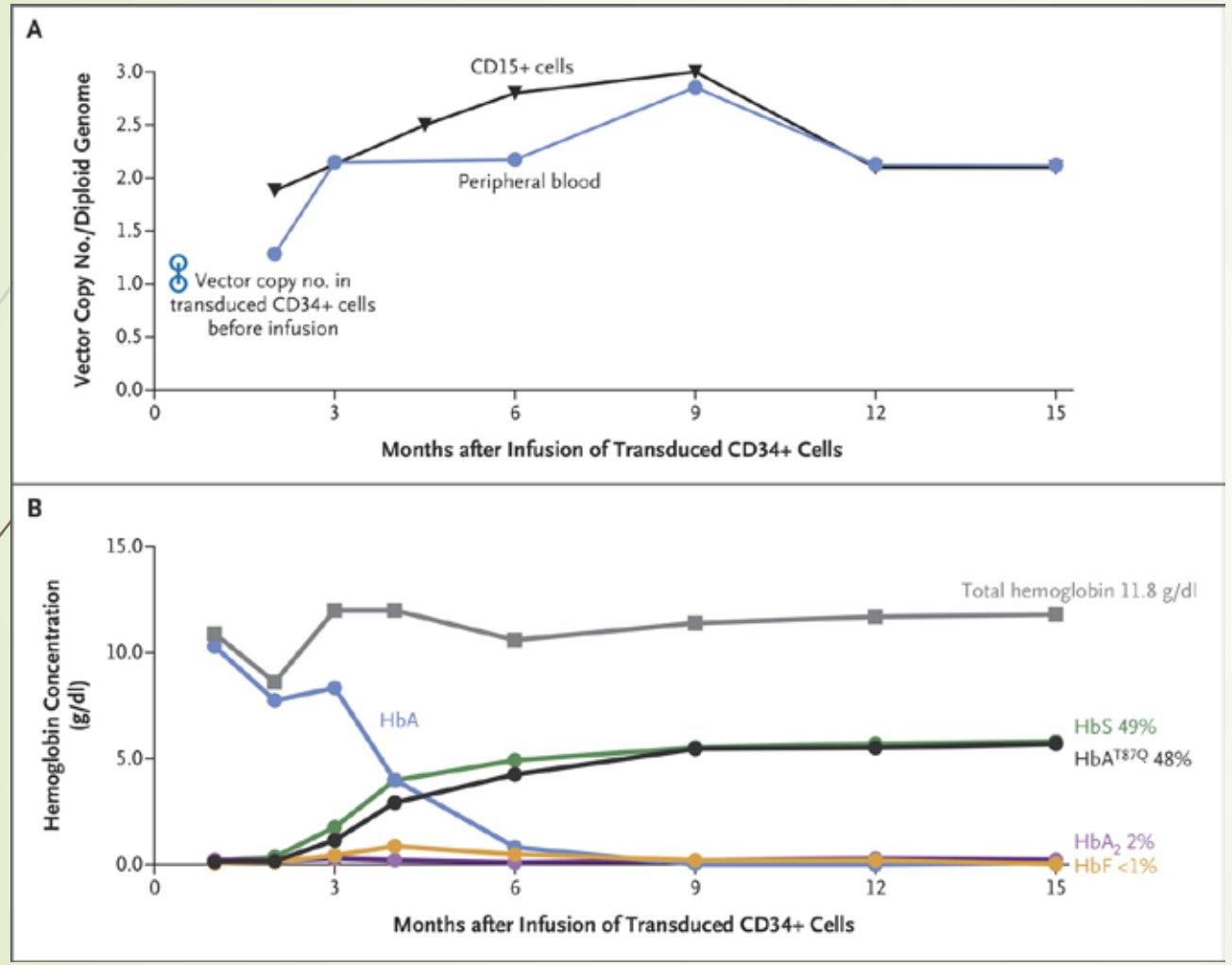
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Gene Therapy in a Patient with Sickle Cell Disease

Jean-Antoine Ribeil, M.D., Ph.D., Salima Hacein-Bey-Abina, Pharm.D., Ph.D., Emmanuel Payen, Ph.D., Alessandra Magnani, M.D., Ph.D., Michaela Semeraro, M.D., Ph.D., Elisa Magrin, Ph.D., Laure Caccavelli, Ph.D., Benedicte Neven, M.D., Ph.D., Philippe Bourget, Pharm.D., Ph.D., Wassim El Nemer, Ph.D., Pablo Bartolucci, M.D., Ph.D., Leslie Weber, M.Sc., Hervé Puy, M.D., Ph.D., Jean-François Meritet, Ph.D., David Grevent, M.D., Yves Beuzard, M.D., Stany Chrétien, Ph.D., Thibaud Lefebvre, M.D., Robert W. Ross, M.D., Olivier Negre, Ph.D., Gabor Veres, Ph.D., Laura Sandler, M.P.H., Sandeep Soni, M.D., Mariane de Montalembert, M.D., Ph.D., Stéphane Blanche, M.D., Philippe Leboulch, M.D., and Marina Cavazzana, M.D., Ph.D.

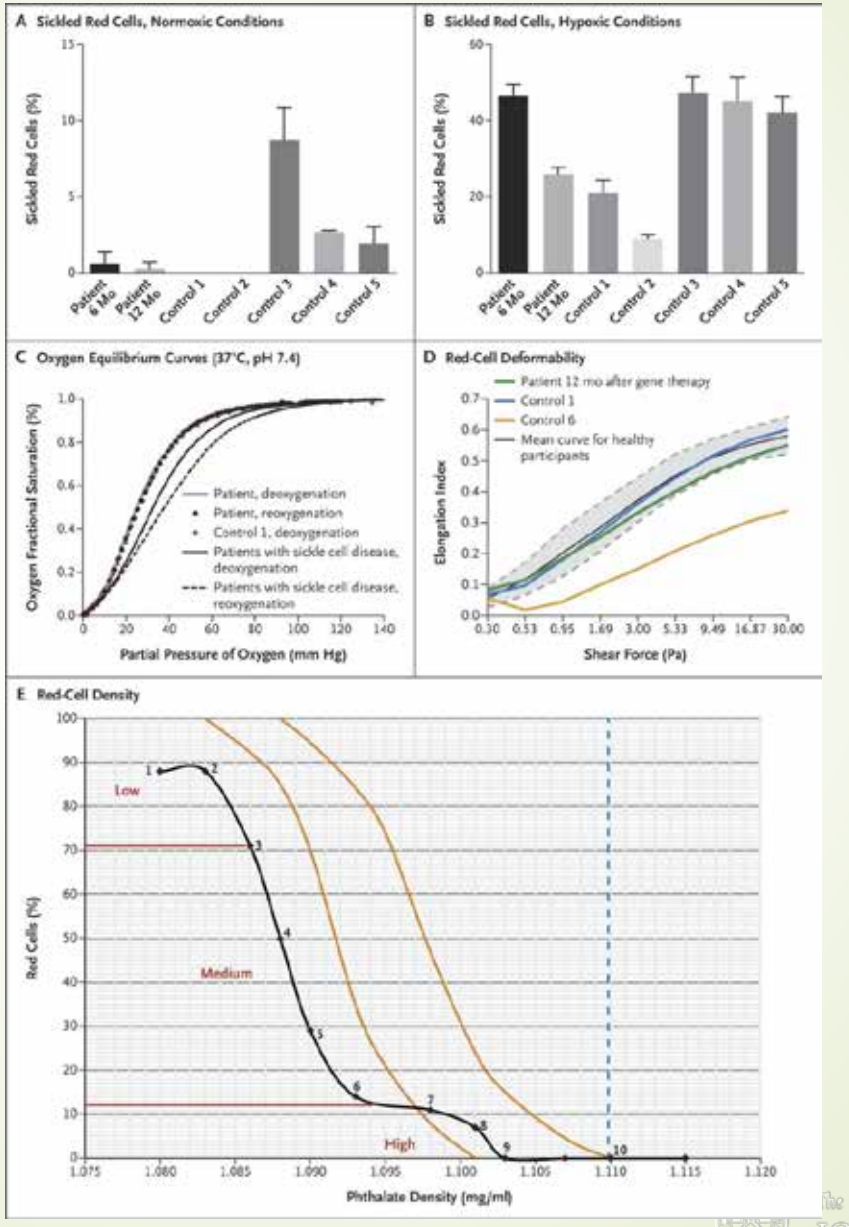
Engraftment with Transduced Cells and Therapeutic Gene Expression in the Patient.



The NEW ENGLAND JOURNAL of MEDICINE

Ribeil J et al. N Engl J Med 2017;376:848-855.

Results of Sickle Cell Disease–Specific Red-Cell Assays.



Ribeil J et al. N Engl J Med 2017;376:848-855.

the NEW ENGLAND JOURNAL of MEDICINE

Key Laboratory Values before Gene Therapy (at Screening) and at 3-Month Intervals after Infusion of Transduced CD34+ Cells.

Table 1. Key Laboratory Values before Gene Therapy (at Screening) and at 3-Month Intervals after Infusion of Transduced CD34+ Cells.

Measure	Normal Range	Screening*	Month 3*	Month 6	Month 9	Month 12	Month 15
Total hemoglobin (g/dl)	13.0–18.0	10.1	12.0	10.6	11.4	11.7	11.8
Red-cell count (per mm^3)	4,500,000–6,200,000	3,700,000	3,900,000	3,700,000	4,000,000	4,200,000	4,300,000
Reticulocyte count (per mm^3)	20,000–80,000*	238,000	259,000	132,000	131,000	143,000	141,000
Mean corpuscular hemoglobin (pg/red cell)	25–30	28	31	29	28	28	28
Mean corpuscular hemoglobin concentration (g/dl)	31–34	35	34	35	36	35	35
Platelet count (per mm^3)	150,000–450,000	356,000	52,000	122,000	157,000	168,000	201,000
Neutrophil count (per mm^3)	1500–7000	4200	2400	3100	2500	3000	2200
Total bilirubin (μmol/liter)	0–17	50	15	20	14	12	12
Lactate dehydrogenase (U/liter)	125–243	626	285	254	226	274	212
C-reactive protein (ng/ml)	<500	191	814	129	ND	135	158
Ferritin (μg/liter)	22–275	265	869	1095	ND	520	363
Transferrin (g/liter)	1.9–3.2	1.4	1.6	1.7	ND	1.5	1.7
Transferrin saturation (%)	16–35	72	ND	ND	35	56	40
Serum transferrin receptor (mg/liter)	0.8–1.7	5.7	3.0	2.3	ND	2.6	2.5
Iron (μmol/liter)	12–30	26	18	14	ND	20	17
Hepcidin (ng/ml)	1–20	ND	ND	ND	ND	12.9	19.9
Alanine aminotransferase (U/liter)	5–45	22	76	125	116	53	41
Aspartate aminotransferase (U/liter)	5–40	53	57	71	50	49	35

* Exchange transfusion was performed before gene therapy was initiated, and supportive red-cell transfusions were completely discontinued 88 days after transplantation. ND denotes not done.

Ribeil J et al. N Engl J Med 2017;376:848-855.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH Open Access

Cellular function reinstitution of offspring red blood cells cloned from the sickle cell disease patient blood post CRISPR genome editing

Jianguo Wen[1], Wenjing Tao[2], Suyang Hao[1] and Youli Zu[1*]

ARTICLE

doi:10.1038/nature20134

CRISPR/Cas9 β-globin gene targeting in human haematopoietic stem cells

Daniel P. Dever[1]*, Rasmus O. Bak[1]*, Andreas Reinisch[2], Joab Camarena[1], Gabriel Washington[1], Carmencita E. Nicolas[1], Mara Pavel-Dinu[1], Nivi Saxena[1], Alec B. Wilkens[1], Sruthi Mantri[1], Nobuko Uchida[3]†, Ayal Hendel[1], Anupama Narla[4], Ravindra Majeti[2], Kenneth I. Weinberg[1] & Matthew H. Porteus[1]

Obrigado!

ricardo.helman@einstein.br