Comparison of Transfusion Adverse Events in Children with Sickle Cell Disease (SCD) Receiving Simple or Automated Red Blood Cell Exchange (aRBX) Transfusions for Stroke Prevention

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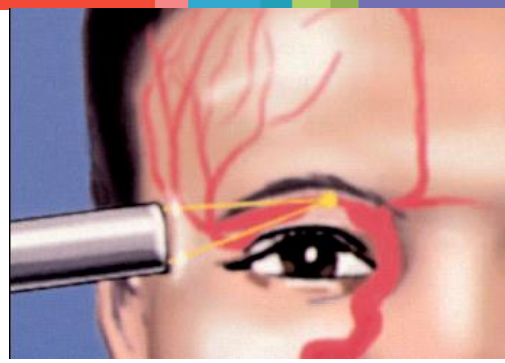
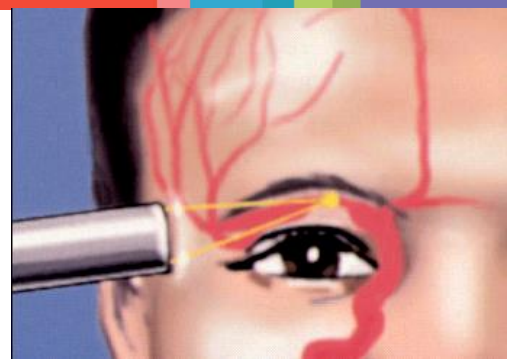
Disclosure

- Presented analysis part of larger study funded by Terumo BCT

Stroke Prevention in SCD

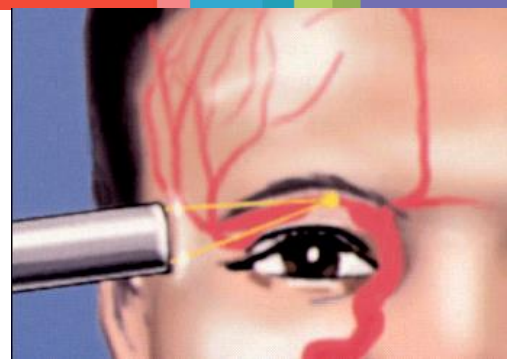




Stroke Prevention in SCD

- STOP trial randomized 130 children with a Transcranial Doppler MCA velocity > 200 cm/sec to observation or transfusions

Transfusions (n=63)	Standard care (n=67)



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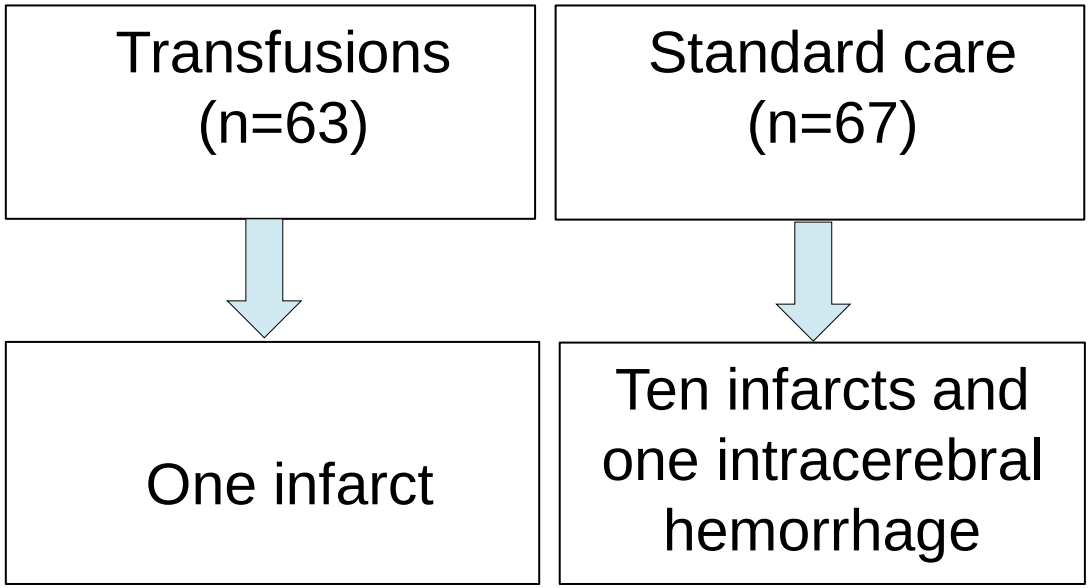

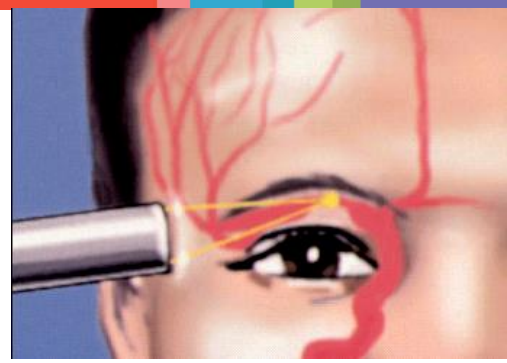

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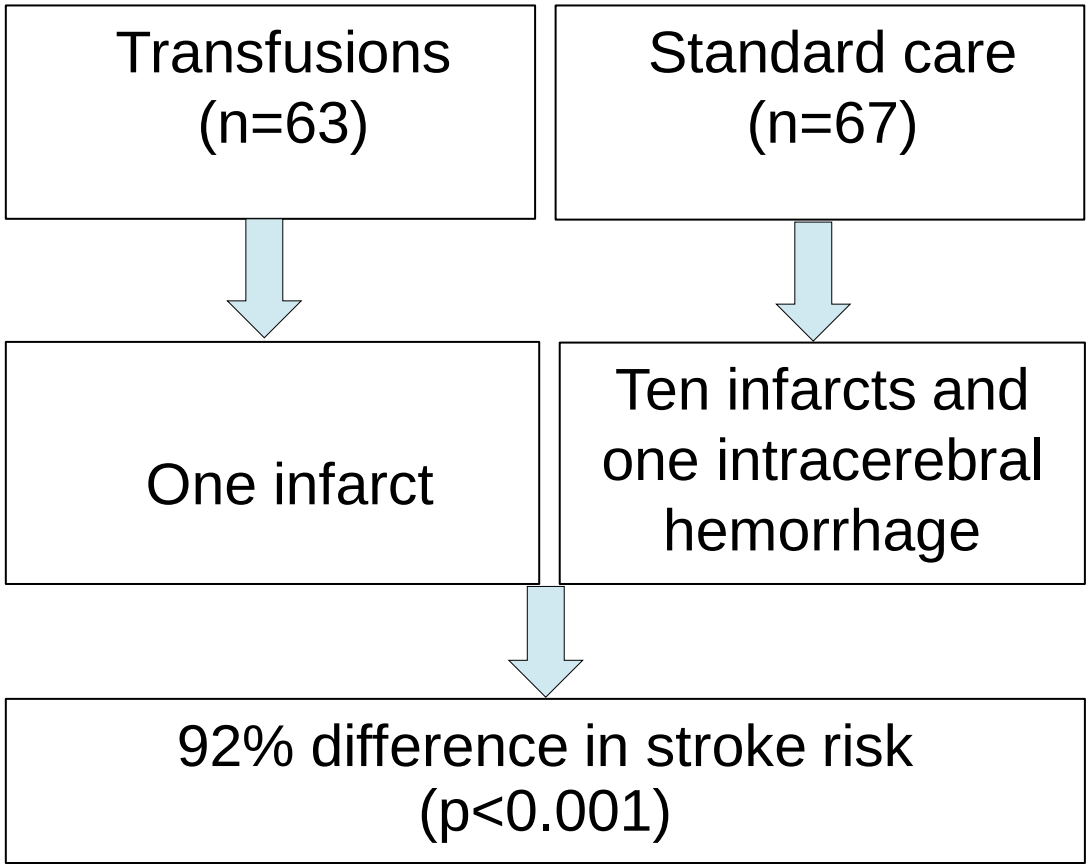

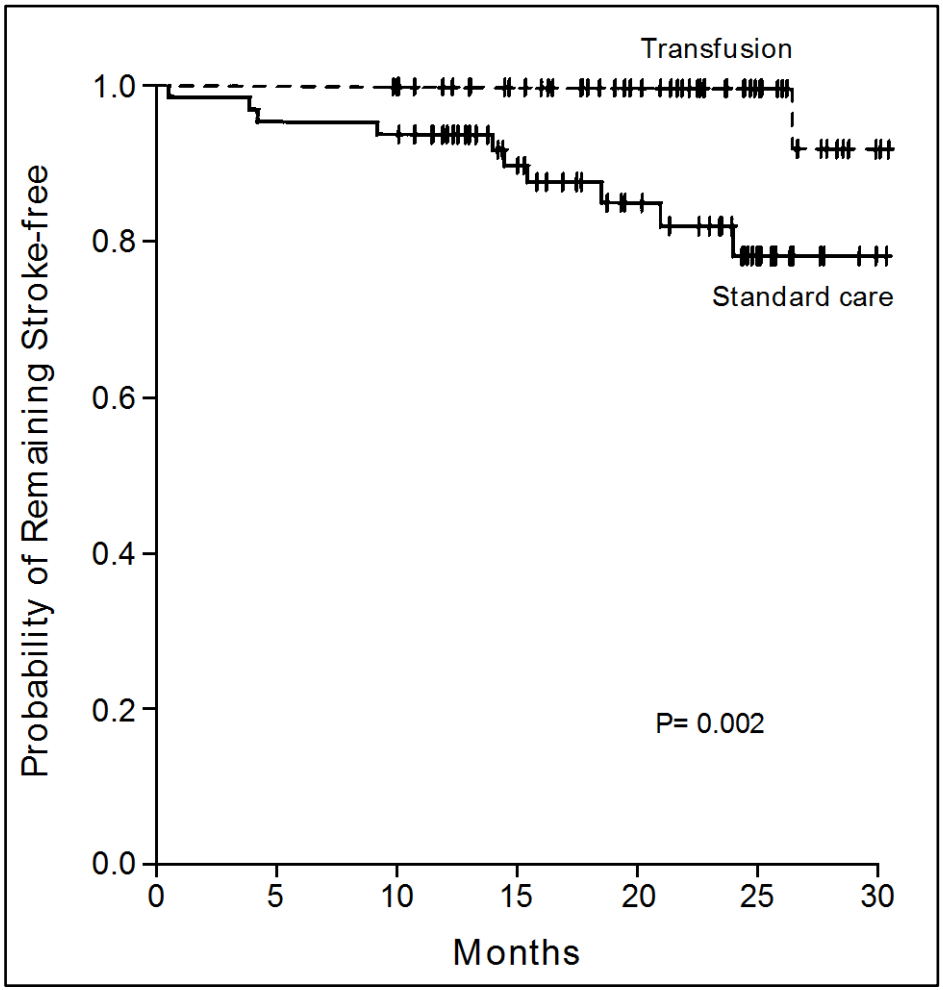

Adams. NEJM 1998 339 (1) 5-11.

Stop II → When Can We Stop Transfusions??

- Patients from STOP I (n=79)
  - –Chronic transfusions for 30 months
  - –Normal TCD, MRI and MRA
  - –Randomized to continue or stop transfusions

41 patients randomized to stop transfusions	38 patients randomized to continue transfusions

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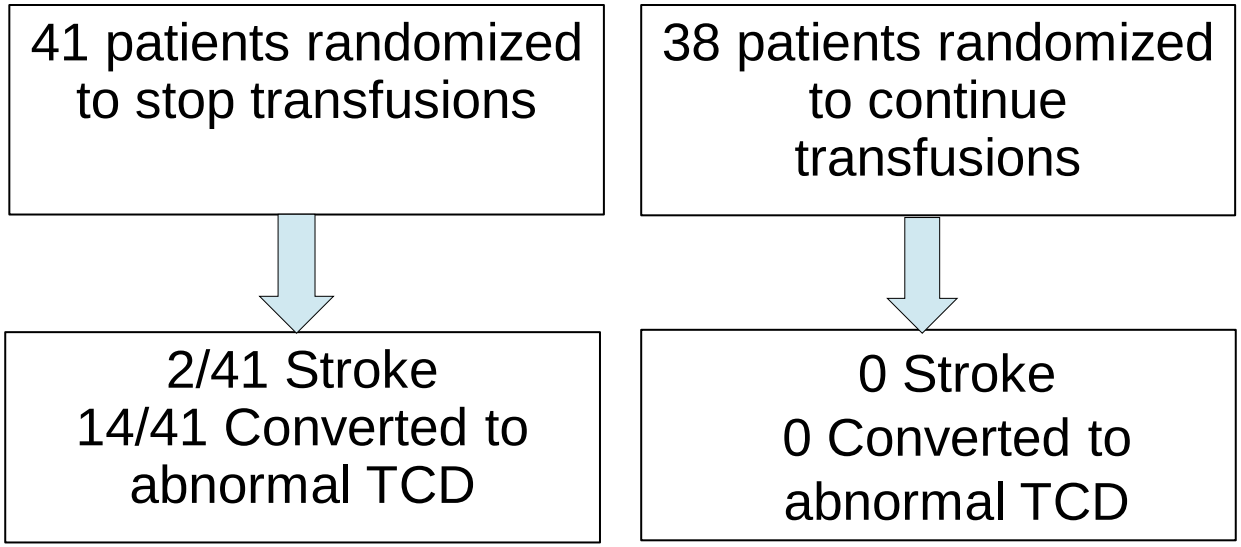

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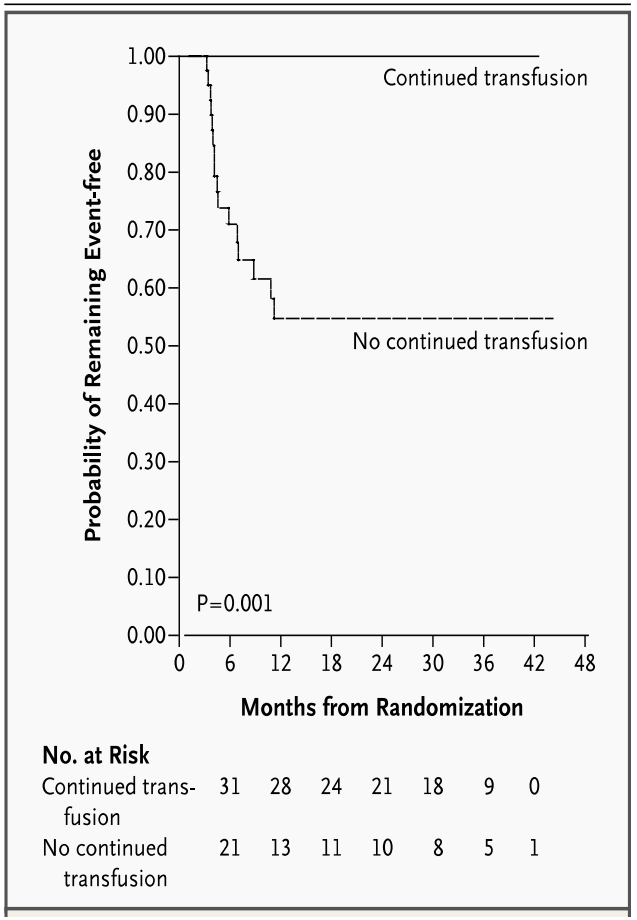
2/41 Stroke
14/41 Converted to abnormal TCD

0 Stroke
0 Converted to abnormal TCD

Study discontinued early



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  - All patients transfused ~ every 4 weeks to maintain target pre-transfusion HbS < 30%
  - Automated exchange preferred for patients transfused for stroke prevention if appropriate IV access available
    - Two peripheral IVs or 11.4F Double lumen Vortex™ Port
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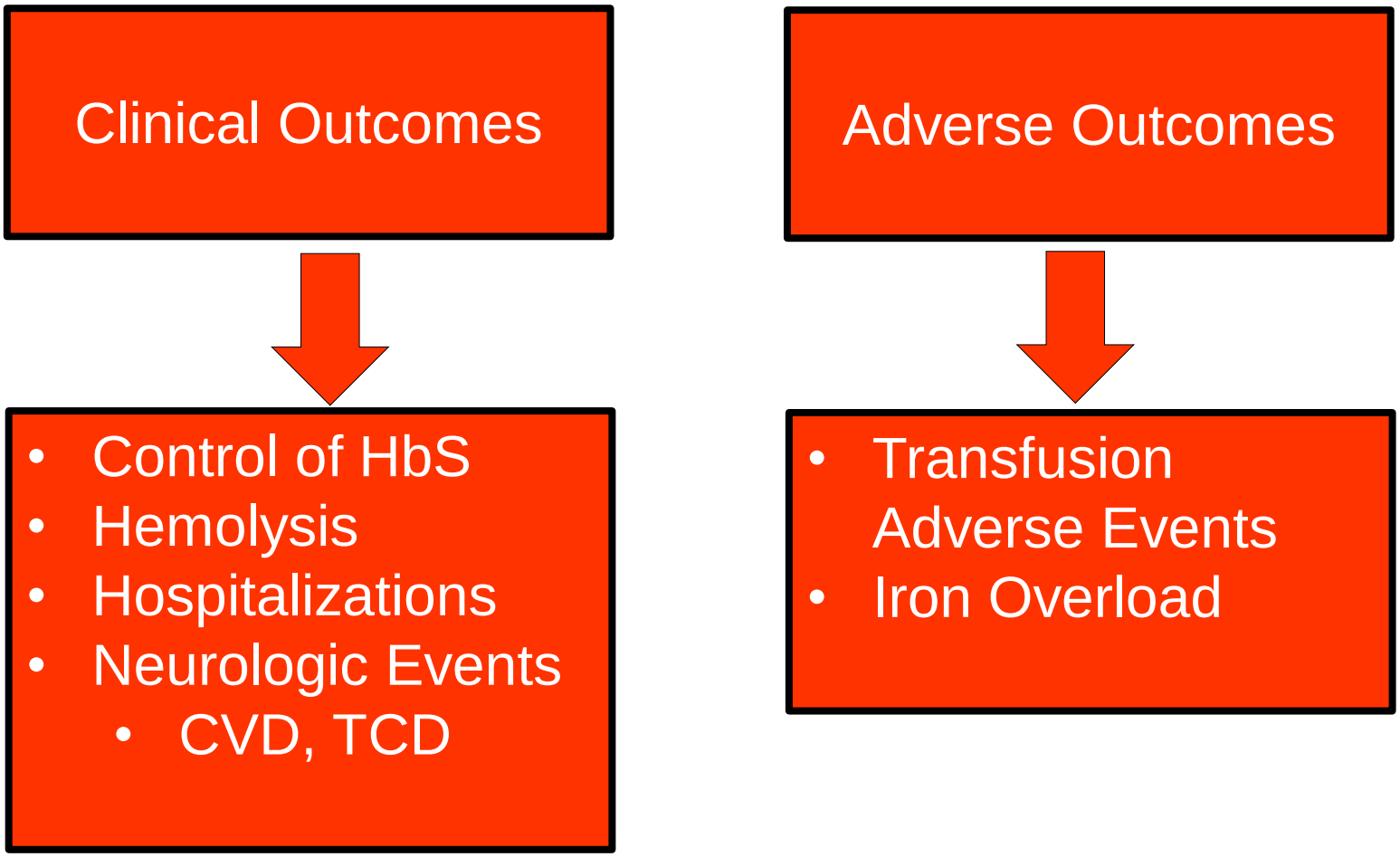
- Unique risk / benefit profile for available methods for transfusion (simple vs automated red blood cell exchange, aRBX)

Study Objectives

- Study objective : Compare clinical and adverse outcomes between simple and aRBX



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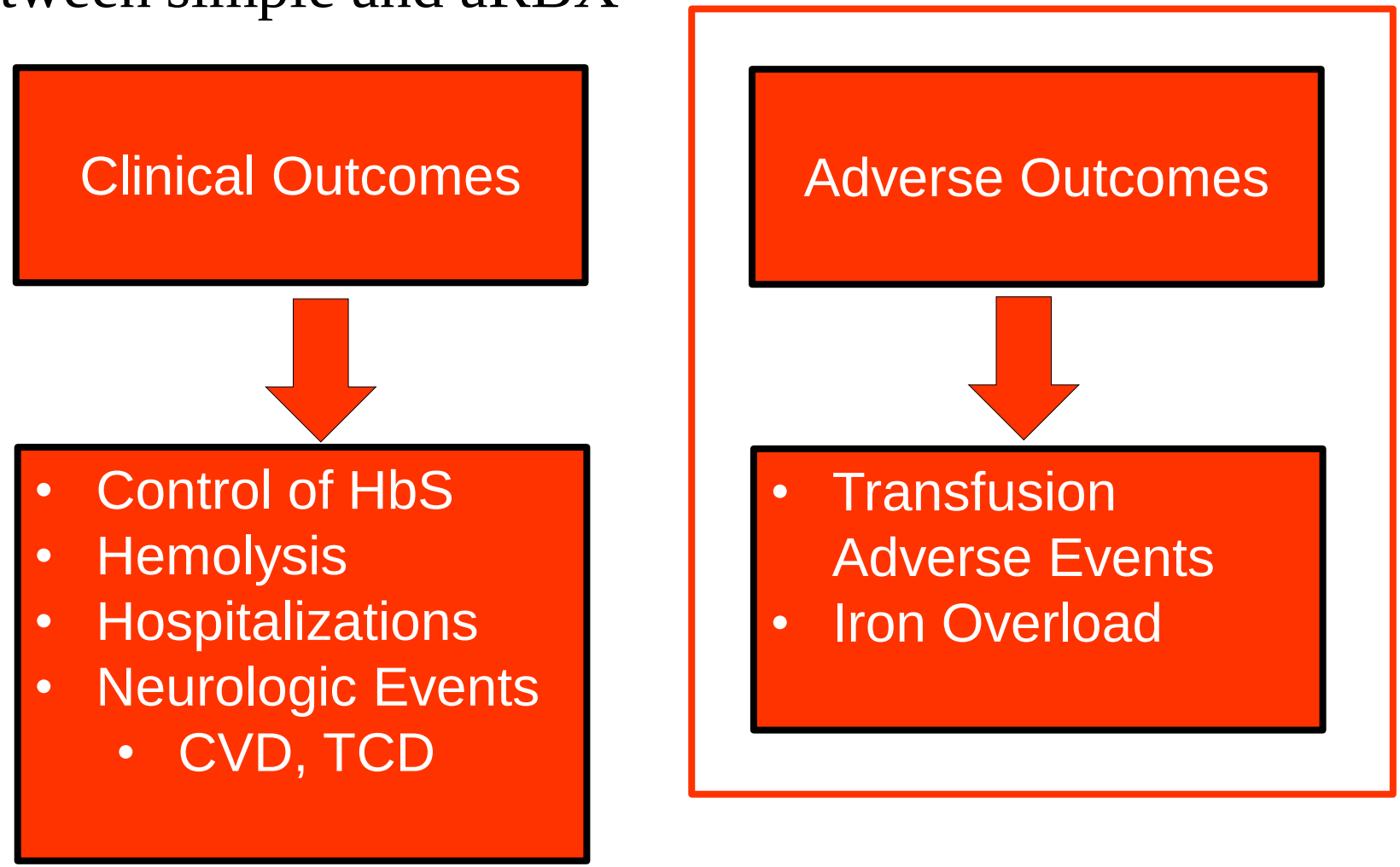

Methods

- Retrospective analysis of data captured for clinical care of chronically transfused patients
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- All nursing, physician and blood bank records for all transfusions reviewed to capture potential adverse events (AEs)
- CDC Hemovigilance definitions
  - Alloimmunization
  - Febrile non-hemolytic transfusion reactions (FNHTR)
  - Delayed hemolytic transfusion reaction (DHTR)
  - Transfusion associated circulatory overload (TACO)
  - Allergic reactions
  - Transfusion related acute lung injury (TRALI)
  - Transfusion transmitted infections (TTI)
- Gastrointestinal symptoms (GI) – any abdominal pain, nausea/vomiting that required an intervention
- Citrate/hypocalcemia symptoms that required an intervention

Methods

- Iron Overload - average ferritin over 6 months > 1000ng/mL
  - Serum ferritin frequently monitored
  - Other methods to assess iron (MRI, SQUID) only performed if ferritin consistently high

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- Statistical Analysis
  - Generalized estimating equation (GEE) models used to calculate odds ratio (OR) of outcomes with simple compared to exchange
    - GEE models relationship between repeated measures outcomes (adverse events) and predictor (transfusion method of simple or aRBX) allowing for within subject correlation
  - Analysis for transfusion adverse events → analyzed per unit (predictor = simple or aRBX unit)
  - Analysis for iron overload → transfusion time divided into 6 month blocks and each time block classified as simple or aRBX (predictor = simple or aRBX time block)

Eligibility

- SCD patients chronically transfused (at least 8 transfusions in a calendar year) at UCSF Benioff Children's Hospital Oakland (BCHO)
- Indication for chronic transfusion therapy = stroke prevention
  - Previous stroke
  - Abnormal TCD
  - Abnormal brain MRI/A
- >75% of care at BCHO Pediatric SCD Program
- Underwent at least 1 year of chronic transfusion therapy between 1998 – 2013 (aRBX first available in 1998)

Study Population

Study Population Demographics (n=56)		
Gender	32 (57.1%) Female	24 (42.9%) Male
Sickle Genotype	55 (98.2%) SS	1 (1.8%) SC
Age start CTT*	7.5 (2 – 19 years)	
Duration of CTT*	7.8 (1 – 23 years)	
Total Units Transfused	13,700 total units 5,238 simple units 8,462 aRBX units	
Units per Patient*	244 (8-933 units)	

* Mean, range

Study Population

- Many patients received a mixture of simple and aRBX transfused units during the time of CTT

Percent of Total Units via Simple Transfusion	N Subjects	Mean Percent of Units via Simple	Minimum Percent of Units via Simple	Maximum Percent of Units via Simple
<25% Simple	17			
25-75% Simple	15			
>75% Simple	24			

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Percent of Total Units via Simple Transfusion	N Subjects	Mean Percent of Units via Simple	Minimum Percent of Units via Simple	Maximum Percent of Units via Simple
<25% Simple	17	13.0%	3.5%	24.7%
25-75% Simple	15	46.5%	26.9%	74.4%
>75% Simple	24	95.5%	76.4%	100%

Intravenous Access

- Types of Intravenous Access in 37 patients with any aRBX

	N	% of 37
Peripheral IV Only	25	67.6%
AV fistula	2	5.4%
Double Lumen Port	10	27.0%

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  - Thrombus
    - 1right atrial thrombus → Port removal

Results – Iron Overload

	Primary aRBX (>75% units via aRBX) N=17	**Mixed Simple/aRBX N=15**	**Primary Simple (>75% units via Simple) N=24**
No / Minimal Iron Overload			
Developed Significant Iron Overload			
Developed Iron Overload on Simple → Improved/Resolved on aRBX			

Results – Iron Overload

	Primary aRBX (>75% units via aRBX) N=17	**Mixed Simple/aRBX N=15**	**Primary Simple (>75% units via Simple) N=24**
No / Minimal Iron Overload	9 (53.0%)		4 (16.7%)
Developed Significant Iron Overload	4 (23.5%)		20 (83.3%)
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- Odds of developing iron overload over time with simple compared to aRBX comparing "pure" patients

  OR 5.1 [2.8-9.0] $p<0.0005$

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Developed Significant Iron Overload	4 (23.5%)	11 (73.3%)	20 (83.3%)
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- Odds of developing iron overload over time with simple compared to aRBX including all patients

  OR 2.7 [1.9-4.0] $p<0.0005$

Results - Transfusion Adverse Events

	Simple 5125 U		**aRBX 8462 U**		**Odds of AE with Simple Compared to aRBX**
	N events	AE/100 U	N events	AE/100 U	OR [95% CI]
Allo-antibodies					
FNHTR					
Allergic					
DHTR					
GI					
Citrate					
Machine Malfunction					
Other (SAE)					
Any AE					
Any AE (citrate & malfunction excluded					

Results - Transfusion Adverse Events

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	N events	AE/100 U	N events	AE/100 U	OR [95% CI]
Allo-antibodies	12		1		
FNHTR	7		4		
Allergic	18		22		
DHTR	1		0		
GI	2		4		
Citrate	N/A		17		
Machine Malfunction	N/A		2		
Other (SAE)	0		1		
Any AE	40		51		
Any AE (citrate & malfunction excluded	40		32		

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	N events	AE/100 U	N events	AE/100 U	OR [95% CI]
Allo-antibodies	12	0.234	1	0.012	
FNHTR	7	0.137	4	0.047	
Allergic	18	0.351	22	0.260	
DHTR	1	0.019	0	0	
GI	2	0.039	4	0.047	
Citrate	N/A	N/A	17	0.200	
Machine Malfunction	N/A	N/A	2	0.024	
Other (SAE)	0	0	1	0.012	
Any AE	40	0.780	51	0.603	
Any AE (citrate & malfunction excluded	40	0.780	32	0.378	

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Allergic	18	0.351	22	0.260	1.57 [0.8-3.1]
DHTR	1	0.019	0	0	N/A
GI	2	0.039	4	0.047	0.97 [0.3-3.7]
Citrate	N/A	N/A	17	0.200	N/A
Machine Malfunction	N/A	N/A	2	0.024	N/A
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Summary

- Despite an increase in unit exposure with aRBX, there was no significant difference in transfusion adverse events with the exception of lower alloimmunization with aRBX
- There were significantly increased odds of iron overload with simple compared to aRBX
- Future Directions: compare clinical outcomes between simple and aRBX
  - New/progression cerebral infarcts or cerebral vascular disease
  - Transcranial doppler
    - Normalization or development of abnormal TCD
  - Pre-transfusion HbS, reticulocyte count
  - Hospitalizations (any, vaso-occclusive pain episode, acute chest syndrome)

Acknowledgements

- Apheresis team at UCSF Benioff Children's Hospital Oakland
  - Keith Quirolo, MD
  - Alicia Garcia, RN, HP (ASCP)
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