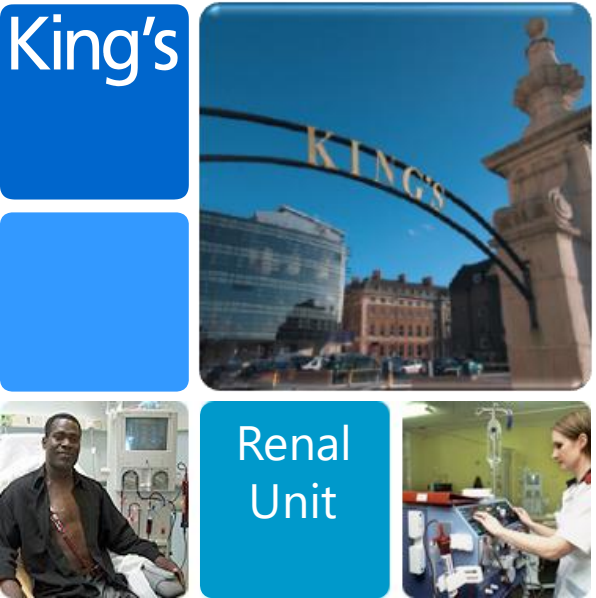
The role of chronic transfusion for SCD patients in work up for renal transplant

UKFHD 56th Academic Meeting
Wednesday 22nd November 2023



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King's College Hospital
University of Nottingham

University of Nottingham
UK | CHINA | MALAYSIA

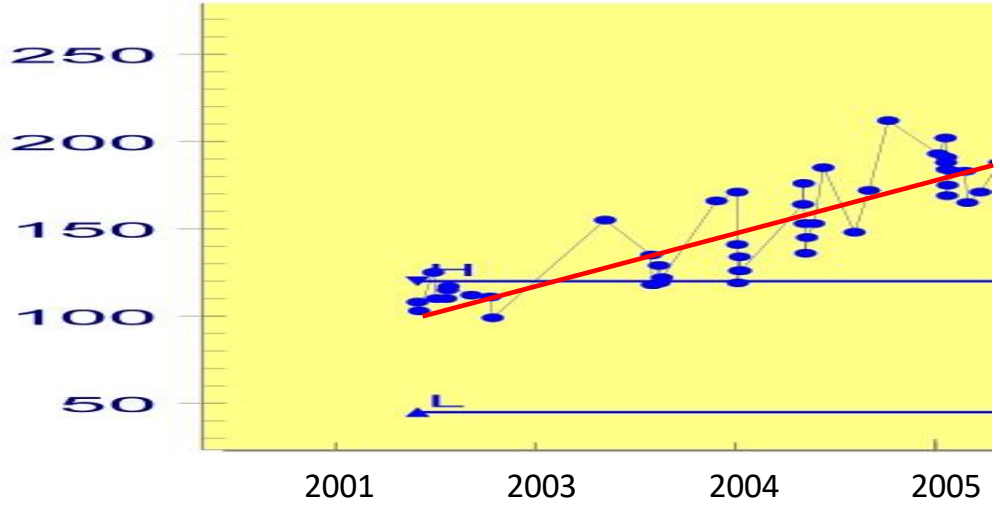
- Mr O

- **2005**
- 43 year old Nigerian man
- HBSS

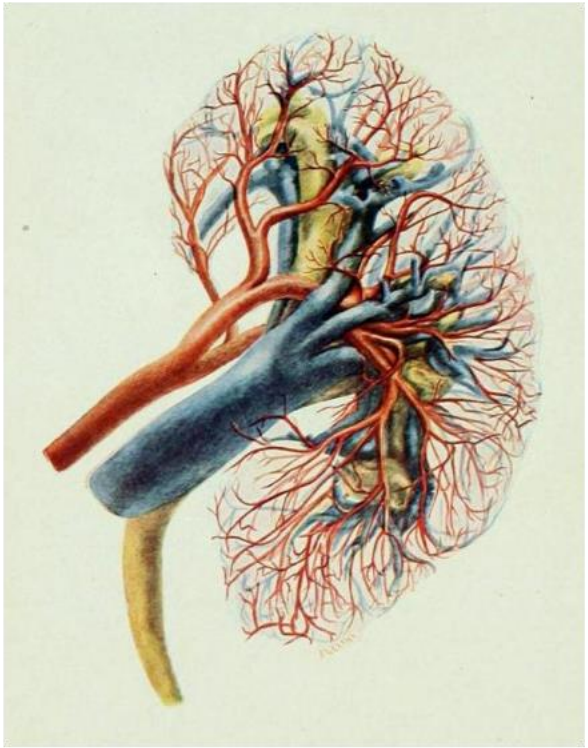
- **PMH**
- Hypertension
- Bilateral avascular necrosis of the hips
- Pulmonary embolism
- Leg ulcers
- Multiple admissions with painful crises

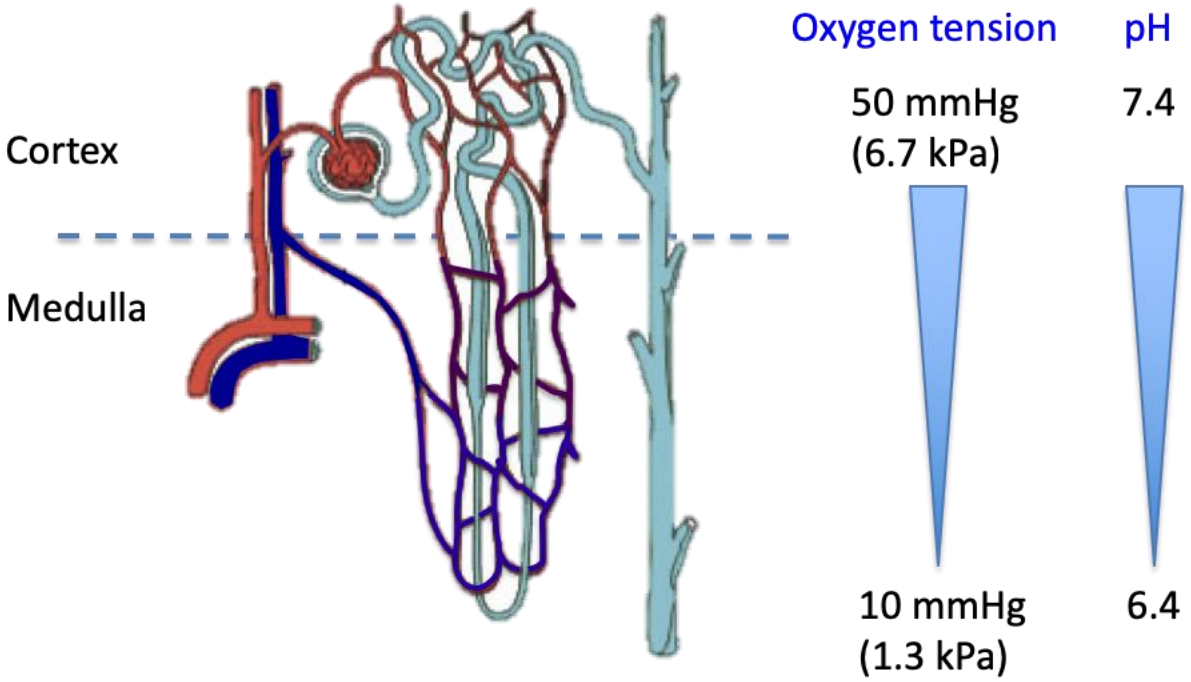
Serum creatinine

- Creatinine 212 µmol/l (eGFR 34 ml/min)
- Protein/creatinine ratio 790 mg/mmol



The kidney is a very vascular organ but has a hypoxic centre





A Textbook of Genito-Urinary Diseases.
Translated by Charles W. Bonney. Dr. Leopold Casper, 1912.

The renal microvasculature is destroyed in sickle cell disease

Normal kidney

Sickle cell disease

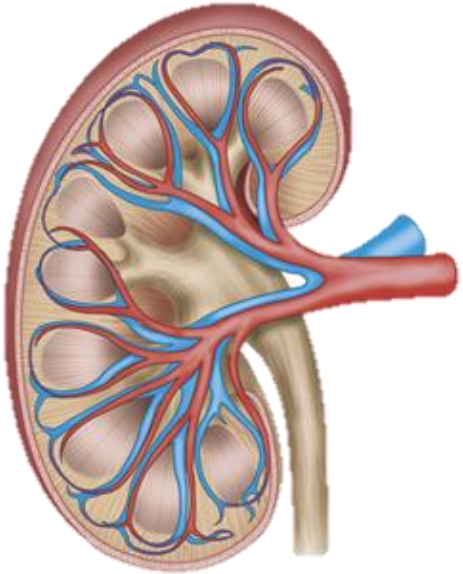
Clinical manifestations

1. Increased GFR from early childhood to young adulthood (300-400ml/min/1.73m^2)

Decreasing GFR from the fourth decade onwards

2. Microalbuminuria leading to proteinuria

3. Supranormal Proximal tubular function leading to hyperphosphataemia and increased creatinine secretion



4. Diminished concentrating ability (hyposthenuria)

5. Impairment of distal hydrogen ion and potassium secretion

6. Haematuria

7. Renal cyst formation

Risk factors for progression of chronic kidney disease in SCD

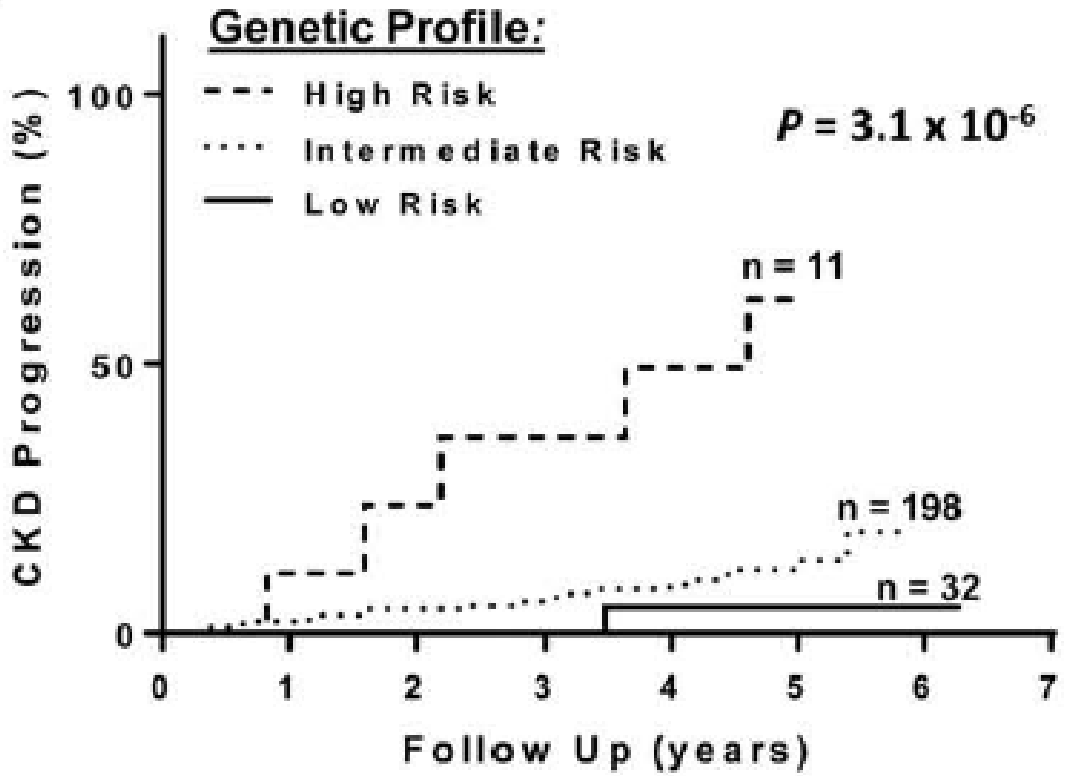
Severe sickle phenotype

- Frequent admissions
- Recurrent acute kidney injury
- High levels of haemolysis

Genetic modifiers

- Alpha-globin genotype,
- Other genetic modifiers: (APOL1, BCL11A)

Combining genetic modifiers can help to stratify patients for risk of progression



Saraf SL et al, Haematologica. 2017 Jan;102

Risk factors for progression of chronic kidney disease in SCD

Other renal insults

- Hypertension
- Diabetes
- Autoimmune disease
- Blood-borne viruses

Management of sickle cell nephropathy

Treatments for sickle cell disease

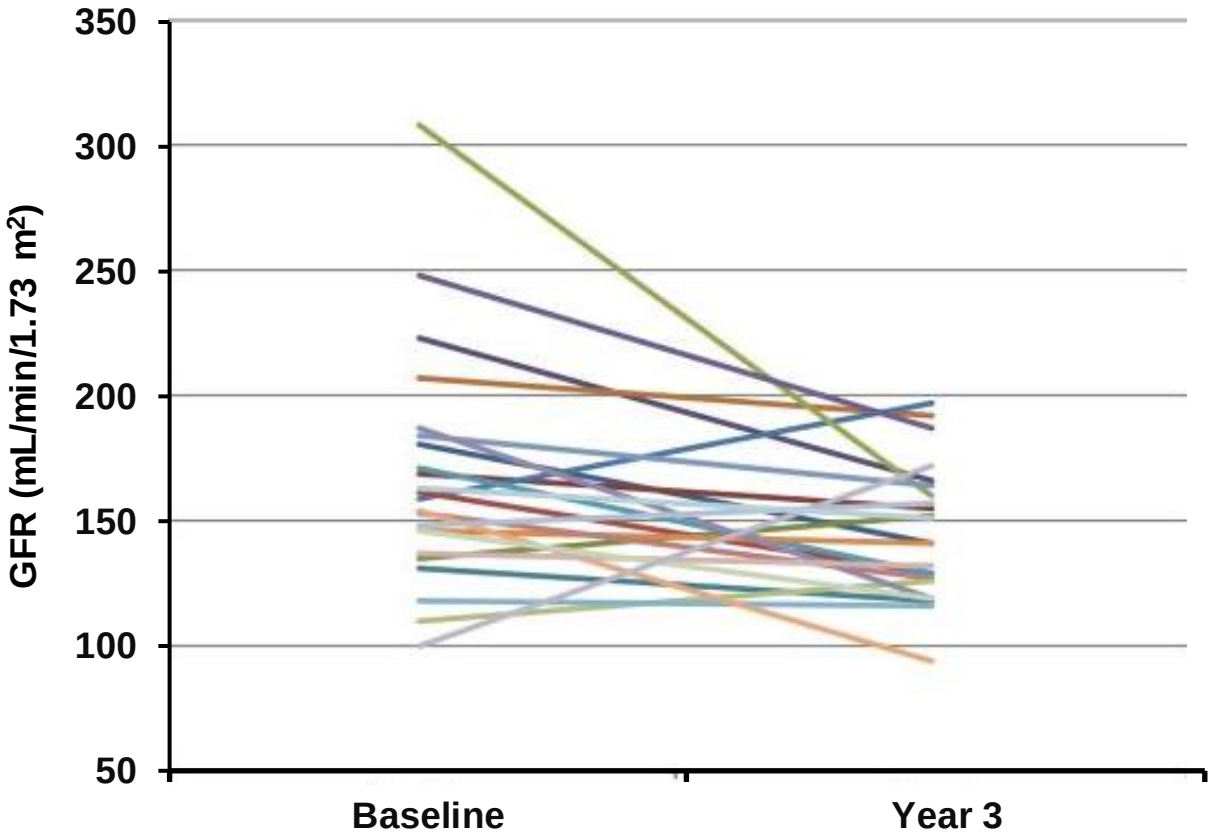
- Hydroxyurea (hydroxycarbamide)
- Crizanlizumab
- Voxeletor
- Transfusion therapy (intermittent or regular)
- Hemopoietic cell transplantation in childhood

Treatments for CKD

- Adequate hydration
- Control of blood pressure if hypertensive
- ACE inhibitors/ARB
- Erythropoietin therapy (± hydroxyurea)
- Dialysis
- Transplantation

- Hydroxyurea (Hydroxycarbamide)
- Exchange transfusion
- Erythropoietin therapy

Hydroxyurea study of long-term effects (HUSTLE) in children with SCD



Aygun B *et al. Am J Hematol* 2013;88:116–119.

Kidney function of transfused children with sickle cell anemia
Baseline data from the TWiTCH study with comparison to non-transfused cohorts

	TWiTCH* (N=121)	UM† (N=119)	HUSTLE‡ (N=74)	*P* value			
				T vs UM	T vs H	UM vs H	Overall
Age in years at screening, mean (SD)	9.5 (2.9)	9.9 (3.2)	9.4 (3.1)	0.311	0.820	0.287	–
Hemoglobin (g/dL), mean (SD)	9.2 (0.8)	8.2 (1.2)	8.0 (1.1)	**<0.001**	**<0.001**	0.270	–
Bedside Schwartz GFR, mean (SD)	140.1 (67)	148.3 (37)	170.5 (38)	0.358	**<0.001**	**<0.001**	–
CKiD Schwartz GFR, mean (SD)	122.3 (29.8)	–	139.7 (24.5)	§	**<0.001**	§	–
Albuminuria patients, N (%)	12 (10.3%)	26 (21.8%)	6 (14.3%)	–	–	–	**0.049**

Alvarez O *et al. Am J Hematol* 2017;92:E637–E639.

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for chronic kidney disease in people with sickle cell disease (Review)

Noemi BA Roy, Abigail Carpenter, Isabella Dale-Harris, Carolyn Dorée, Lise J Estcourt Authors' declarations of interest

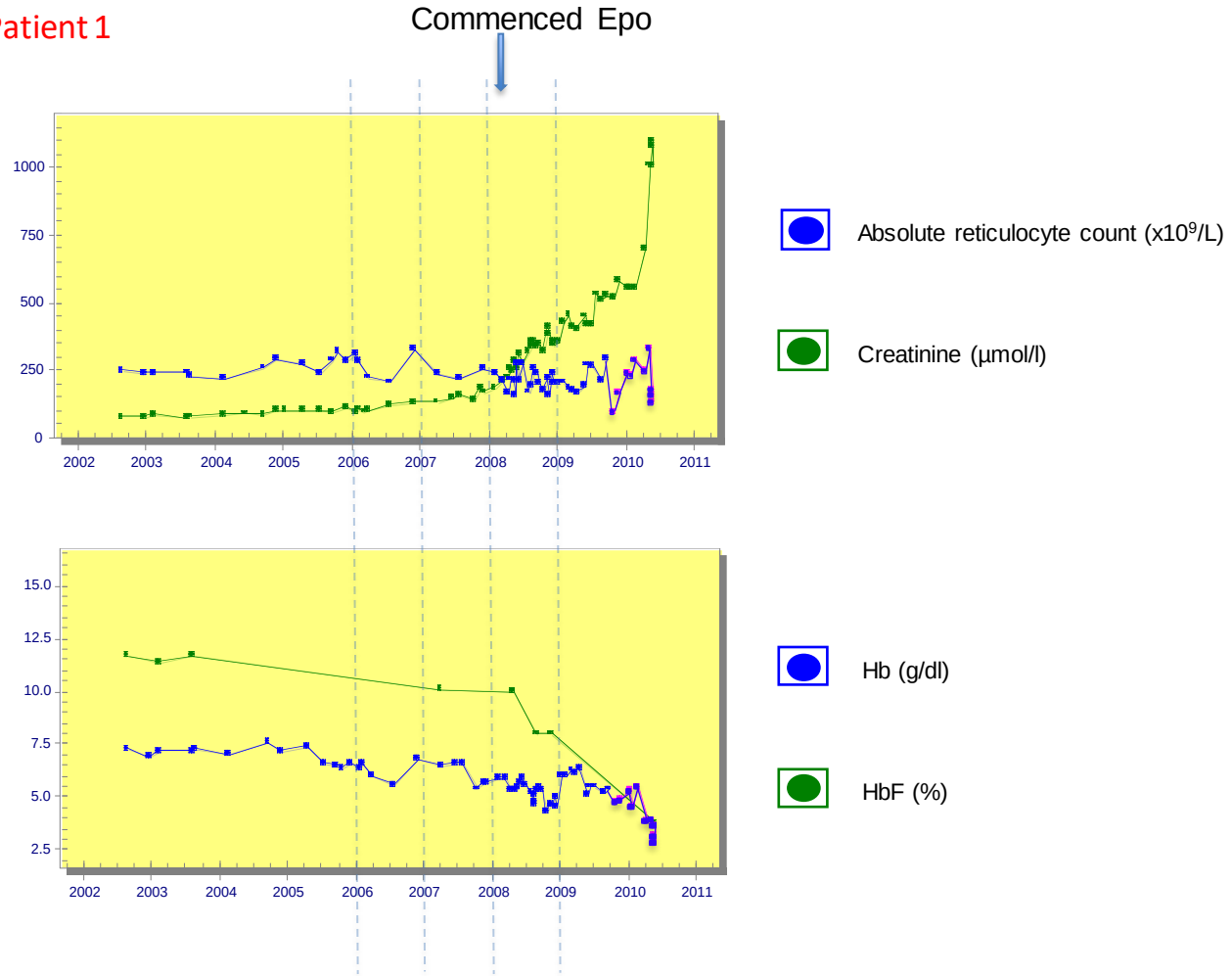
Version published: 04 August 2023 Version history

https://doi.org/10.1002/14651858.CD012380.pub3

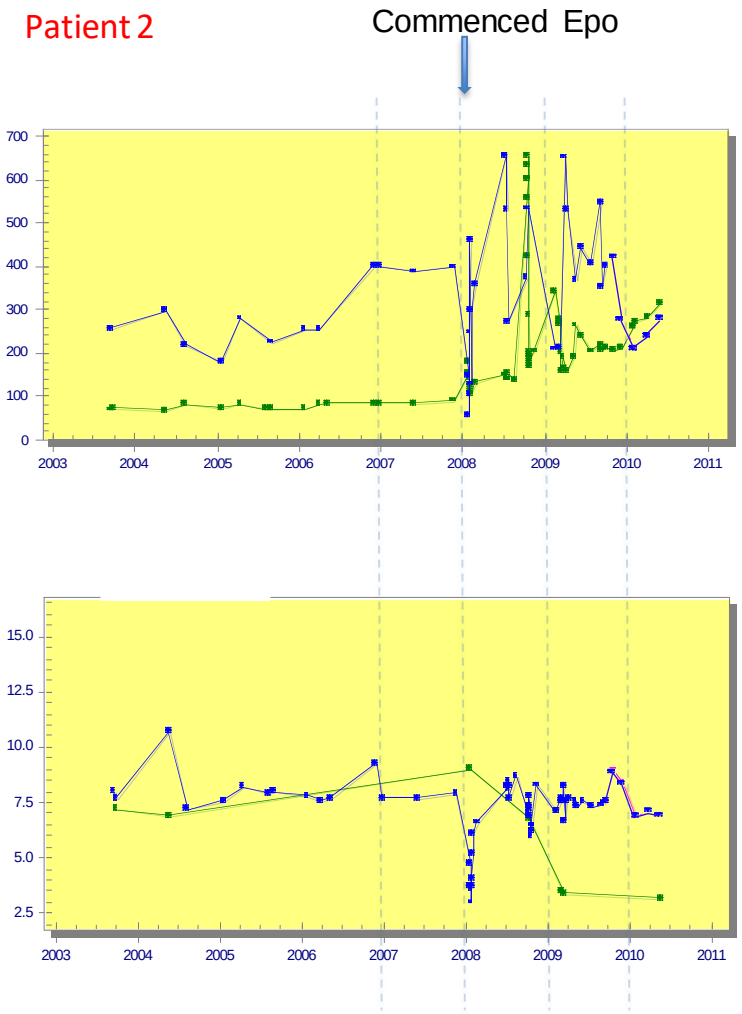
- No RCTs assessed red blood cell transfusions or any combined interventions to prevent or reduce kidney complications.
- Trials of hydroxyurea, ACEIs or red blood cell transfusion in older children and adults are urgently needed to determine any effect on prevention or reduction of kidney complications in people with SCD.

Erythropoietin

Patient 1


Commenced Epo
1000
750
500
250
0
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
15.0
12.5
10.0
7.5
5.0
2.5
Absolute reticulocyte count (x10^9/L)
Creatinine (µmol/l)
Hb (g/dl)
HbF (%)

Patient 2



Absolute reticulocyte count (x10^9/L)

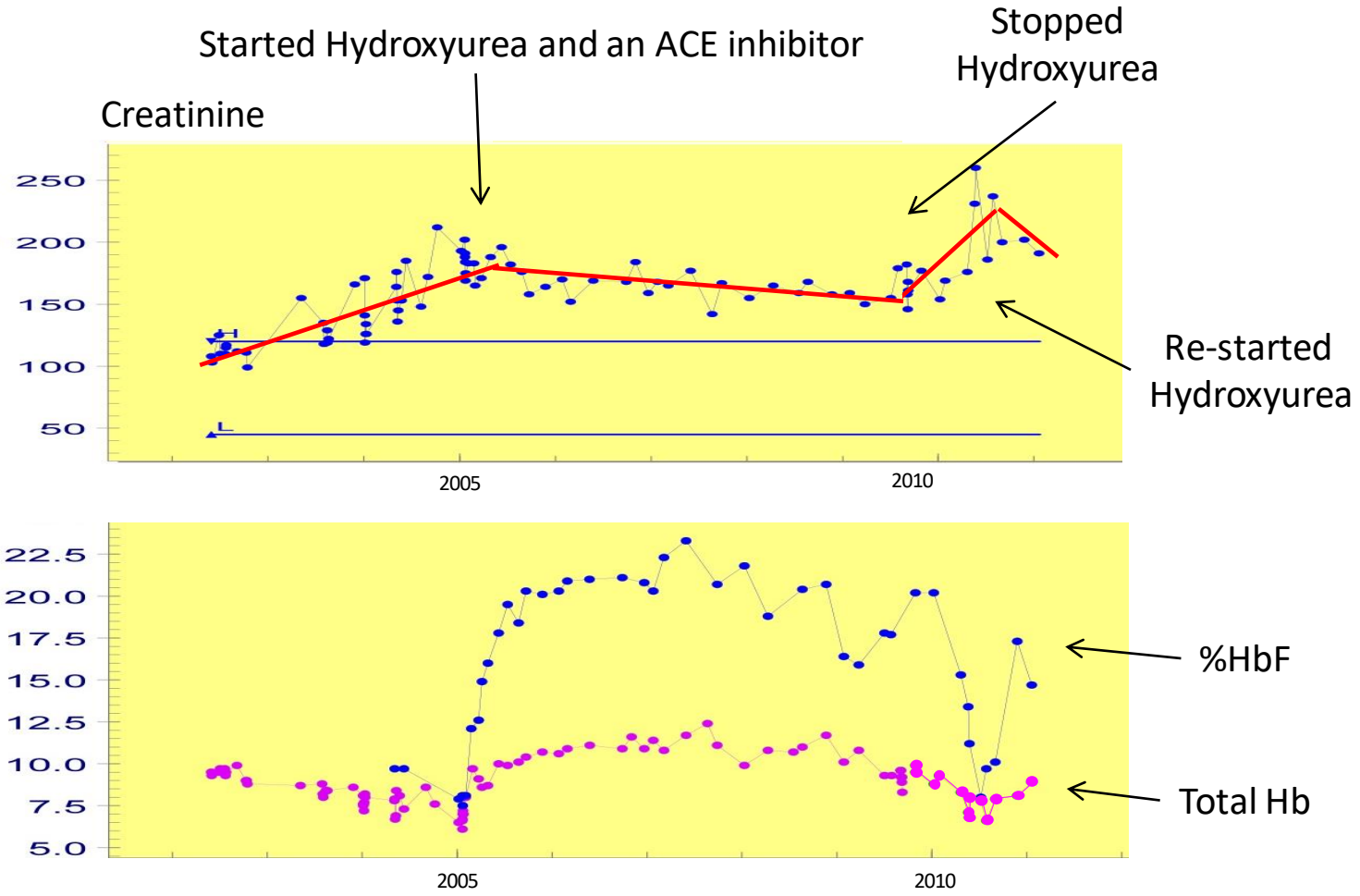
Creatinine (µmol/l)

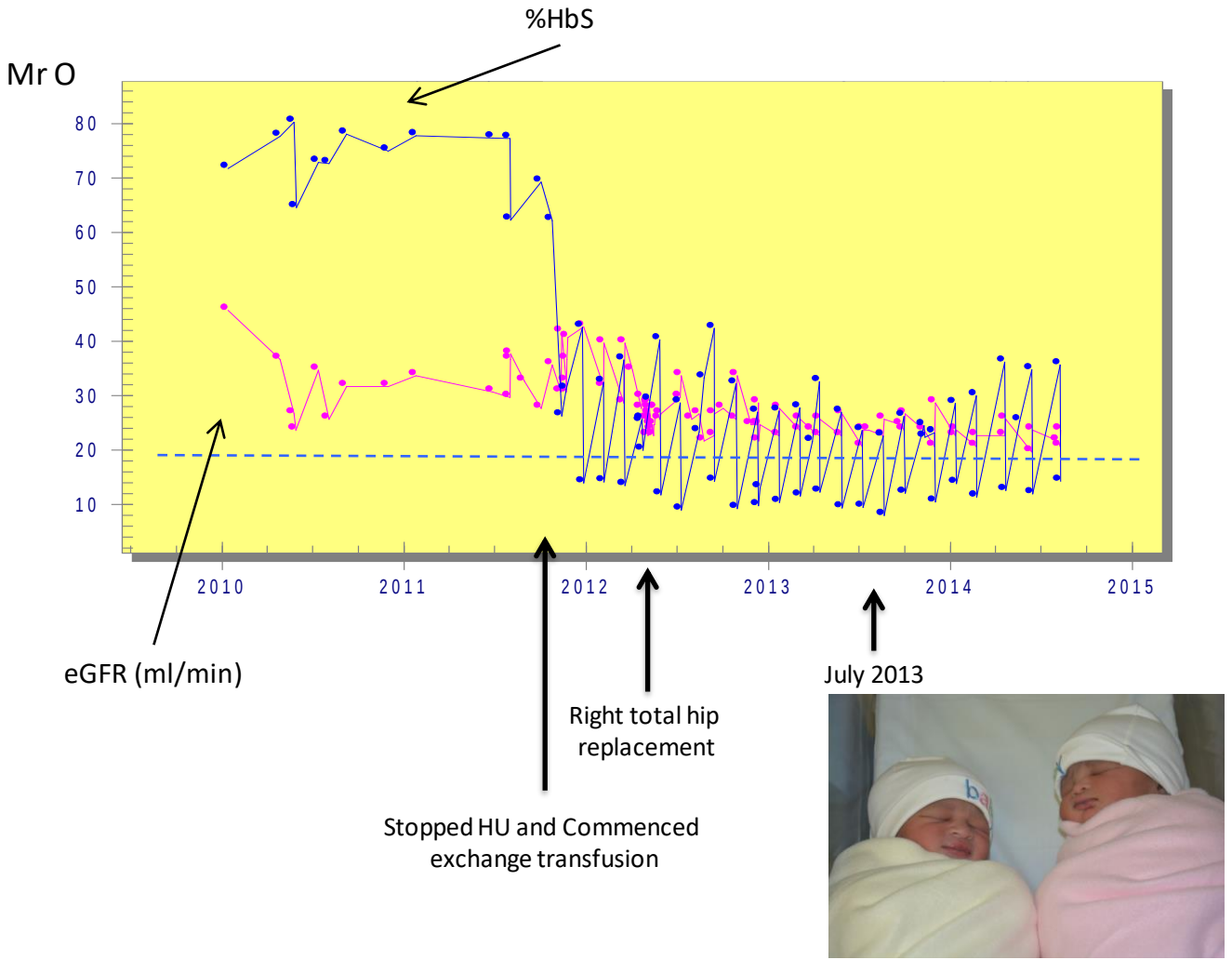
Hb (g/dl)

HbF (%)

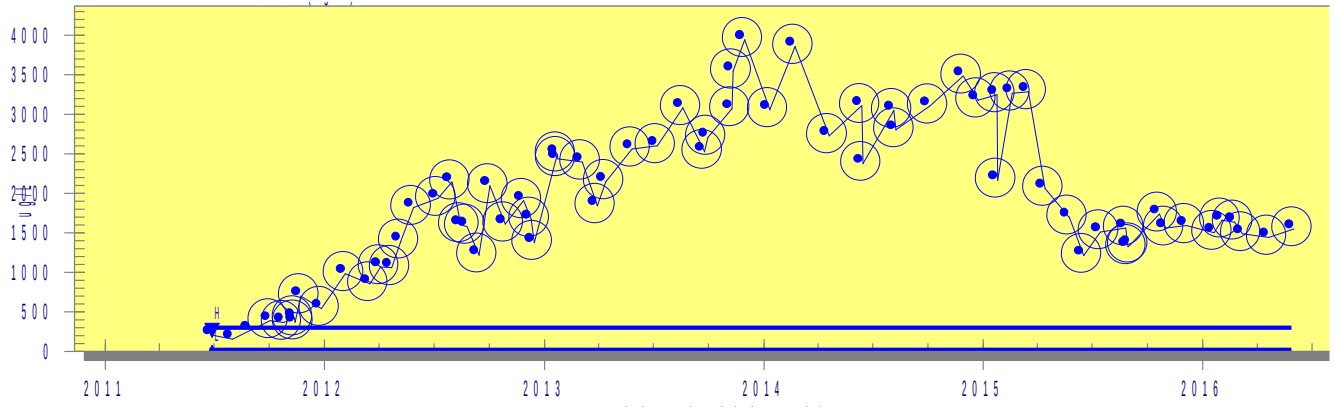
- Returning to Mr O

Mr O

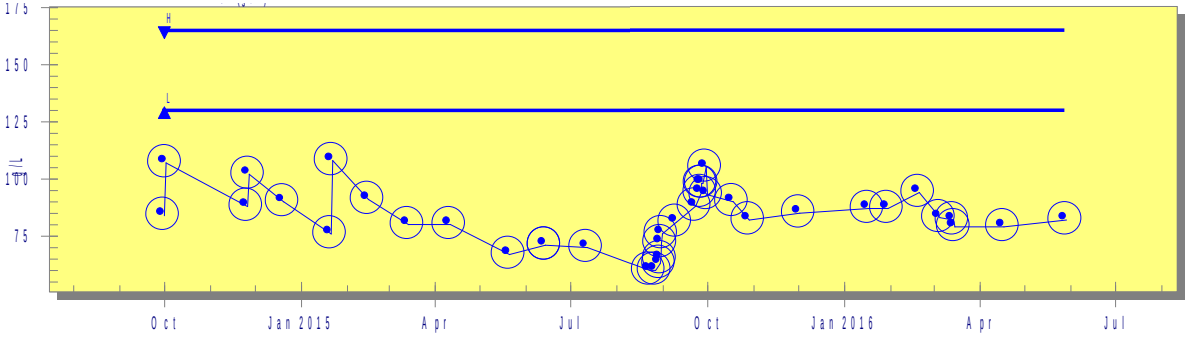

Started Hydroxyurea and an ACE inhibitor
Stopped Hydroxyurea
Creatinine
250
200
150
100
50
H
L
2005
2010
Re-started Hydroxyurea
22.5
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2005
2010
%HbF
Total Hb


%HbS
Mr O
80
70
60
50
40
30
20
10
2010
2011
2012
2013
2014
2015
eGFR (ml/min)
Stopped HU and Commenced exchange transfusion
Right total hip replacement
July 2013

Ferritin



Haemoglobin



* Stopped EBT and commenced HC

** Commenced Epo therapy

* **

Managing end stage kidney disease in people with sickle cell disease

Prognosis for patients with SCD receiving dialysis is poor

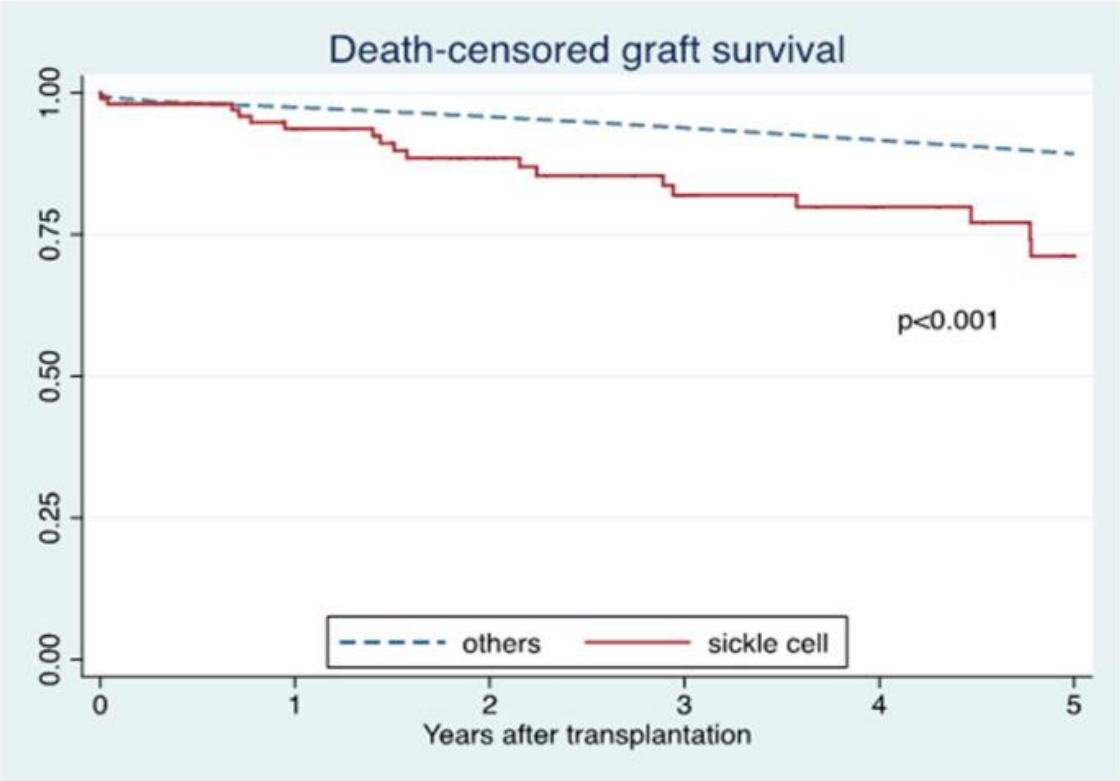
In a retrospective cohort analysis comparing patients with SCD on haemodialysis with an aged-matched (37 years) control group of non-SCD patients receiving Haemodialysis:

- SCD patients were much more likely to die over a 5 year period (46.3 vs 6.4%). Infectious complications and thrombosis of dialysis access was common in the SCD group (no data from the non-SCD control group)

- SCD patients were much less likely to receive a kidney transplant over a 5 year period (26% vs 53.5%)

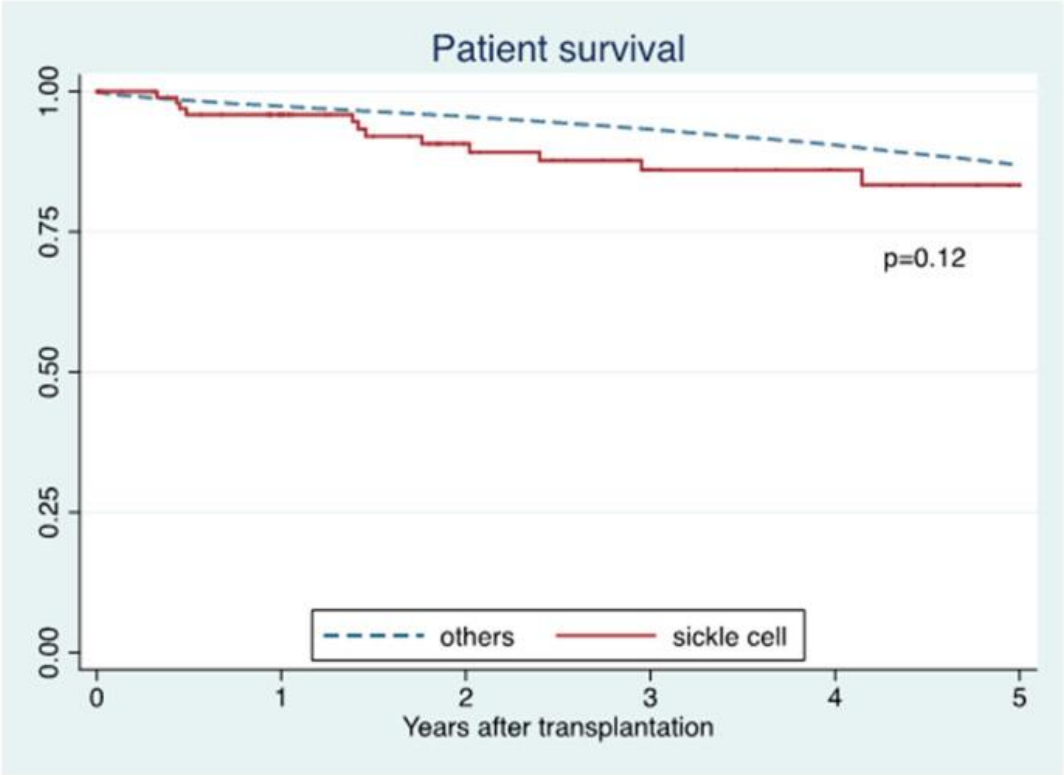
Nielson *et al* Br J Haematol. 2016 Jul;174(1):148-52 Morbidity and mortality of sickle cell disease patients starting intermittent haemodialysis: a comparative cohort study with non- Sickle dialysis patients.

Kidney transplant functional lifespan is good in patients with SCD, but not as good as in patients without SCD



Leeaphorn N, Thongprayoon C, Vaitla P, et al. Outcomes of Kidney Transplant Recipients with Sickle Cell Disease: An Analysis of the 2000-2019 UNOS/OPTN Database. *J Clin Med*. 2021;10(14):3063.

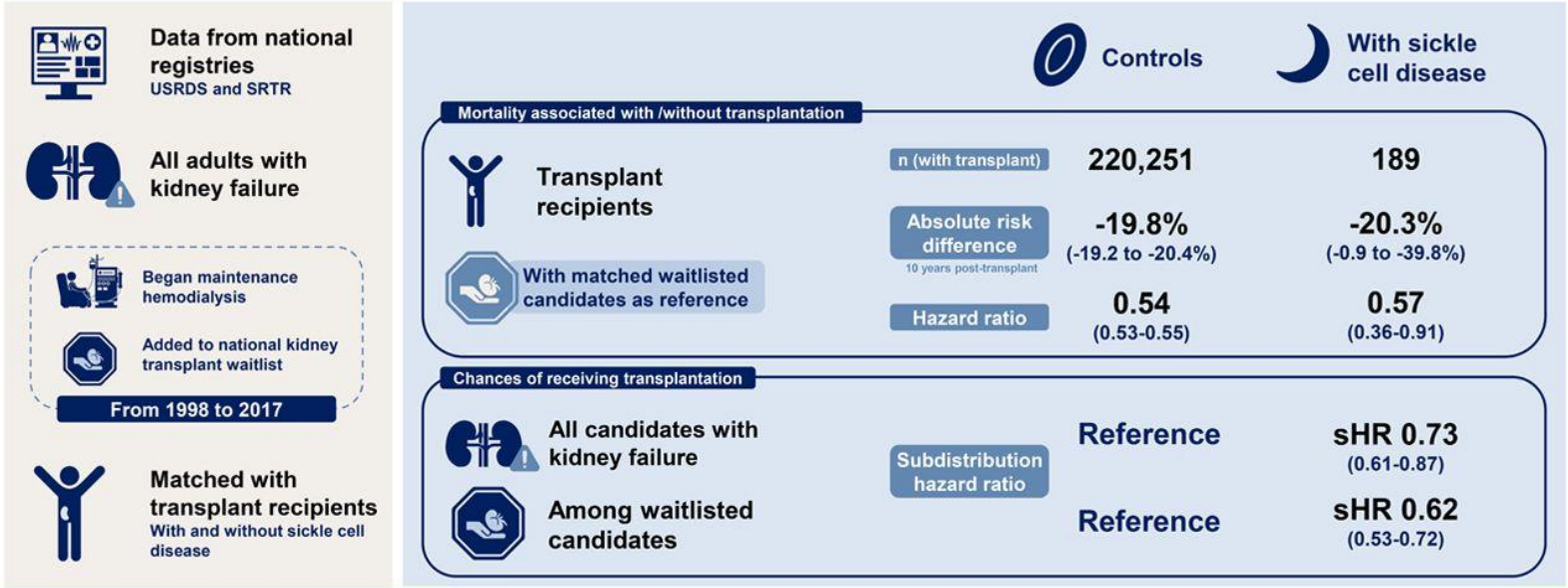
Patients with SCD live longer after a kidney transplantation but not quite as long as patients without SCD



Leeaphorn N, et al. Outcomes of Kidney Transplant Recipients with Sickle Cell Disease: An Analysis of the 2000-2019 UNOS/OPTN Database. J Clin Med. 2021;10(14):3063.

Does having sickle cell disease as the primary diagnosis affect the chances of receiving a transplant?

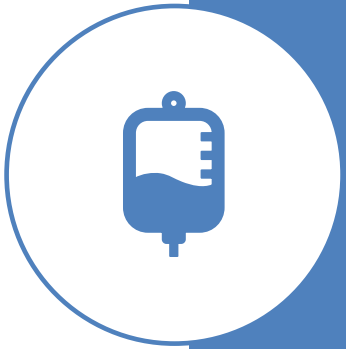
CJASN
Clinical Journal of the American Society of Nephrology



Conclusions Patients with sickle cell disease–associated kidney failure exhibited similarly lower mortality with kidney transplantation compared to those with other etiologies. Nonetheless, sickle cell population was less likely to receive transplantation, even after waitlist registration.

Sunjae Bae, Morgan Johnson, Allan B. Massie, et al. ***Mortality and Access to Kidney Transplantation in Patients with Sickle Cell Disease–Associated Kidney Failure***. CJASN doi: 10.2215/CJN.02720320. **Visual Abstract by Michelle Lim, MBChB, MRCP**

Does regular exchange blood transfusion improve outcomes after kidney transplantation or increase the risk of sensitization and rejection?



PLOS ONE

RESEARCH ARTICLE

Outcomes following kidney transplantation in patients with sickle cell disease: The impact of automated exchange blood transfusion

Joanna C. Willis[1], Moji Awogbade[2], Jo Howard[3], Cormac Breen[4], Allifia Abbas[4], Mark Harber[5], Ali M. Shendi[5,6], Peter A. Andrews[7], Jack Galliford[8], Raj Thuraisingham[9], Alice Gage[9], Sapna Shah[1], Claire C. Sharpe[1,10]*

PLoS One. 2020 Aug 13;15(8):e0236998. doi: 10.1371/journal.pone.0236998. eCollection 2020.

- Retrospective multicenter study, 34 patients with SCD transplanted
- Follow up over a 20 year period
- All 6 London Renal Units

Patient characteristic			EBT (n=20)	No EBT (n=14)	p value
Female gender			8 (40%)	8 (57%)	0.32
Median age at transplantation in years (range)			39.5 (23-52)	34 (25-45)	0.99
Median year of transplantation (range)			2012 (2006–2017)	2005 (1996-2017)	0.01
Type of Tx	LD		7 (35%)	5 (36%)	
	DBD		8 (40%)	8 (57%)	0.37
	DCD		5 (25%)	1 (7%)	
Mean HLA mismatches		A	1.05	0.71	0.33
		B	1.2	0.86	0.32
		DR	0.65	0.43	0.62
Immunosuppression:					
Induction	Basiliximab		18 (90%)	11 (79%)	
	ATG		0	1 (7%)	
	Alemtuzumab		1 (5%)	0	
	Unknown		1 (5%)	2 (14%)	
Maintenance	Tacrolimus		15 (75%)	6 (43%)	0.06
	Ciclosporin		5 (25%)	8 (57%)	
	Prednisolone		18 (90%)	13 (93%)	
	Azathioprine		1 (5%)	4 (29%)	
	MMF		16 (80%)	9 (64%)	

Table 1. *Patient characteristics in the two groups (those receiving EBT and those not receiving EBT)*

Median age at the time of transplantation was 36 years (range 23 – 52 years).

20/34 patients (59%) received EBT for a prolonged period of time at 4-6 weekly intervals, commencing between 31 months pre-transplant and 48 months post-transplant.

EBT is associated with better renal function

		EBT	No EBT	UK average DBD/DCD/LD (2004-2006 cohort)[2,3]
1 year	Patient survival	95	86	97/95/99
	n	*19*	*12*	
	Graft survival	94	77	93/94/96
	n	*18*	*10*	
	Median eGFR	45	33	53
5 years	Patient survival	88	44	90/86/96
	n	*13*	*5*	
	Graft survival	67	50	85/87/92
	n	*10*	*4*	
	Median eGFR	34	12	
10 years	Patient survival	60	29	76/72/91
	n	*3*	*2*	
	Graft survival	33	0	76/76/82
	n	*3*	*0*	
	Median eGFR	29	n/a	

Table 2. *Patient and death-censored graft survival (in %), and median eGFR (in ml/min/1.73m^2) at 1, 5 and 10 years post-transplantation in those on an EBT programme (EBT) compared to those not on an EBT programme (No EBT), alongside UK data for DBD, DCD and LD transplants (Source: NHSBT[2] & Renal Registry[3]). Numbers of patients available at each follow-up included below each row of data (n).*

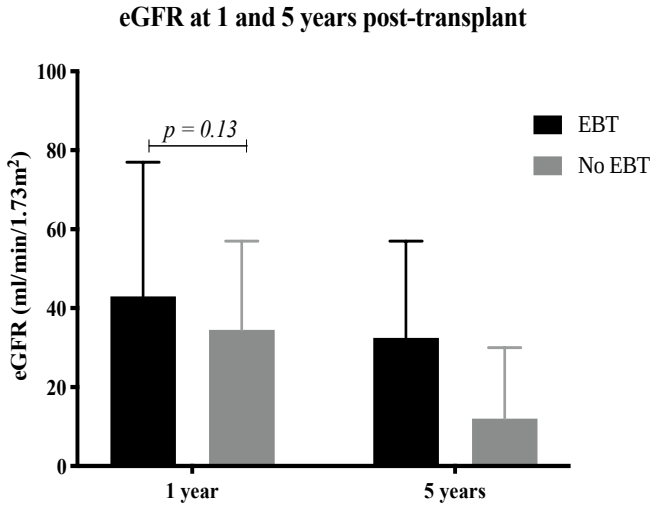


Figure 2*. Median eGFR (calculated by MDRD/ml/min/1.73m^2) at 1 and 5 years post-transplant with and without EBT. Error bars represent range.*

EBT is associated with lower rates of recurrent disease, lower rates of rejection and no increased risk of developing HLA-specific antibodies

	EBT	No EBT	p value
Median cRF	34%	71%	0.07
Incidence of DSA	20%	21%	0.92
Incidence of rejection	25%	58%	0.06
Incidence of recurrent SCN	20%	50%	0.08

Table 3. *Sensitization and graft specific outcomes in those on an EBT programme compared with those not on an EBT programme.*

□

EBT is associated with better patient and graft survival in our cohort

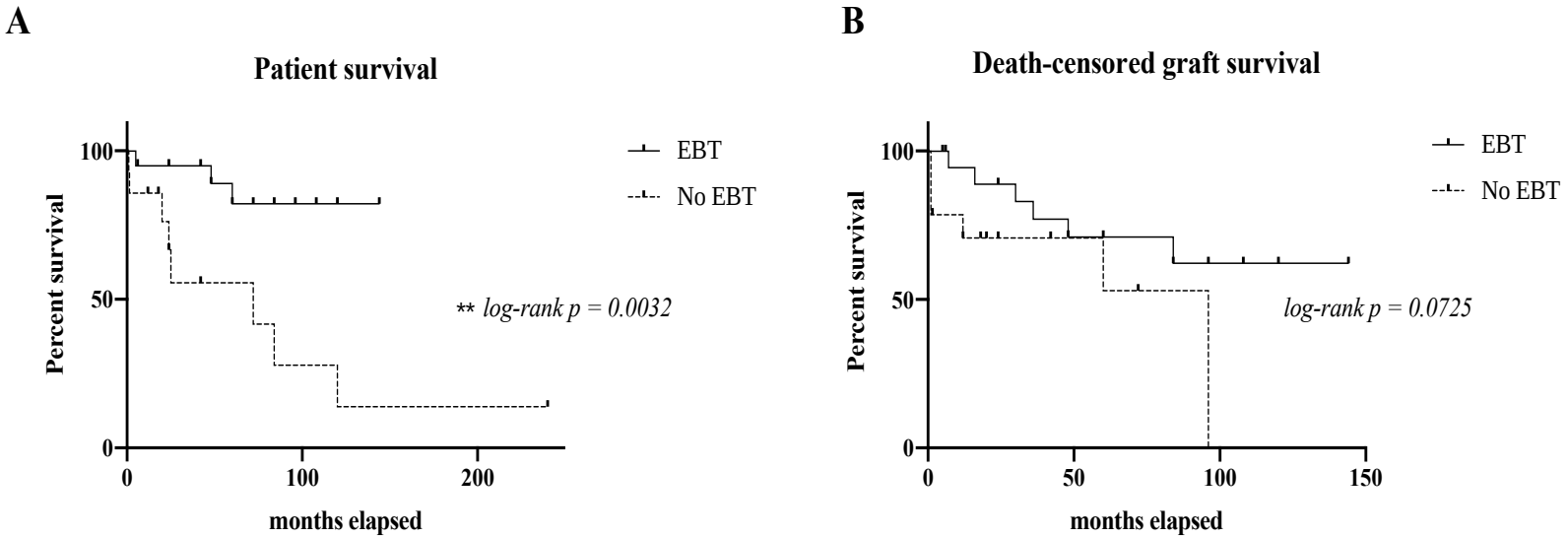
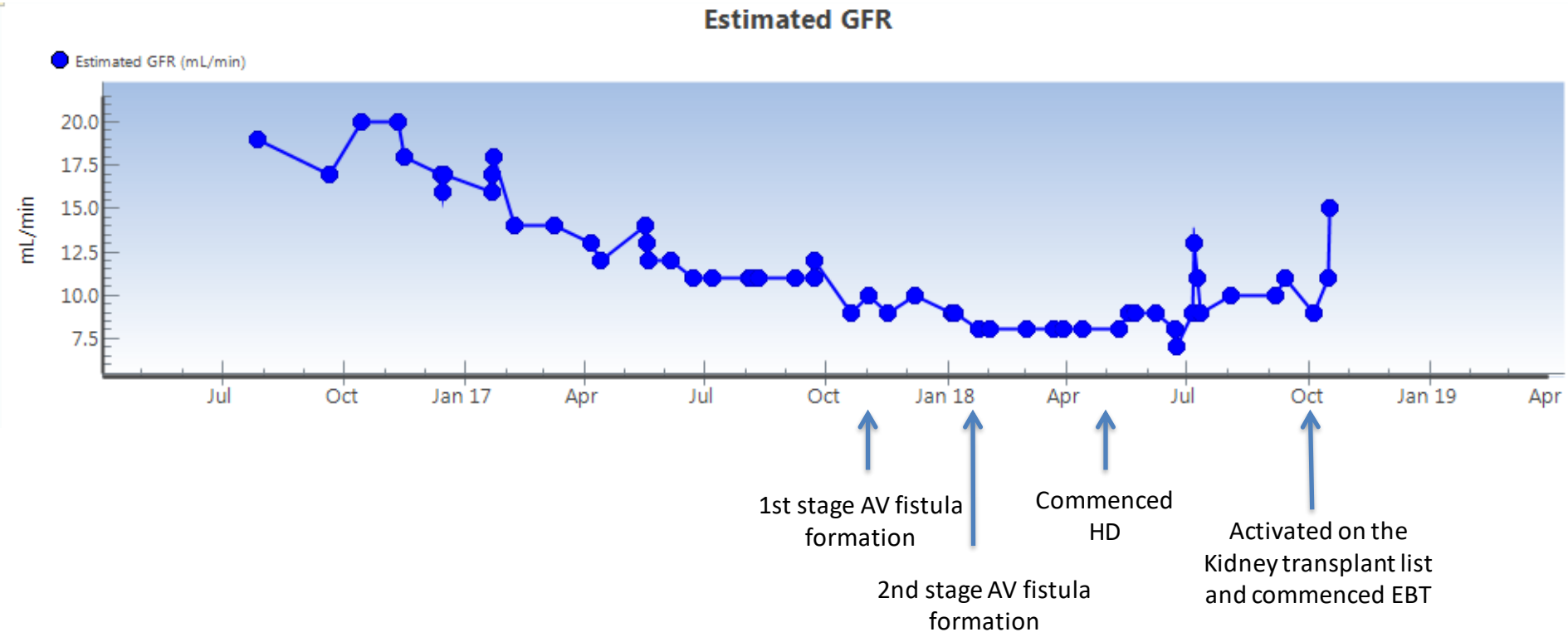
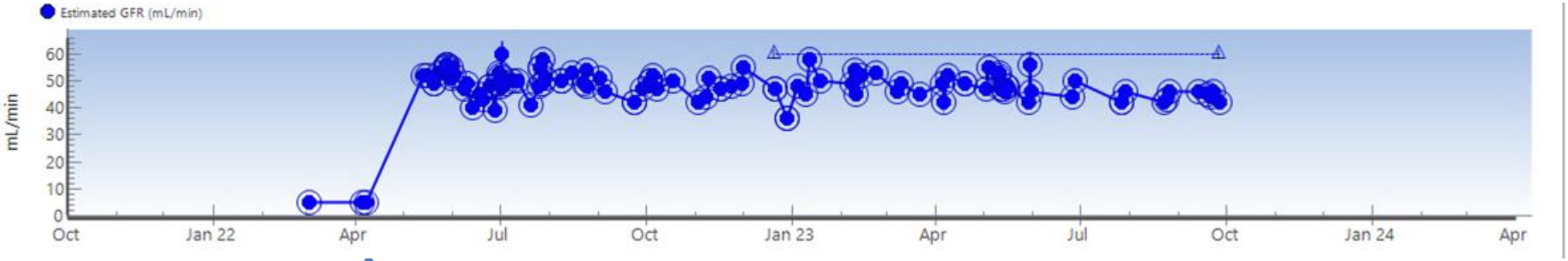


Figure 1. *Kaplan-Meier survival curves comparing (A) patient survival, and (B) death-censored graft survival with and without EBT.*

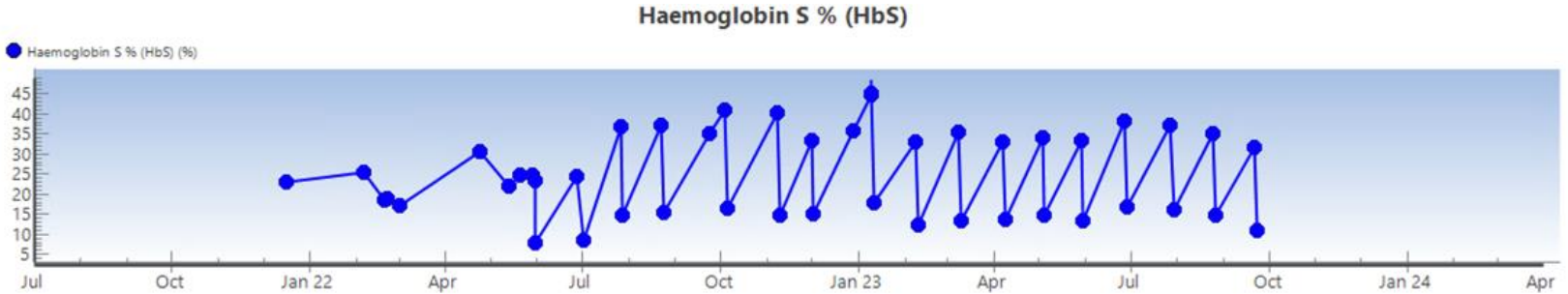
Mr O

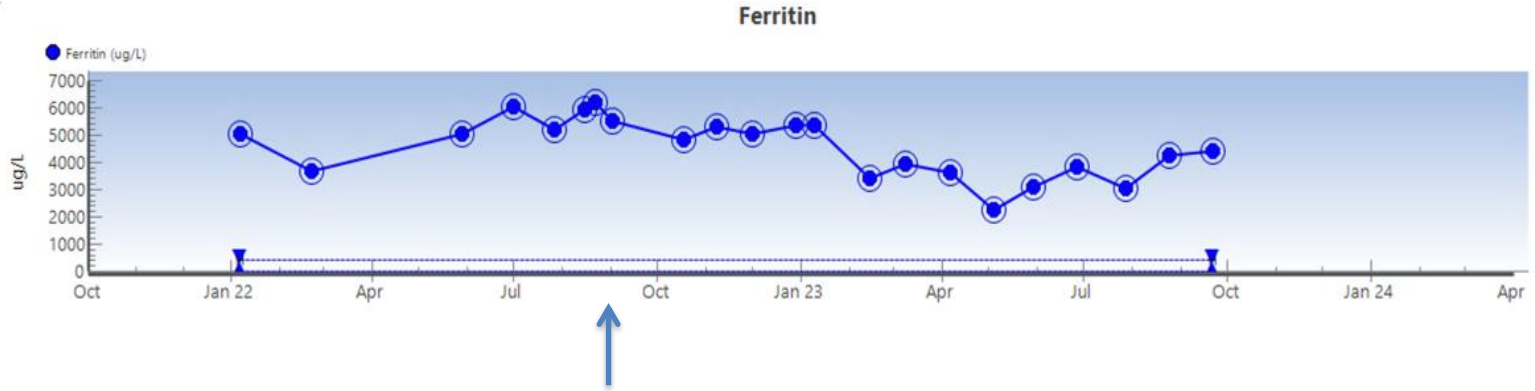

Estimated GFR
Estimated GFR (mL/min)
mL/min
20.0
17.5
15.0
12.5
10.0
7.5
Jul
Oct
Jan 17
Apr
Jul
Oct
Jan 18
Apr
Jul
Oct
Jan 19
Apr
1st stage AV fistula formation
2nd stage AV fistula formation
Commenced HD
Activated on the Kidney transplant list and commenced EBT

Estimated GFR



Received a cadaveric kidney transplant





Started on
Deferiprone

Conclusion

- Sickle cell nephropathy is a relatively common and significant complication of sickle cell disease. Although most patients don't progress to end-stage kidney failure, this complication is becoming more common.

- Moderate to severe renal impairment is associated with a markedly increased risk of mortality

- Hydroxycarbamide or regular exchange transfusion may be beneficial in stabilizing deteriorating renal function

- Patients with advanced CKD require regular top up transfusions to manage severe anaemia

- Patients with SCD wait longer for transplants but the benefits of receiving one are the same as for people without SCD

- Early transplantation should be considered in patients with SCD and kidney failure. Patient optimization with regular exchange transfusion may be beneficial both pre and post transplantation but further studies are required.

Thank you