Cerebrovascular Disease in SCD: Hemominas Foundation Experience

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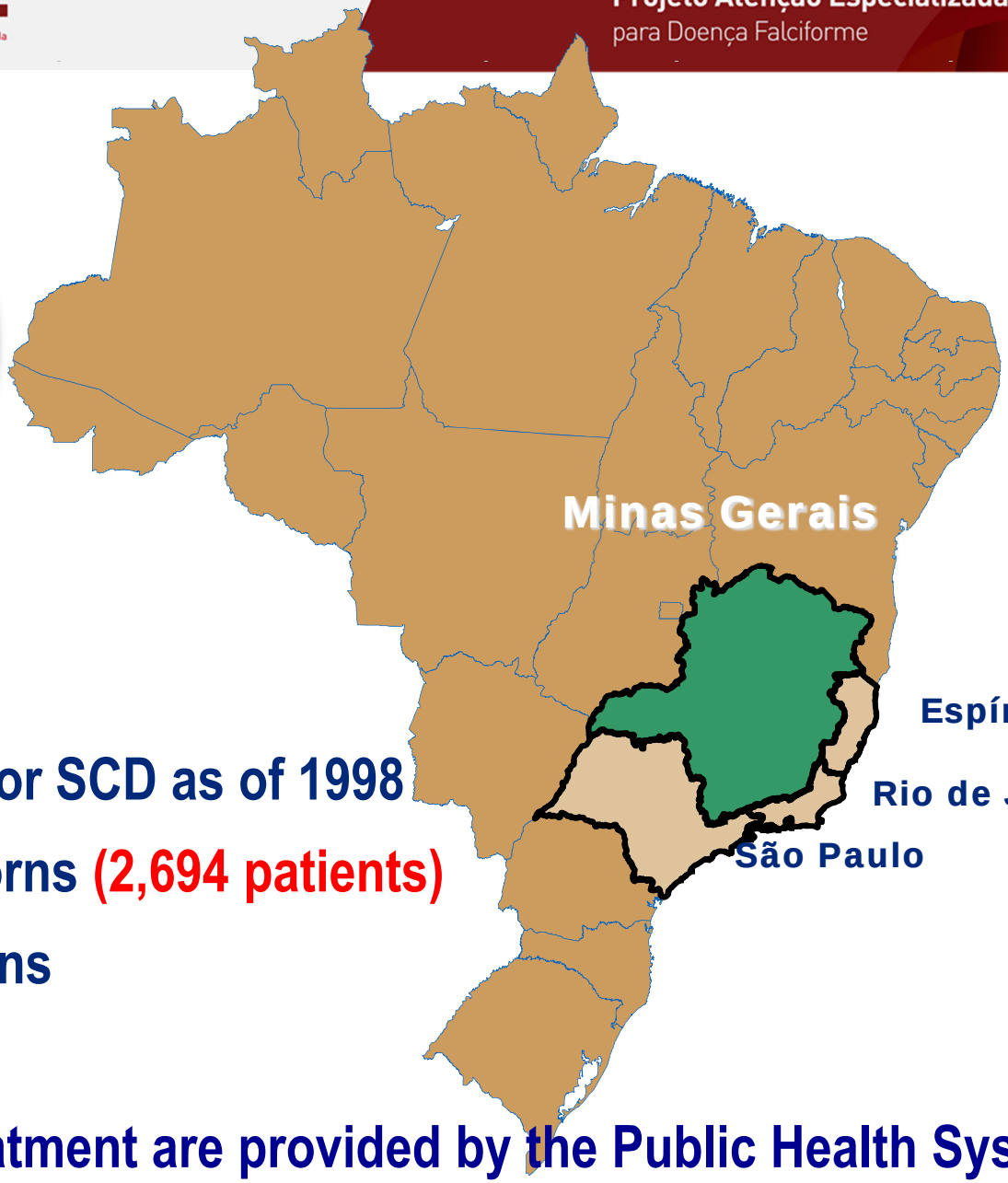


Newborn screening for SCD as of 1998

SCD = 1:1,400 newborns (2,694 patients)

Hb AS = 1:32 newborns

All follow-up and treatment are provided by the Public Health System

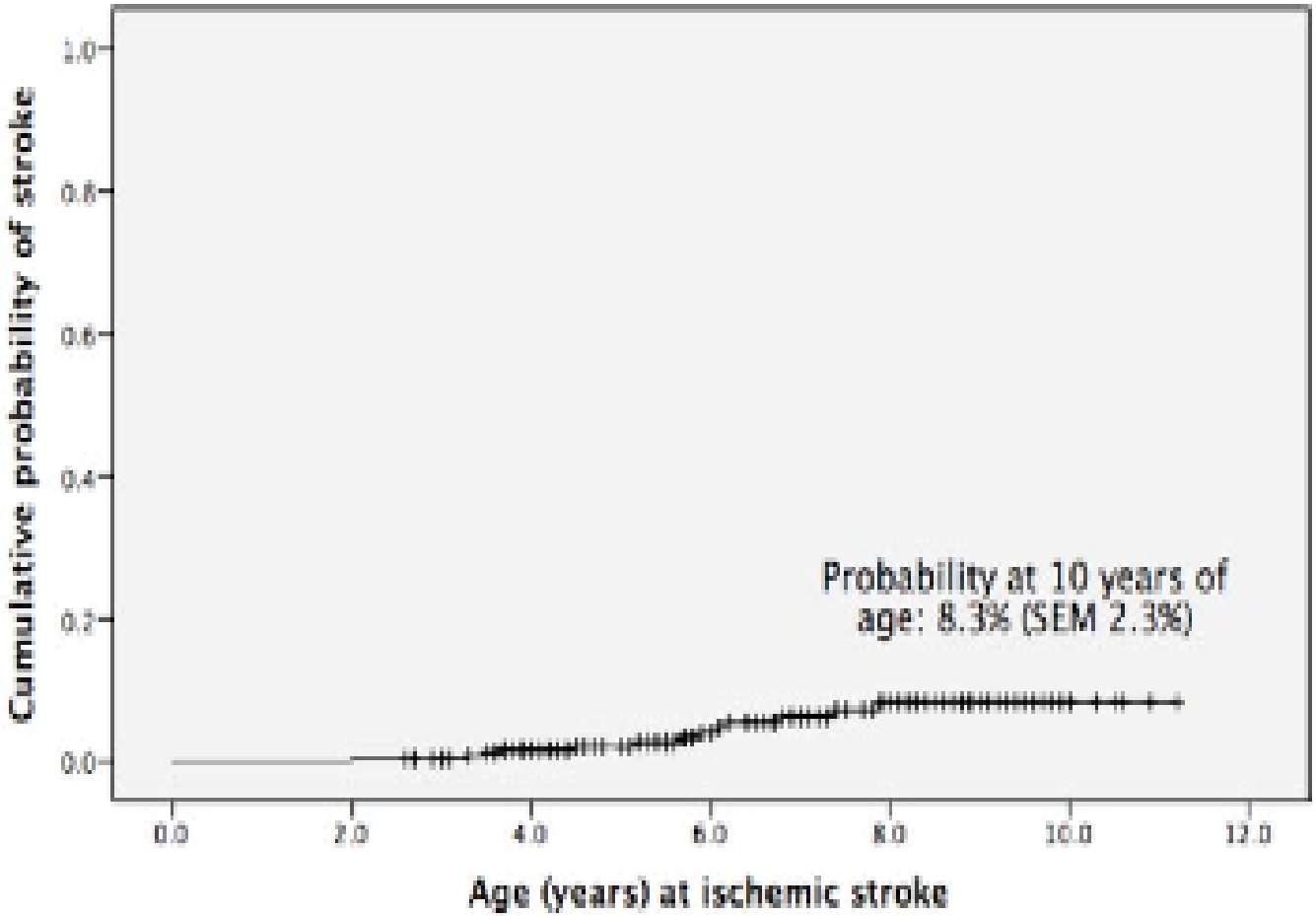
Risk of Stroke in Children With Sickle Cell Disease

Condition	Stroke/year (%)	Source
Healthy child	0.003	Broderick et al, 1993
Adult with atrial fibrilation	5.0	Goldstein et al, 2001
Child with HbSS (without TCD screening)	0.5 a 1.0	Ohene-Frempong et al, 1998
SCD with silent infarct on MRI	2.0 a 3.0	Miller et al, 2001
SCD with TCD velocity ≥ 200 cm/s without Tx	10.0 a 13.0	Adams et al, 1997
SCD with TCD velocity ≥ 200 cm/s with Tx	< 1.0	Adams et al, 1992 Adams et al, 1998
SCD with previous stroke without Tx	≈ 30.0	Pegelow et al, 1995
SCD with previous stroke with Tx	≈6.0	Pegelow et al, 1995

Adams. Arch Neurol 2007

Stroke Rate at BH Blood Center, Brazil

Overt stroke incidence: 0.77/100 patients-year*



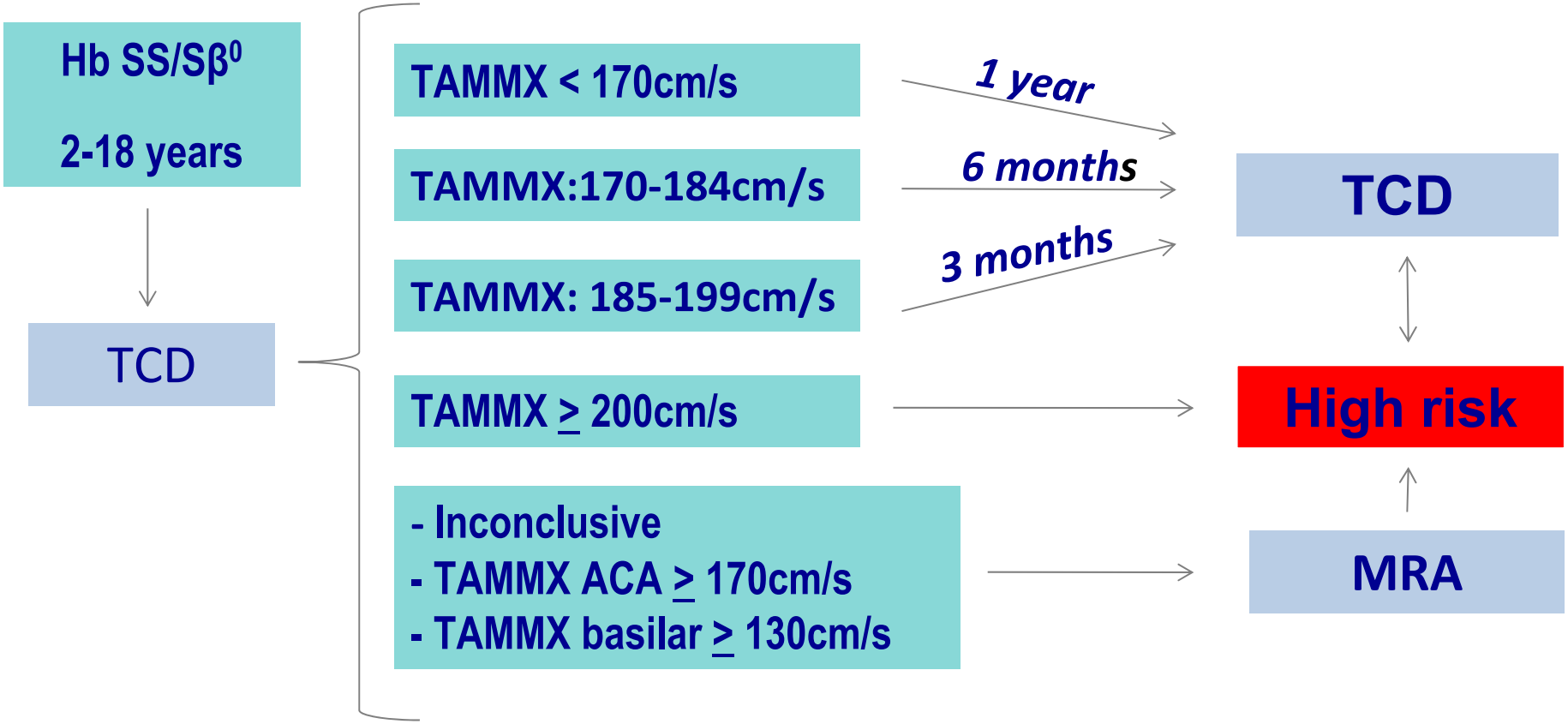
* Silva CM, Giovani P, Viana MB, PB&C, 2011

Objectives

1. To describe the impact of TCD screening on ischemic stroke primary prevention

2. To assess the associated complications of chronic transfusion

Primary Prevention - Hemominas Foundation Protocol



Methods

- TCD screening (beginning in 2007), according to STOP Protocol (Hb SS/Hb Sβ^0, 2-18 years old)
- Regular manual exchange transfusion for high-risk patients (matched for ABO, Rh [CDE/cde], Kell, Kidd, and Duffy antigens)
- Serological tests every 6 months (HCV, HBV, HIV, Chagas' Disease HTLV I/II, Syphilis)
- Medical files review: 2007-2013 (Hb SS/Hb Sβ^0thal: 577; Hb SC: 487)

Results

Characteristics of Patients in Regular Blood Transfusion for Primary Prevention of Stroke

- Number of patients at high-risk: 39 (34 abnormal TCD/5 MRA)
  +3 (1 abnormal TCD / 2 MRA)
- Hb SS: 100%
- Female sex: 53.8%
- Age: 6.8 ± 2.5 years
- Observational time: 108 children-year (2.77 year on average)

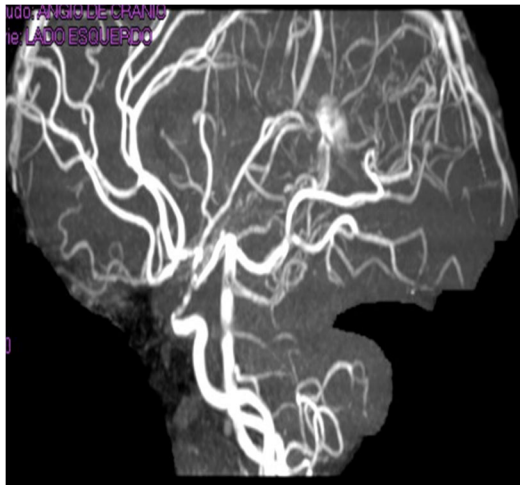
Patients follow-up and outcome

- Pre-transfusion Hb S: 41.2 ± 8.9%
- 34 patients (87.2%) Hb S < 50%
- HU was given to 19 children (without risk reversion on TCD)
- One underwent HSC Transplant (donor: brother)
- One overt stroke event
- No associated-transfusion infections
- No death

Overt stroke event in a 7-year-old boy

MRA 10/12/ 2012 (in regular blood transfusion since 2009)

Another view of the left side



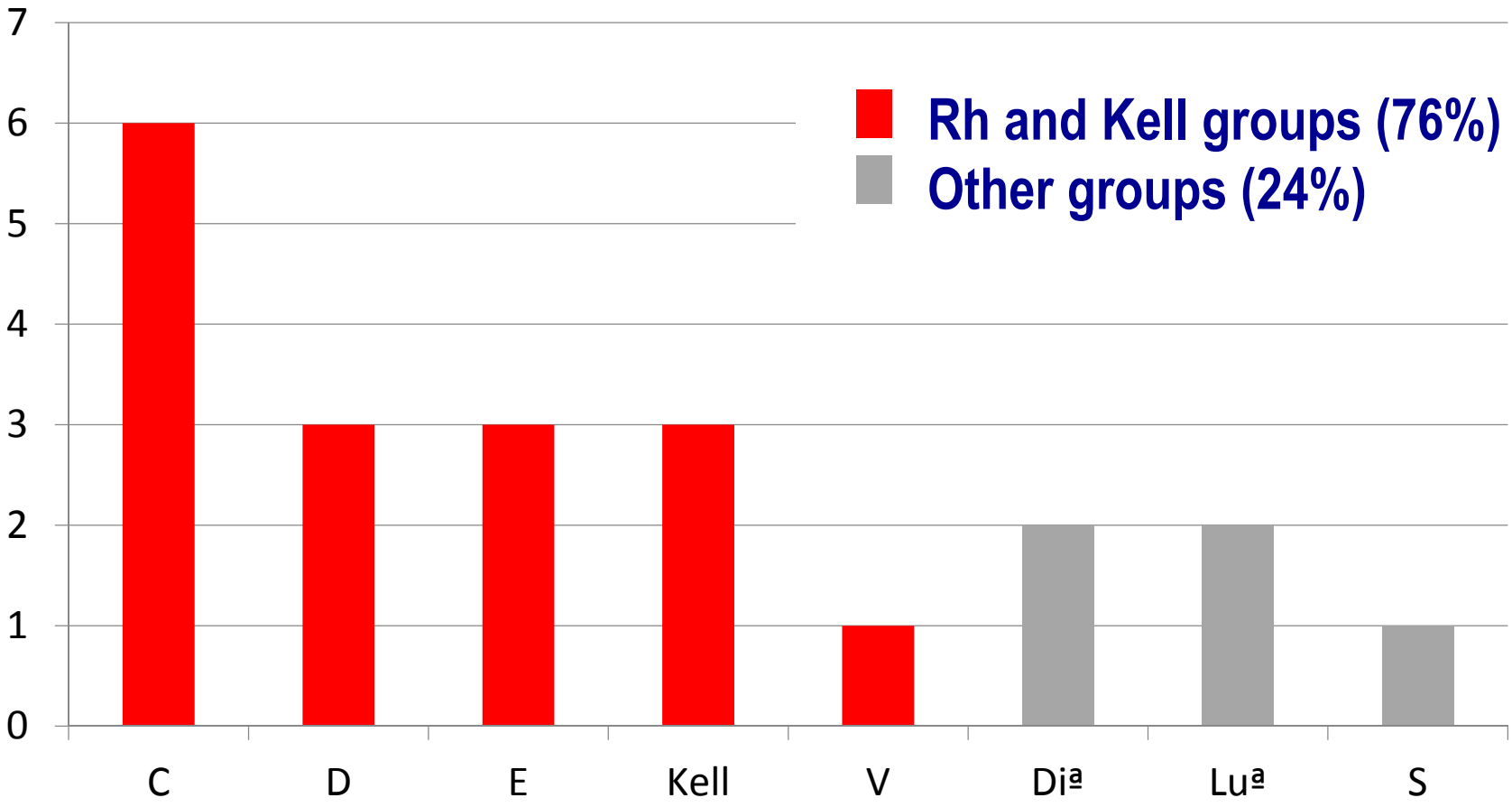
Frontal view

Iron overload control

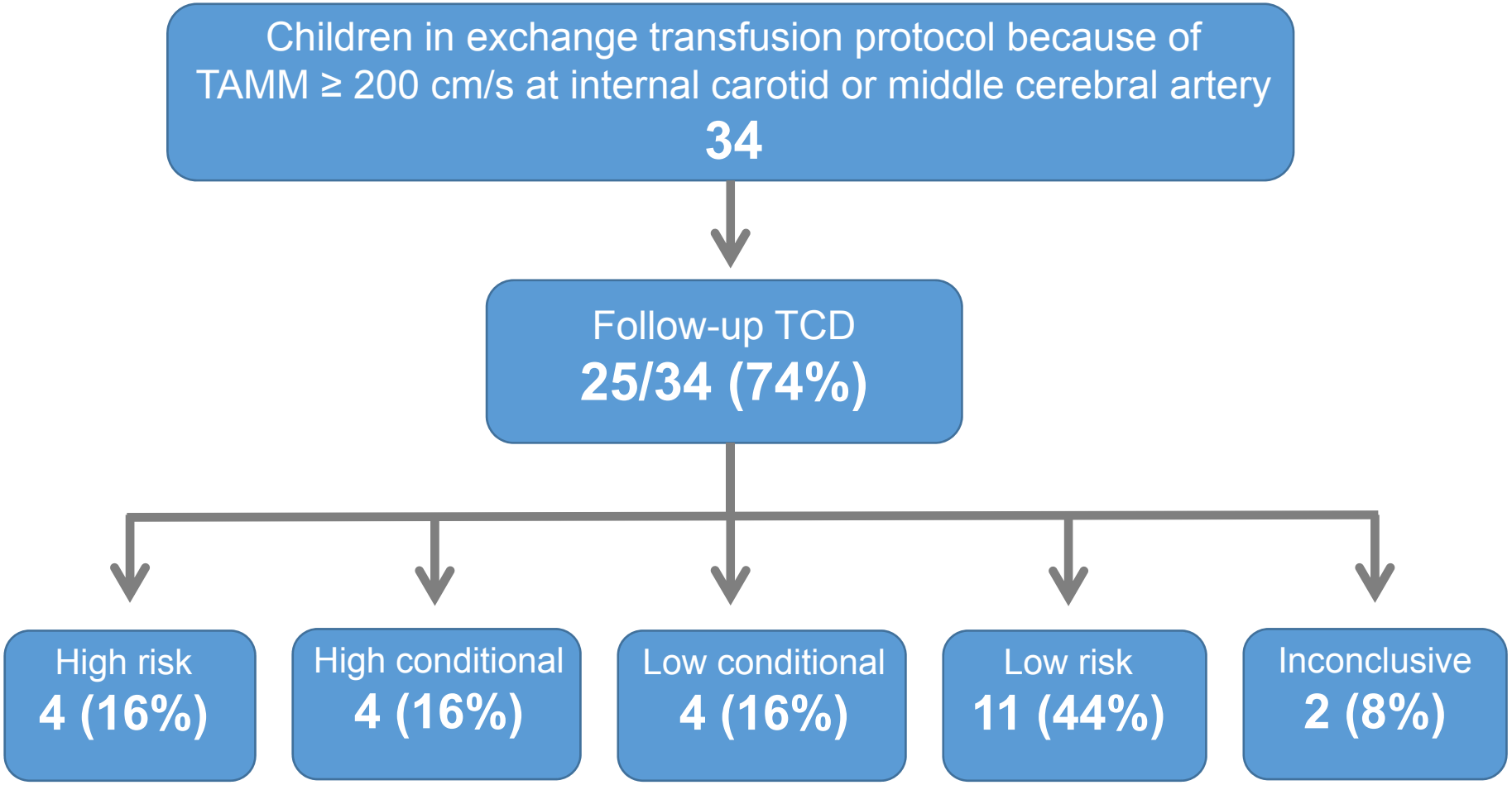
- Ferritin level: 870 ± 513 µg/L
- Oral chelator use: 14 children (35.9%)
- Good compliance, in general

Alloimunization 13 (33%)

Number of cases for each alloantibody



Data	Alloimmunized	Not alloimmunized	p
Begin Tx regime (years old)	7,7	6,2	0,065
PreTx HbS (%)	45,7	39,0	0,027
Pre Tx Total Hb (g/dL)	8,7	8,9	0,52
Reticulocytes count (%)	10,7	11,4	0,66
Number of Tx	47,4	42,5	0,52


Children in exchange transfusion protocol because of TAMM ≥ 200 cm/s at internal carotid or middle cerebral artery
34
Follow-up TCD
25/34 (74%)
High risk
4 (16%)
High conditional
4 (16%)
Low conditional
4 (16%)
Low risk
11 (44%)
Inconclusive
2 (8%)

Data	HR reversion	Not HR reversion	p
TAMMX (cm/s)	231.4	219.7	0.12
Pretransfusional HbS (%)	39,9	43,7	0.23
Pretransfusional Total Hb (g/dL)	9,0	8,5	0.10
Reticulocytes count (%)	10,4	12,1	0.17
Regular blood exchange regime (days)	**483**	**910**	**0,003**
Begin Tx regime (years old)	6,6	6,7	0,95

Cerebrovascular disease is a progressive process: when is the ideal point to intervention?

Conclusions

- TCD is useful to track high-risk cases; prophylactic transfusions are effective in preventing ischemic stroke
- Over half of the patients had reduction to low or conditional risk on TCD tests
- Iron overload can be controlled with chelation
- Alloimmunization is a major concern in these children

Ideal donors, imperfect results in sickle cell disease

"Even as the indications for transfusions continue to expand, serious hazards of transfusions such as alloimmunization can create almost insurmountable challenges for some patients. Strategies to avoid or manage this risk are desperately needed".

- **Comment on Chou et al., page 1662, by Dr. Alexis Thompson.**

High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors.

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Blood; August, 2013

THANK YOU!

MCG, Augusta – January, 2002

Molecular Study in SCA Cerebrovascular Disease: preliminary results

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ADCY9 rs2238432

Genotype	Overt stroke		TOTAL
	Yes	No	
GG	16 (6.1%)	246 (93.9%)	262 (100%)
GA	4 (3.9%)	99 (96.1%)	103 (100%)
AA	0 (0%)	10 (100%)	10 (100%)
Total	20 (5.3%)	355 (94.7%)	375 (100%)

p=0.52

GG vs GA+AA p=0.45; OR 0.56; 95%CI 0.18-1.73

Allele A previously associated with decreased stroke risk (Sebastiani, et al. 2005; Flanagan et al., 2011)

TEK rs489347

Genotype	Overt stroke		TOTAL
	Yes	No	
GG	6 (3.2%)	179 (96.8%)	185 (100%)
GC	10 (7.2%)	128 (92.8%)	128 (100%)
CC	3 (10%)	27 (90%)	30 (100%)
Total	19 (5.4%)	334 (94.6%)	353 (100%)

p=0.15

GG vs GC+CC p=0.09; OR 2.5; 95%CI 0.93-6.74

Allele G previously associated with increased stroke risk (Sebastiani, et al. 2005; Flanagan et al., 2011)

IL-10 G-1082A

Genotype	Overt stroke		TOTAL
	Yes	No	
AA	7 (4.5%)	147 (95.5%)	154 (100%)
AG	8 (5%)	153 (95%)	161 (100%)
GG	3 (6.8%)	41 (93.2%)	44 (100%)
Total	18 (5%)	341 (95%)	359 (100%)

p=0.83

AA vs AG+GG p=0.81; OR 1.19; 95%CI 0.45-3.15

IL-10 C-592A

Genotype	Overt stroke		TOTAL
	Yes	No	
CC	8 (5.3%)	143 (94.7%)	151 (100%)
CA	11 (6.2%)	167 (93.8%)	178 (100%)
AA	1 (2.1%)	46 (97.9%)	47 (100%)
Total	20 (5.3%)	356 (94.7%)	376 (100%)

p=0.55

CC vs CA+AA p=1.0; OR 1.01; 95%CI 0.40-2.53

IL-4R S503P

Genotype	Overt stroke		TOTAL
	Yes	No	
CC	10 (4.9%)	196 (95.1%)	206 (100%)
TC	7 (4.9%)	137 (95.1%)	144 (100%)
TT	3 (11.5%)	23 (88.5%)	26 (100%)
Total	20 (5.3%)	356 (94.7%)	376 (100%)

p=0.34

CC vs TC+TT p=0.82; OR 1.23; 95%CI 0.5-3.02

Allele T previously associated with increased stroke risk (Hoppe et al., 2004 and 2007)

G6PD A376G

Isoform	Overt stroke		TOTAL
	Yes	No	
BB	17 (6.1%)	261 (93.9%)	278 (100%)
BA	2 (3.7%)	52 (96.3%)	54 (100%)
AA	1 (2.3%)	43 (97.7%)	43 (100%)
Total	20 (5.3%)	356 (94.7%)	376 (100%)

p=0.45

BB vs BA+AA p=0.31; OR 0.49; 95%CI 0.14-1.7

G6PD deficiency previously associated with high risk TCD (Bernaudin et al., 2008)

intracranial vasculopathy (Thangarajh et al., 2012)

Absence of association (Rees et al., 2009; Flanagan et al., 2011)

MTHFR C677T

Genotype	Overt stroke		TOTAL
	Yes	No	
CC	7 (5.6%)	199 (94.4%)	126 (100%)
CT	2 (2.5%)	79 (97.5%)	81(100%)
TT	1 (6.7%)	14 (93.3%)	15 (100%)
Total	10 (4.5%)	212 (95.5%)	222 (100%)

p=0.53

CC vs CT+TT p=0.52; OR 0.55; 95%CI 0.14-2.18

Absence of association (Cumming et al., 1999; Silva et al., 2011)

VCAM-1 G1238C

Genotype	Overt stroke		TOTAL
	Yes	No	
GG	17 (5.2%)	309 (94.8%)	326 (100%)
GC	3 (6%)	47 (94%)	50 (100%)
CC	0 (0%)	0 (0%)	0 0%)
Total	20 (5.3%)	356 (94.7%)	376 (100%)

p=0.74; OR 1.16; 95%CI 0.33-4.11

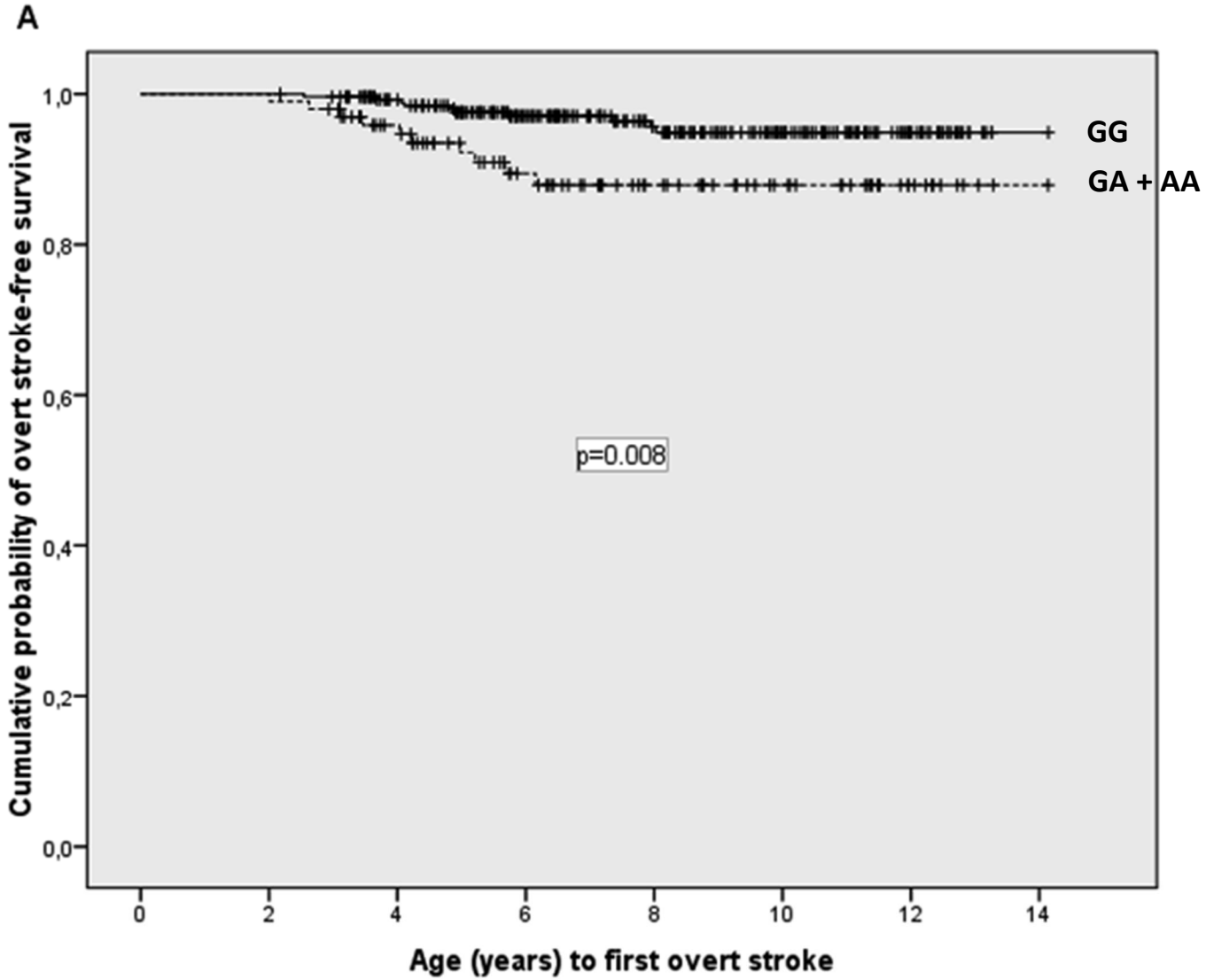
Allele C previously associated with decreased stroke risk (Taylor et al., 2002)

TNF G-308A

Genotype	Overt stroke		TOTAL
	Yes	No	
GG	10 (3.6%)	266 (96.4%)	276 (100%)
GA	10 (10.6%)	84 (89.4%)	94 (100%)
AA	0 (0%)	6 (100%)	6 (100%)
Total	20 (5.3%)	356 (94.7%)	376 (100%)

p=0.03
GG vs GC+CC p=0.02; OR 2.96; 95%CI 1.19-7.33

Allele G previously associated with increased stroke risk (Hoppe et al., 2004 and 2007)
Absence of association (Vicari et al., 2011; Flanagan et al., 2011)


A
Cumulative probability of overt stroke-free survival
1,0
0,8
0,6
0,4
0,2
0,0
GG
GA + AA
p=0.008
0
2
4
6
8
10
12
14
Age (years) to first overt stroke

HBA deletion status

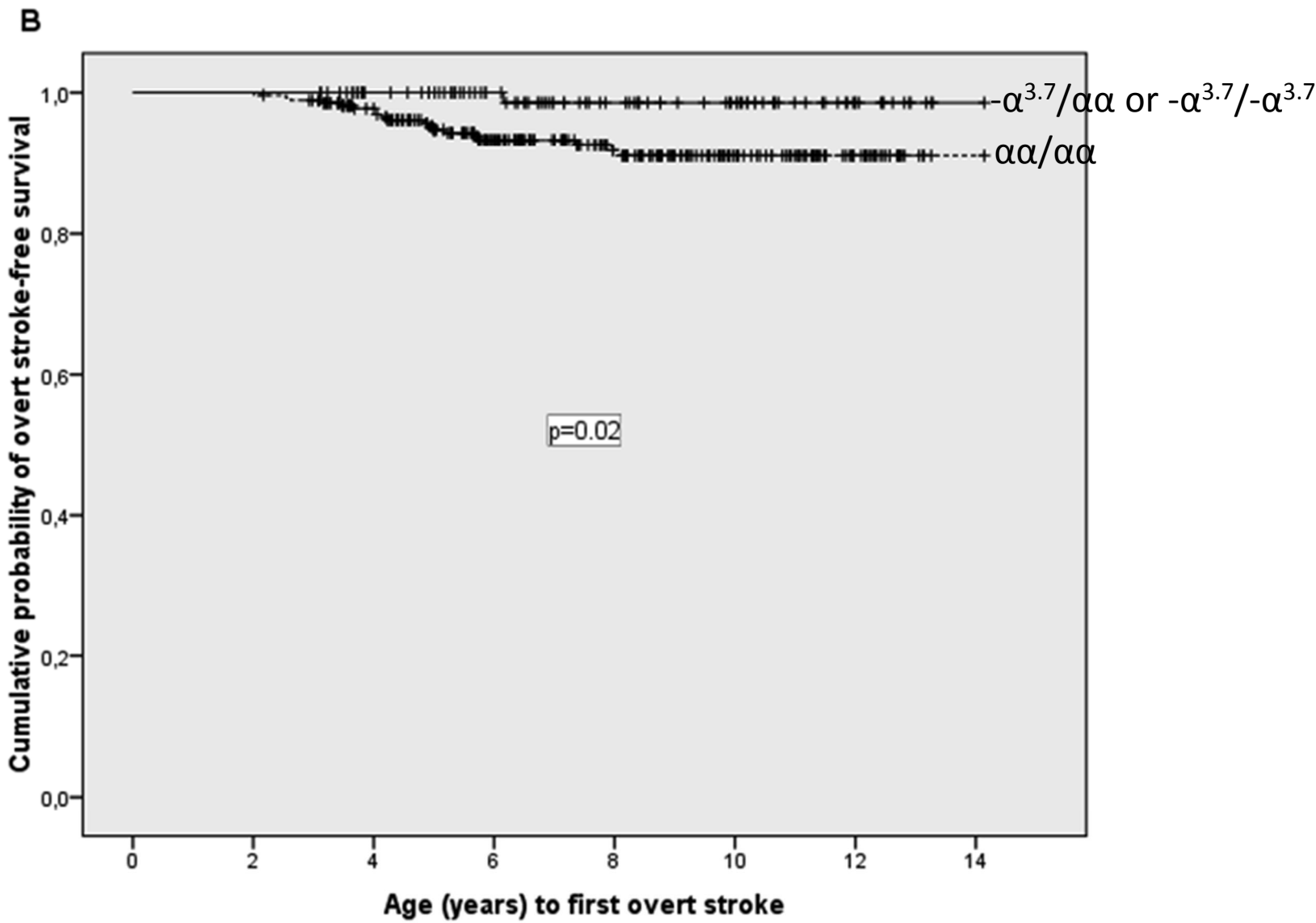
Genotype	Overt stroke		TOTAL
	Yes	No	
αα/αα	19 (7%)	254 (93%)	273 (100%)
αα/-$\alpha^{3.7}$	1 (1%)	95 (99%)	96 (100%)
-$\alpha^{3.7}$/-$\alpha^{3.7}$	0 (0%)	7 (100%)	7 (100%)
Total	20 (5.3%)	356 (94.7%)	376 (100%)

p=0.05

αα/αα vs αα/-$\alpha^{3.7}$or -$\alpha^{3.7}$/-$\alpha^{3.7}$ p=0.02; OR 0.13; 95%CI 0.17-0.99

Confirmation of our previously results (Belisário et al., 2010)

Many others


B
Cumulative probability of overt stroke-free survival
1,0
0,8
0,6
0,4
0,2
0,0
p=0.02
-α3.7/αα or -α3.7/-α3.7
αα/αα
0
2
4
6
8
10
12
14
Age (years) to first overt stroke