

# Journée filière FilRouge Retour ASH 2025

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30/01/26





American Society of Hematology  
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# Left Atrial Reservoir Strain as a Novel Echocardiographic Marker of Diastolic Dysfunction and Mortality Risk in Sickle Cell Cardiomyopathy

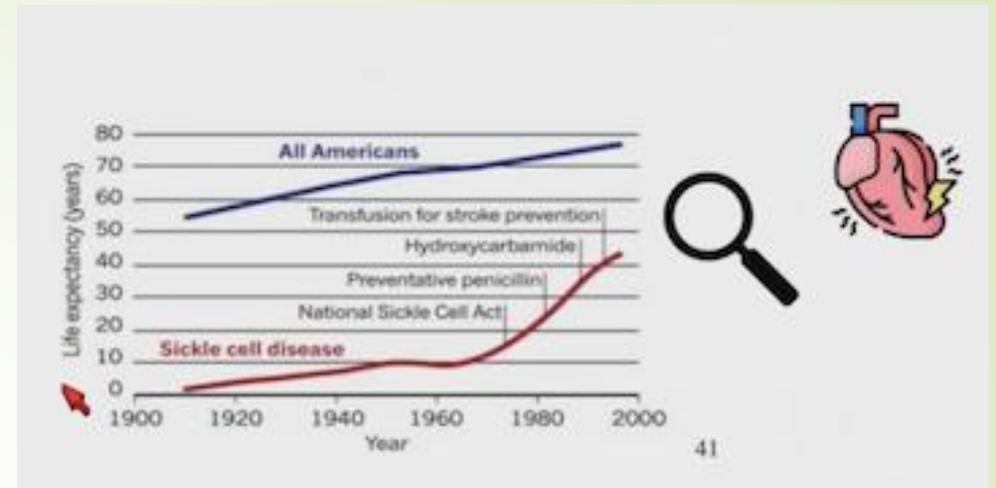
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Thomas d'Humières, MD, PhD

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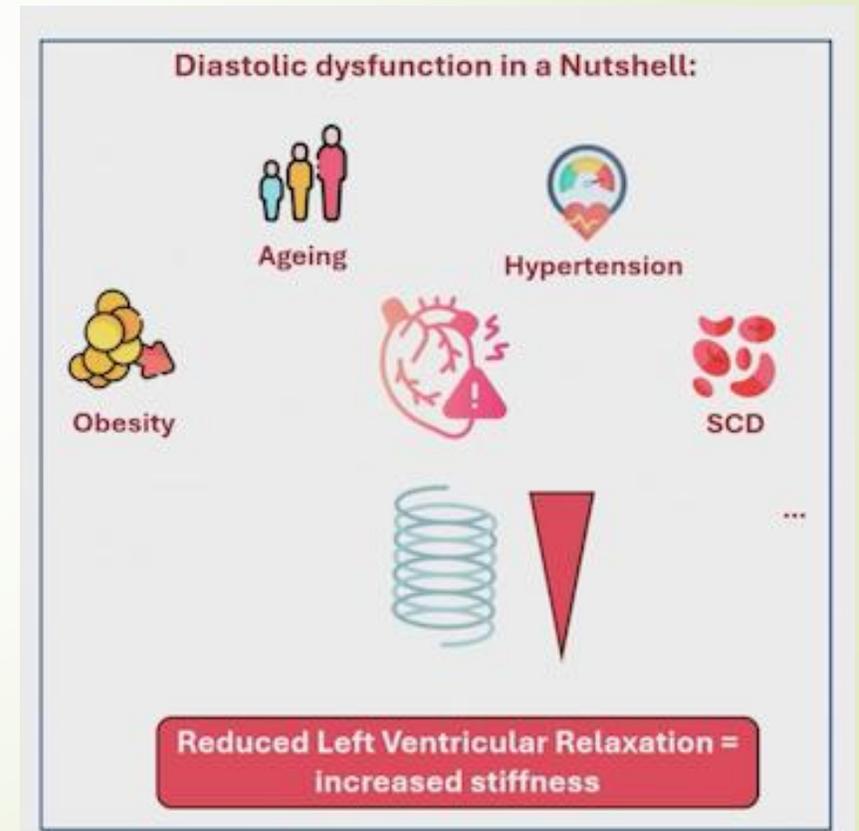
# Contexte

- 1<sup>ère</sup> maladie génétique
- Augmentation de l'espérance de vie
- Vieillesse de la population drépanocytaire
  
- Complications cardiovasculaires : 20-30%
- HTAP, dysfonction diastolique, ICG



# Dysfonction diastolique

- Rapportée chez 15-30% des patients SCD
- Cause majeure d'IC et de mortalité

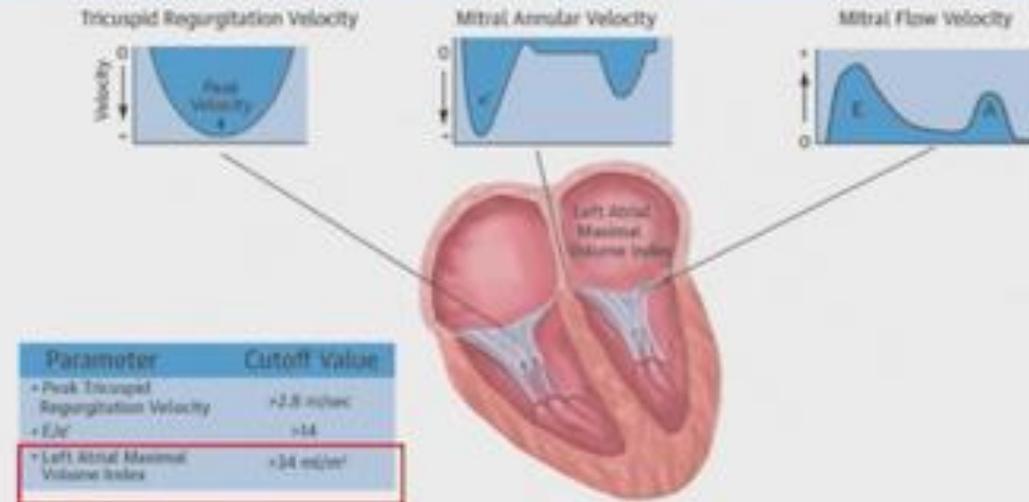


# Dysfonction diastolique

## Left Atrial Volume using Echocardiography

### A cornerstone of diastolic and LV filling pressure evaluation

#### A. Echocardiography Parameters for Estimation of LV Filling Pressure



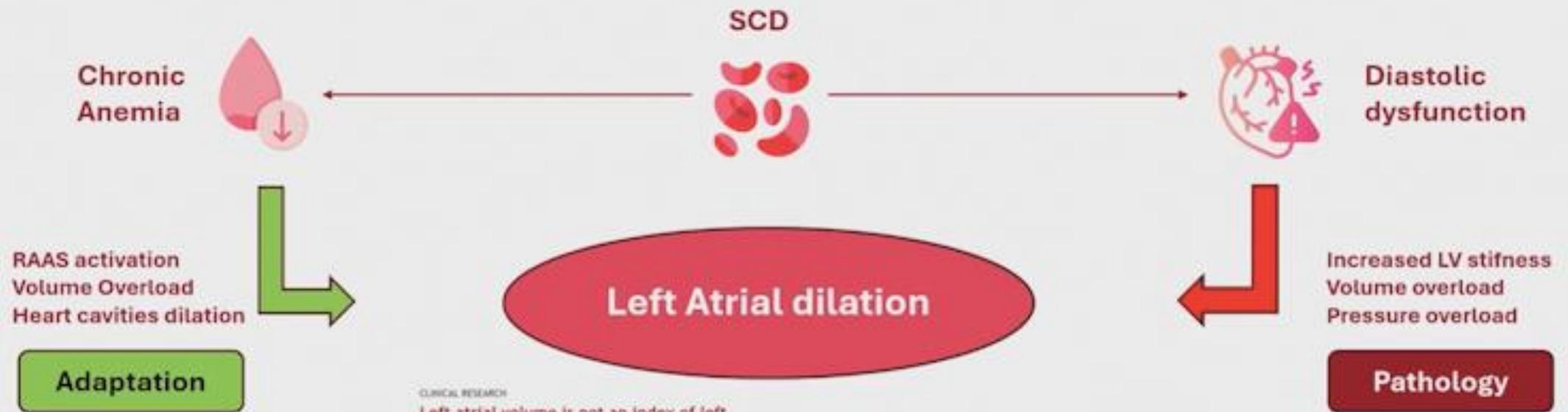
- LAV is one of the three main parameters to evaluate diastolic dysfunction complicated with increased LV pressure
- LAVi > 34 mL/m<sup>2</sup> is a major criteria in favor
- In the « general » population....

# Dysfonction diastolique

## LAV in the context of SCD

A population **never included** in studies that defined abnormal diastolic function

And **SCD changes everything**:



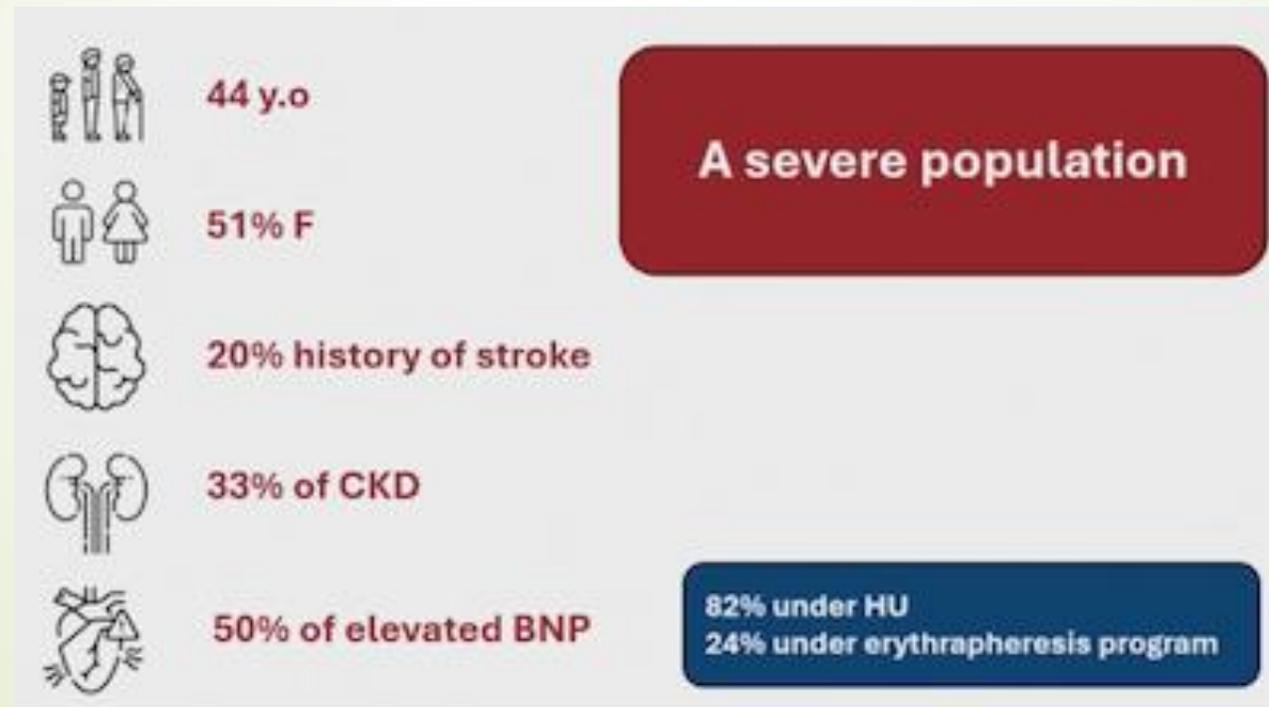
CLINICAL RESEARCH

Left atrial volume is not an index of left ventricular diastolic dysfunction in patients with sickle cell anaemia

Veronique Herveau<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Magali Chahine<sup>1</sup>,  
Pierre Lamy<sup>1</sup>, Mounir Elabbas<sup>1</sup>,  
Katalin Szendrői Szendrői<sup>1</sup>, Stéphanie Elie<sup>1</sup>,  
Robert Goss<sup>1</sup>, Aron Cohen<sup>1</sup>, Richard Ismail<sup>1</sup>,  
François Lévesque<sup>1</sup>

# Résultats

- 150 SS/Sb° inclus entre 12/2018 et 05/2023
- Strain du réservoir de l'OG mesuré pour 142 patients (95%)



# Résultats

## LA-RS is associated with disease severity independantly of anemia

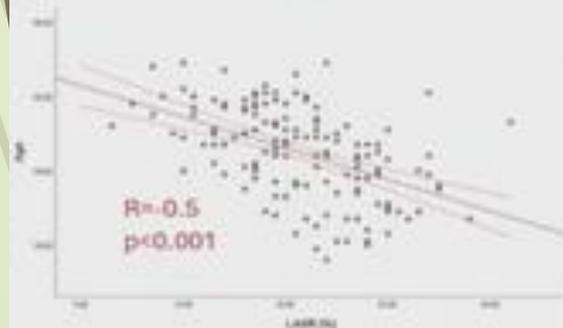
LA-RS is independant of anemia



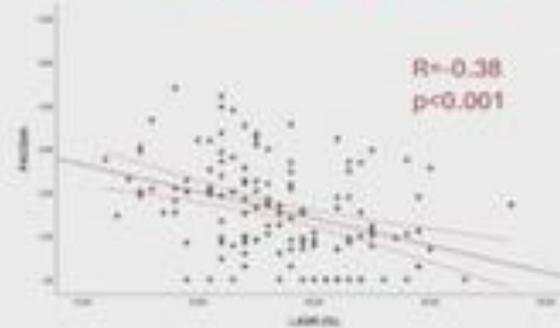
LA strain correlates with :



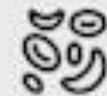
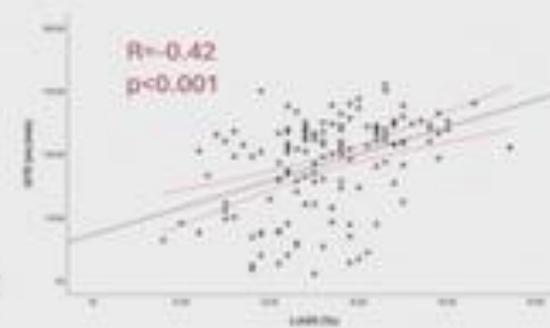
Age



Blood pressure, Atrial arrhythmia,  
6min WT, NT pro-BNP



CKD



Hemolysis (LDH)



# Résultats

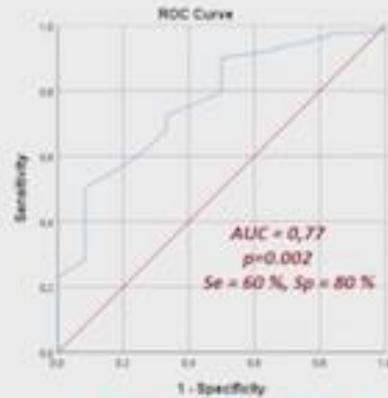
## What LA-SR can be considered bad?

*Discriminant analysis and Survival*

Median follow up of 3.1 years IQR [2,3; 4,1], 8% of patients lost to follow up  
12 (8%) of mortality

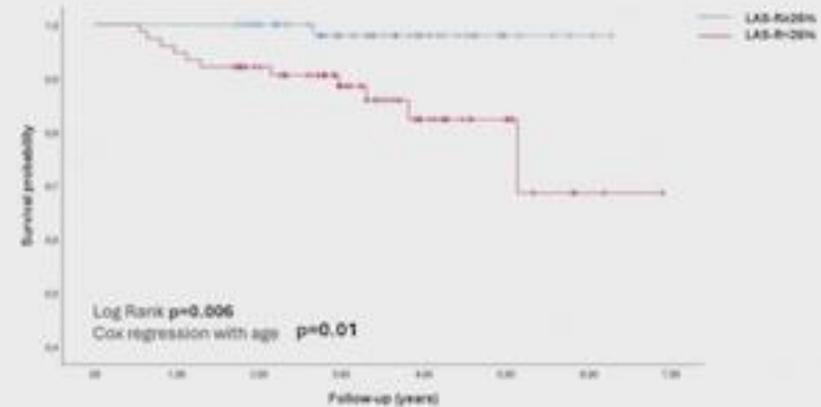
LA-SR was the only diastolic parameters associated with mortality in multivariate analysis

Variables in the Equation						
Step 1*	OR	B	S.E.	Wald	df	Sig.
		-1.03	.201	6.182	1	.024



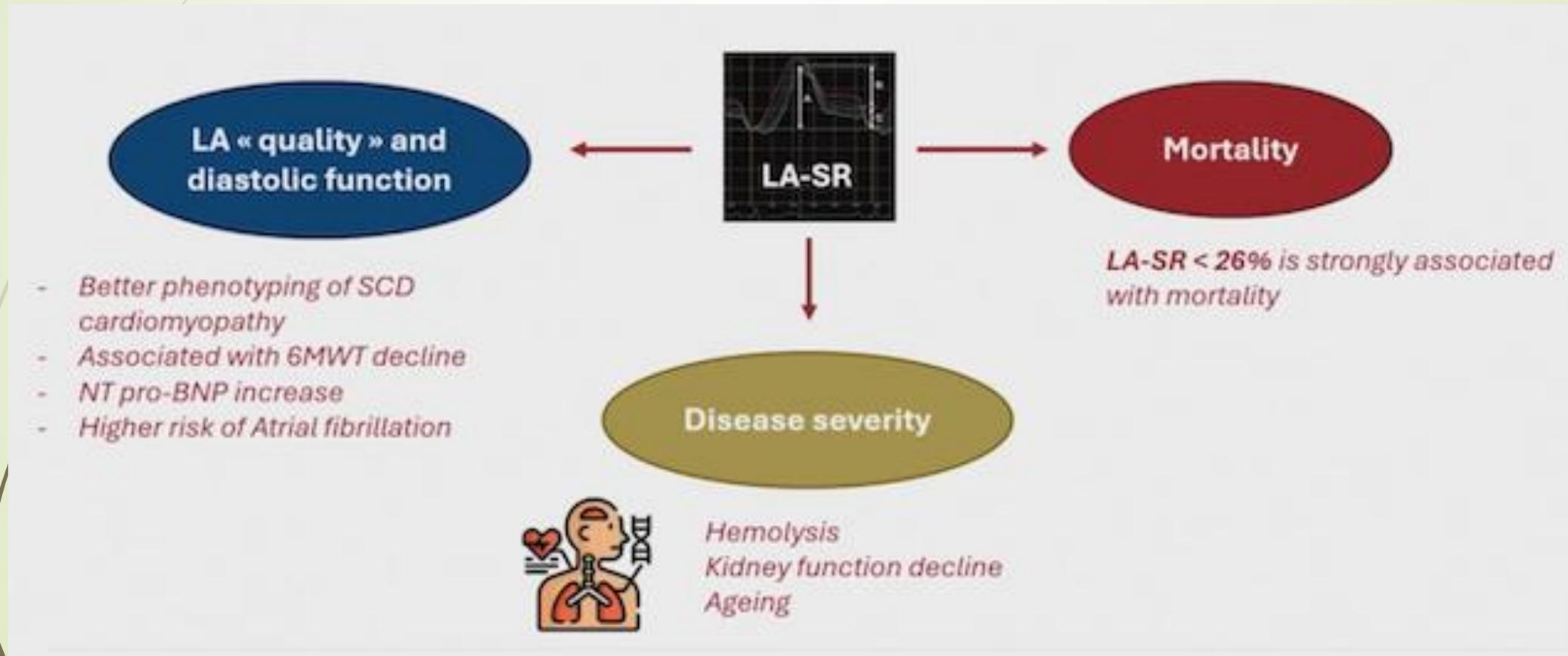
LA-SR < 26%

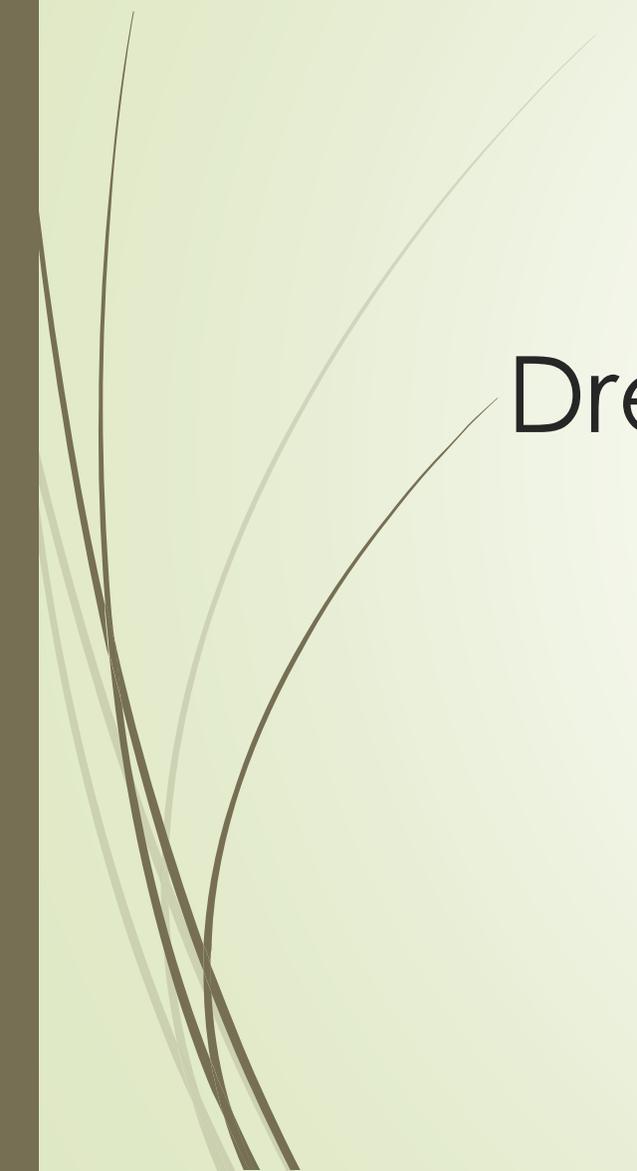
Optimal threshold to predict all cause mortality



LA-SR<26% is associated with all-cause mortality with an OR=7 (p<0.001)

# Conclusion





# Drépanocytose et Néphropathie



# Contexte

- 50% des patients SCD de plus de 50 ans
- Multiplie par 3 le risque de mortalité
  
- FDR :
  - APOL1 G1/G2
  - DT2
  - HTA
  - Absence d'a-thal
  - Faible taux HbF



# Recommandations actuelles

- ▶ Cible TA < 130/80 mmHg
- ▶ Débuter screening albuminurie dès l'enfance
- ▶ Discuter IEC ou ARAl si albuminurie persistance (enfant et adulte)
  
- ▶ HU peut aider à réduire l'albuminurie

# Rationnel

## **Sodium-glucose cotransporter 2 (SGLT2) inhibitors:**

- Developed for treatment of type 2 DM
- Inhibit renal glucose reabsorption
- Reduce glomerular hyperfiltration
- Have a natriuretic effect
- Improve renal cortical oxygenation
- Potentially stimulate erythropoiesis via mimicking hypoxia in the renal medulla
- Glucosuria increases susceptibility to urinary tract infections

Curr Opin Nephrol Hypertens. 2020 Mar;29(2):190-198

# Rationnel

**DAPA – CKD** (dapagliflozin; *N Engl J Med* 2020 Oct 8;383(15):1436-1446)  
**EMPA-KIDNEY** (empagliflozin; *N Engl J Med* 2023;388:117-127)  
**CREDENCE** (canagliflozin; *N Engl J Med* 2019; 380:2295-2306)

- SGLT2 inhibition vs placebo
- in patients with chronic kidney disease,
- added to background therapy including an ACE inhibitor or ARB,
- with or without type 2 diabetes
- reduced progression of CKD significantly
- All 3 trails stopped at interim analysis because of efficacy!

*Farxiga met all primary and secondary endpoints in groundbreaking Phase III DAPA-CKD trial for the treatment of patients with chronic kidney disease*

**Landmark EMPA-KIDNEY trial showed significant benefit of Jardiance® in reducing kidney disease progression or cardiovascular death by 28% vs. placebo in people with chronic kidney disease**





# Et chez les patients drépanocytaires ???

Deux interrogations :

- Déshydratation => risque de CVO ?
- Hyperviscosité par augmentation de l'Hb ?



# Design

- Étude multicentrique rétrospective
- Relecture de tous les dossiers des patients ayant eu des iSGLT2
- Fonction rénale et albuminurie
- Collecte des hospitalisations et des infections urinaires

# Résultats

## 39 patients were prescribed dapagliflozin:

- 22 female (56%), 17 male (44%)
- Median age 54 years (range 24-75)
  
- For renal protection: 28 (72%)
- For diabetes: 6 (15%)
- For heart failure: 5 (13%)

## Genotype:

	N (%)
HbSS	34 (87%)
HbSC	3 (7.7%)
HbS / beta(0) thal	1 (2.6%)
HbS / beta(+) thal	1 (2.6%)

# Résultats

## Results: staging of chronic kidney disease (CKD)

### Cohort:

- Baseline CKD stage available for 33/39 (85%)

### On treatment:

- 23/39 (61%) hydroxyurea
- 12/39 (31%) regular transfusion
- 6/39 (15%) erythropoietin
- 32/39 (82%) ACE inhibition / ATII receptor blocker
- 6/39 (15%) antihypertensive(s)

UKKA eGFR category	A1	A2	A3	Unknown	Total
G1	0	0	2	1	3
G2	0	0	7	0	7
G3a	2	2	8	4	16
G3b	0	1	9	1	11
G4	0	0	2	0	2
G5	0	0	0	0	0
Total	2	3	28	6	39

# Résultats

## Results: start of dapagliflozin treatment

### Non-diabetic indications (NICE recommendations) for introducing SGLT2 inhibition:

1. eGFR 20-45 mL/min/1.73 m<sup>2</sup> AND any ACR: n=13 (33%)
2. eGFR > 45 ml/min/ 1.73 m<sup>2</sup> AND ACR > 25 mg/mmol n=19 (49%)

Section 3		PEOPLE WITHOUT DM
1.	We recommend initiating SGLT-2 inhibition in people with chronic kidney disease, irrespective of primary kidney disease,* for any of the following clinical scenarios: (a) eGFR of $\geq 20$ mL/min/1.73m <sup>2</sup> and a urinary albumin-to-creatinine ratio (uACR) of $\geq 25$ mg/mmol† (b) Symptomatic heart failure, irrespective of ejection fraction	1A
2.	We recommend initiating SGLT-2 inhibition to slow rate of kidney function decline in people with an eGFR of 20-45 mL/min/1.73m <sup>2</sup> and a uACR of $< 25$ mg/mmol†.	1B
3.	We suggest clinicians consider initiating SGLT-2 inhibition in people with an eGFR below 20 mL/min/1.73m <sup>2</sup> to slow progression of kidney disease.	2B
* excludes people with polycystic kidney disease, type 1 diabetes, or a kidney transplant † urinary protein-to-creatinine ratio of 35 mg/mmol can be considered equivalent		

# Résultats

## Results: effects of dapagliflozin treatment on eGFR

Before and after start paired samples:

- 36 eGFR samples

Total time on dapagliflozin (n=36):

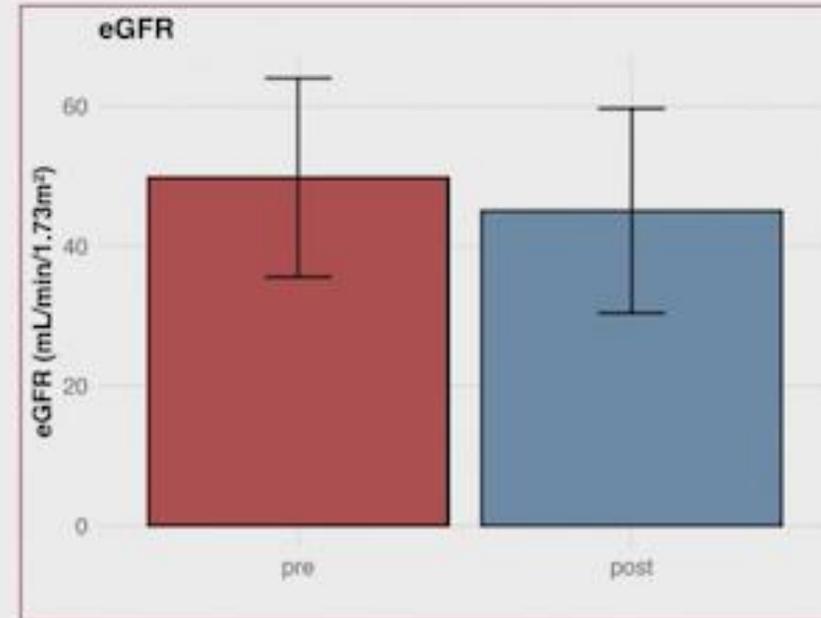
- Median: 16 months
- Range : 1 - 43 months

Time to first test after starting dapagliflozin:

- Median: 4.5 months
- Range : 0.2 – 22.1 months

eGFR before and after start:

- Mean before: 50 mL/min (95% CI 45-54)
- Mean after: 45 mL/min (95% CI 40-50)



Paired sample t-test:  $p < 0.001$

# Résultats

## Results: effects of dapagliflozin treatment on ACR

Before and after start paired samples:

- 25 ACR samples

Time on dapagliflozin (n=25):

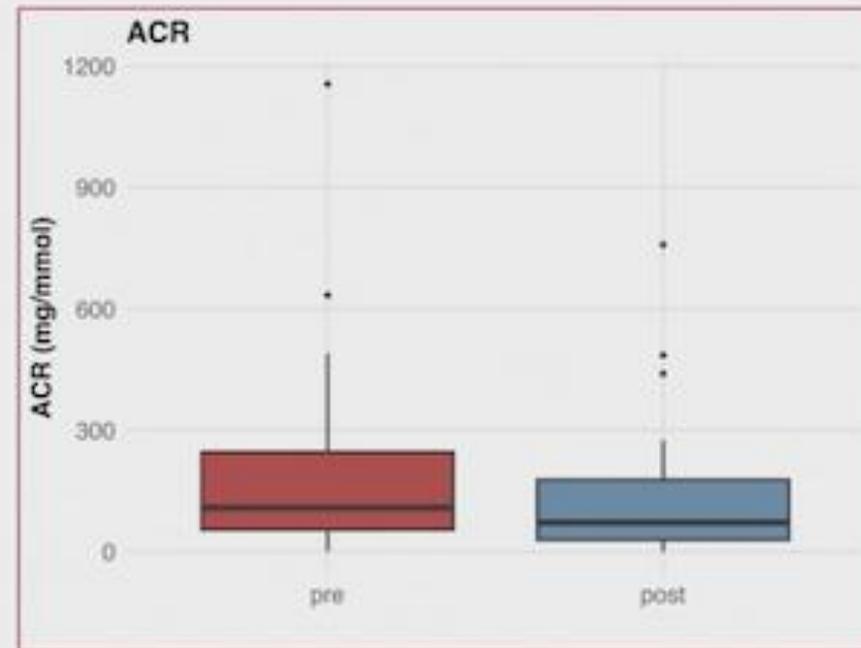
- Median: 16 months
- Range : 1 - 43 months

Time to first test after starting dapagliflozin:

- Median: 6 months
- Range : 0.9 – 22.1 months

ACR before and after start:

- Median before: 109 mg/mmol (range 1-1156)
- Median after: 71 mg/mmol (range 1-759)



Wilcoxon matched pairs test:  $p < 0.001$



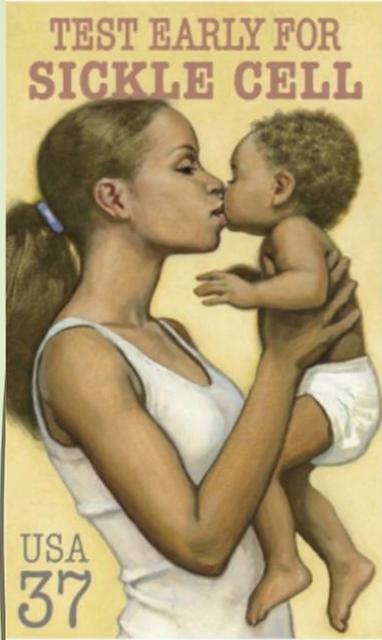
# Effets indésirables

- 2 infections urinaires
- 2 cas de réduction significative de diminution du DFG
- Pas de VOC (dans les limites du recueil de données)



# Discussion

- La plus large cohorte de patients SCD traités par SGLT2i
- Bien toléré et profil de sécurité rassurant
- Aug DFG et réduction ACR non significatif
- Nécessité d'un essai clinique



# La grossesse chez les patientes drépanocytaires

*Proactive Management to Improve Outcomes in High-Risk Sickle Cell Disease Pregnancy*

*Outcomes of pregnancies in Sickle Cell patient Treated with Hydroxyurea : find from the ESCORT-HU Cohort Studies*

*Prediction model for maternal pregnancy complications in sickle cell disease*



# Introduction



- **Situation à très haut risque** (taux élevé de morbidité et de mortalité maternelle et périnatale), nécessitant une prise en charge spécialisée et multidisciplinaire
- Pourquoi ?
- Développement de deux nouveaux « organes » : le placenta et le foetus.
- **Augmentation des résistances vasculaires pulmonaires**
- **Stress cardio-pulmonaire accru.**
- **Hypercoagulabilité (risque accru de thromboses).**
- **Expansion importante du volume plasmatique, entraînant une chute prévisible de l'hémoglobine.**
- **Acidose relative** favorisant la déformation des globules rouges drépanocytaires (sickling).
  
- Complications :
- Complications liées à **l'exacerbation de la drépanocytose : le syndrome thoracique aigu et les épisodes vaso-occlusifs plus fréquents,**
- **Complications obstétricales : la prééclampsie, les accouchements prématurés, etc.**

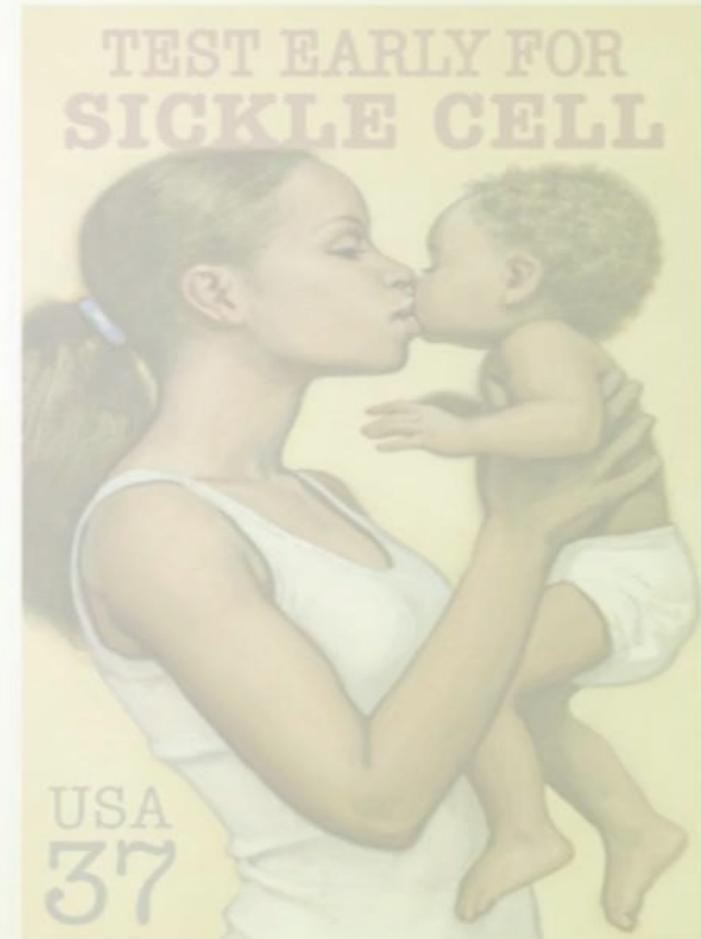
# Prise en charge proactive de la grossesse

## Proactive Management to Improve Outcomes in High-Risk Sickle Cell Disease Pregnancy

Mofiyin A. Obadina, MD and Lydia H. Pecker, MD, MHS

Sickle Cell Center for Adults  
Associate Professor of Medicine  
Johns Hopkins University School of Medicine

American Society of Hematology Meeting  
Orlando, FL  
December 7, 2025



# Prise en charge proactive de la grossesse La Transfusion

## ➤ Réduction de la mortalité

**Table 1.** Chronic transfusion therapy significantly improves sickle cell disease pregnancy-related complications

Pregnancy complication improved by CTT	Number of studies involved in the meta-analysis	Total number of pregnant SCD individuals	OR (95% CI)
Overall maternal mortality	7	955	0.23 (0.06–0.91)
Vaso-occlusive pain crises	11	1219	0.26 (0.09–0.76)
Pulmonary complications (pulmonary infections and embolisms and acute chest syndrome)	9	1019	0.25 (0.09–0.72)
Pulmonary embolism	3	237	0.07 (0.0–0.41)
Perinatal mortality	8	1140	0.43 (0.19–0.99)
Neonatal death	5	374	0.26 (0.07–0.93)
Preterm birth	9	1123	0.59 (0.37–0.96)

In 2015, a pivotal paper by Malinowski and colleagues demonstrated a comprehensive meta-analysis of published studies on sickle cell disease and transfusion therapy, providing the most reliable and extensive source of data to date on this topic. Their analysis, encompassing multiple studies and hundreds of pregnant individuals with SCD, demonstrates significant improvements in various maternal and fetal outcomes with chronic transfusion therapy. Specifically, the meta-analysis shows reduced odds of overall maternal mortality, vaso-occlusive pain crises, pulmonary complications, pulmonary embolism, perinatal mortality, neonatal death, and preterm birth. CI, confidence interval; OR, odds ratio; SCD, sickle cell disease.

# Prise en charge proactive de la grossesse

## La Transfusion

### ➤ Réduction des complications pulmonaires

**Table 1.** Chronic transfusion therapy significantly improves sickle cell disease pregnancy-related complications

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# Prise en charge proactive de la grossesse La Transfusion

## ➤ Prévention des CVO

### In meta-analysis & randomized studies, prophylactic transfusions reduce pain crisis

Study	Study Design	Subjects	Pain Crises OR (95% CI)
Malinowski et al, Blood, 2015	Meta-analysis of transfusions for SCD pregnancy	1,219	0.26 (0.09 – 0.76)
Brunetta et al, EJHaem, 2025	Meta-analysis 2 RCTs*	108	0.197 (0.08 – 0.49)
Charache et al, NEJM, 1996	Phase 3 of Hydroxyurea for HbSS adults	299	0.64 (0.43 – 0.94)

\*Koshy et al 1988; Oteng-Ntim et al, 2024 - Transfusions initiated later



# Prise en charge proactive de la grossesse

## La Transfusion

- **Recommande l'introduction plus proactive de la transfusion prophylactique**
- **Objectif d'hémoglobine à 10 g/dL et une fraction S entre 30 et 50 %. Nous commençons idéalement avant la conception ou dès le diagnostic de grossesse.**



# Prise en charge proactive de la grossesse

## La Transfusion

- ▶ Limites
  - ▶ Accès aux soins et à des transfusions sûres
  - ▶ surcharge en fer
  - ▶ risques d'allo-immunisation et patientes déjà allo-immunisées



Quelles autres alternatives pour la prise en charge proactive de la grossesse ?

# Grossesses et HU : Etude ESCORT-HU



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Helping hematologists conquer blood diseases worldwide



## Outcomes of Pregnancies in Sickle Cell Patients Treated with Hydroxyurea : Findings from The ESCORT-HU Cohort Studies

**Anoosha Habibi**, Giovanna Cannas, Maria Dimopoulou, Laure Joseph, Caroline Makowski, Emmanuelle Bernit, Jean-Benoît Arlet, Sylvain Le Jeune, Gonzalo De Luna, Justine Dautremer, Noelis Thomas-Boizan, Flevari Pagona, Corinne Charneau, Pierre Cougoul, Benjamin Carpentier, Louis Affo, Jean-Baptiste Valentin, Pierre Rohrllich, Corentin Orvain, Agathe Masseur, Violaine Laurant-Noël, Thierry Pistone, Elsa Ngwem, Nicolas Gambier, Benoît Faucher, Marilucy Lopez-Sublet, Arnaud Desclaux, Mariane de Montalembert, Marie-Françoise Barrault, Scylia Alexis-Fardini, Narcisse Elenga, Estelle Jean, Stanislas Nimubona, Stéphanie Ngo, Nathalie Lemonne, Laura Thomas-Bourgneuf, Gylna Loko, Maryse Etienne-Julan, Frédéric Galactéros, Pablo Bartolucci



# Grossesse et HU

## Hydroxyurée

- Approuvé par l'AEM depuis 2007
- Seul médicament qui réduit significativement la mortalité dans la drépanocytose
- Non recommandé durant la grossesse en raison des données animales montrant une possible tératogénicité :
- En études animales, des **malformations tératogènes** ont été observées **uniquement à des doses élevées (150 mg/kg)** causant des malformations squelettiques et du système nerveux central, avec **toxicité embryonnaire** caractérisée par diminution viabilité foetale, retard de croissance.
- Actuellement, il est recommandé d'arrêter l'hydroxyurée 6 mois avant la conception.



# Grossesse et HU

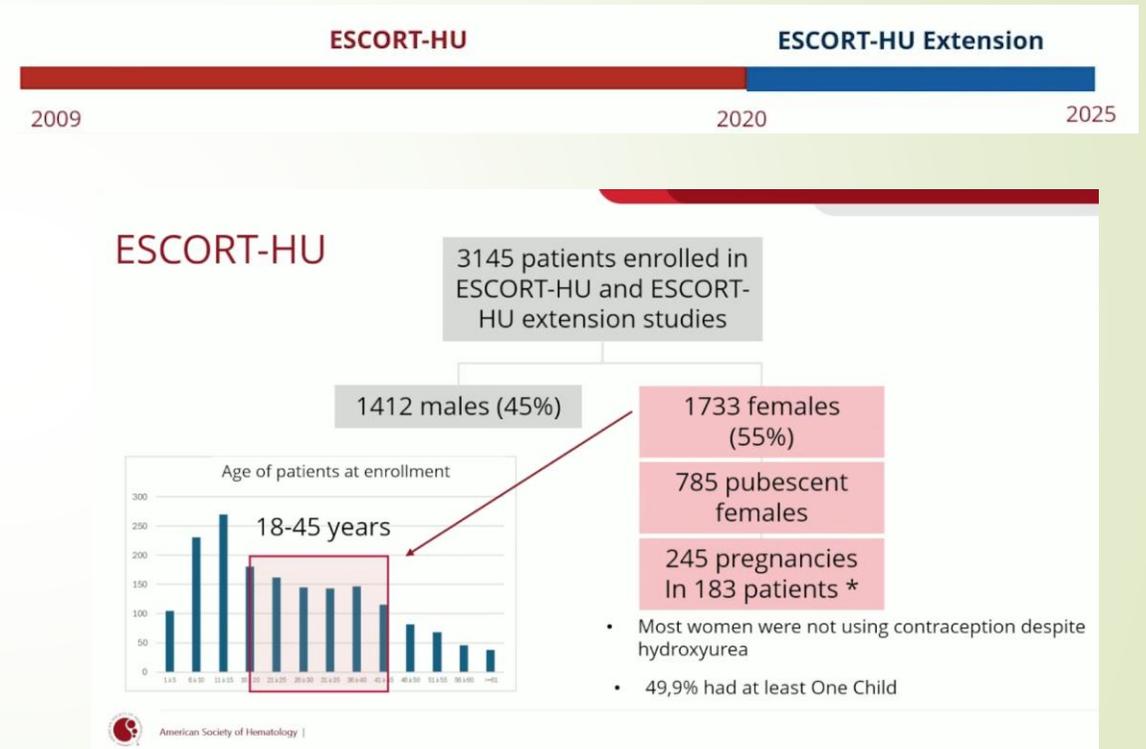
## Etudes réalisées

- ▶ Safety of Hydroxyurea in Pregnancy: A Systematic Review of the Literature, Sulaimani *et al*, 2025
  - ▶ Revue systématique de la littérature décrivant les issues de grossesse et les issues néonatales après une exposition à l'HU pendant la grossesse jusqu'en juillet 2024
  - ▶ 7 227 grossesses, dont 567 grossesses (7,8 %) exposées à l'HU
  - ▶ drépanocytose (n = 502)
  - ▶ **Aucun effet tératogène ou hématologique sur le fœtus n'a été observé dans ces cas**
- ▶ Pregnancy outcomes with hydroxyurea use in women with sickle cell disease, Kroner *et al*, 2022.
  - ▶ 1780 grossesses dont 241 exposées à l'hydroxyurée
  - ▶ **Risque accru de fausses couches et mort in utero quand le traitement était pris juste avant ou en début de grossesse,**
  - ▶ l'exposition aux 2e et 3e trimestres était associée à des résultats plus favorables.
  - ▶ Interprétation limitée car certains facteurs (transfusion) ne sont pas détaillés.

# Grossesse et HU

## Etudes ESCORT-HU et ESCORT-HU Extension

- Étude prospective non interventionnelle européenne (2009-2025).
- 3145 patients inclus (enfants et adultes), 1733 femmes (55%), 785 en âge de procréer.
- 245 grossesses rapportées chez 183 femmes.

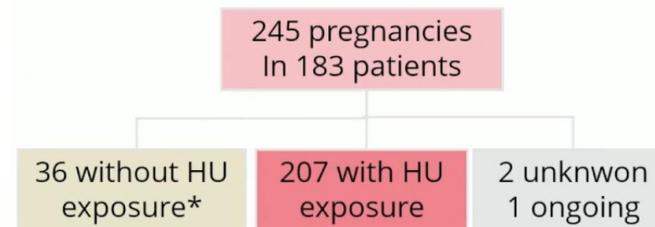


# Grossesse et HU

## Etudes ESCORT-HU et ESCORT-HU Extension

- 207 grossesses se sont déroulées durant l'exposition à l'hydroxyurée.
- 36 ont interrompu le traitement avant la conception.
- Dosage moyen d'hydroxyurée : 16 mg/kg/jour.

### Pregnancies Reported During the Studies



- 95% of patients: HbSS or  $s\beta^{0Thal}$
- Mean age: 30.7+ 5 years
- Mean HU dosage: 16 mg/kg/day

\* without HU exposure = HU stopped before conception

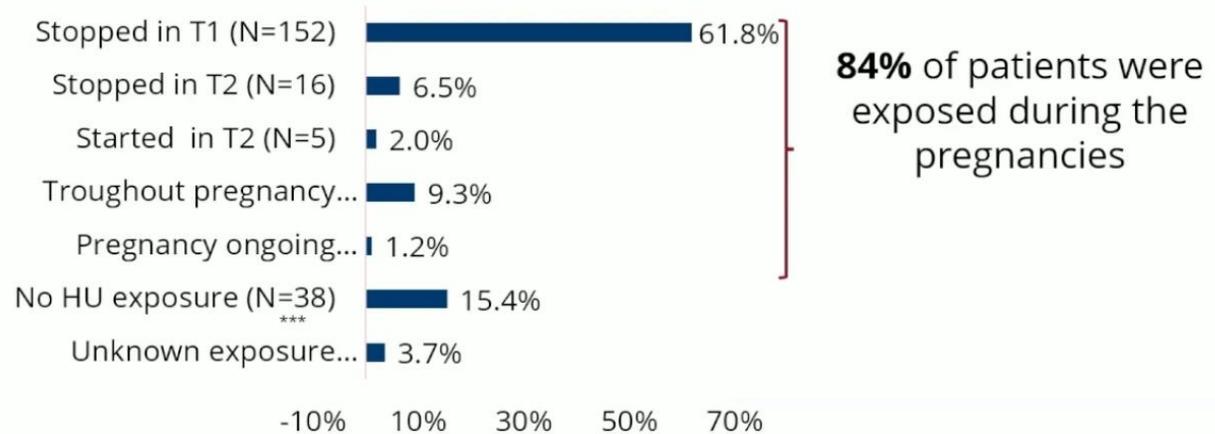


# Grossesse et HU

## Etudes ESCORT-HU et ESCORT-HU Extension

- 84 % exposées durant la grossesse,
- 62% durant le 1<sup>er</sup> trimestre, période à risque teratogène supposé

### HU Exposure During Pregnancy



# Grossesse et HU

## Résultats

- ▶ Une seule malformation congénitale détectée, mineure, non liée au traitement selon les investigateurs.
- ▶ Pas de différence significative des issues globales entre groupe exposé/non exposé.
- ▶ 9 patientes ont poursuivi le traitement toute la grossesse : 5 naissances normales, 4 prématurées.
- ▶ Pas de mortalité maternelle rapportée (mortalité habituellement 15 fois celle de la population générale).
- ▶ 74 % des grossesses ont abouti à des naissances vivantes, taux plus élevé que certaines études précédentes.
- ▶ 2 interruptions médicales dans le groupe exposé liées à des complications maternelles sévères.

### Outcome of Pregnancies

*9 pregnancies were exposed throughout the pregnancy : (History of DHTR)*

- 5 Normal Births
- 4 Premature Births

Outcome	HU Exposure N=207		Non HU exposure N=36		unknown N=2
<b>Maternal Mortality</b>	<b>0</b>	<b>0%</b>	<b>0</b>	<b>0%</b>	
<b>Live Birth</b>	<b>134</b>	<b>74%</b>	<b>26</b>	<b>74%</b>	<b>1</b>
<b>Prematurity</b>	<b>31</b>	<b>17%</b>	<b>4</b>	<b>11%</b>	<b>0</b>
<b>Miscarriage</b>	<b>36</b>	<b>17%</b>	<b>8</b>	<b>22%</b>	<b>1</b>
<b>Stillbirth</b>	<b>1</b>		<b>0</b>		<b>0</b>
<b>Voluntary abortion</b>	<b>25</b>	<b>12%</b>	<b>0</b>		<b>0</b>
<b>Therapeutic abortion</b>	<b>2</b>		<b>1</b>		<b>0</b>



# Grossesse et HU

## Résultats

- ▀ Risque de fausses couches dans les 2 groupes

### Outcome of Pregnancies

Outcome	HU Exposure N=207		Non HU exposure N=36		unknown N=2
Maternal Mortality	0	0%	0	0%	
Live Birth	134	74%	26	74%	1
Prematurity	31	17%	4	11%	0
<b>Miscarriage</b>	<b>36</b>	<b>17%</b>	<b>8</b>	<b>22%</b>	<b>1</b>
Stillbirth	1		0		0
Voluntary abortion	25	12%	0		0
Therapeutic abortion	2		1		0

	Pregnancies reported by 737 females (N = 1513) <sup>b</sup>	Hydroxyurea at conception only (N = 97)	Hydroxyurea at conception and during pregnancy (n = 125)	Hydroxyurea during pregnancy only (N = 16) <sup>c</sup>	No hydroxyurea exposure (N = 1154)
Miscarriage	394 (26.0%)	17 (17.5%)	54 (43.2%)	3 (18.8%)	279 (24.2%)

*Korner & al. Am J Hematol. 2022;97:603-612.*





# Grossesse et HU

## Conclusion

- L'exposition précoce accidentelle à l'hydroxyurée pourrait ne pas être aussi dangereuse qu'anticipé.
- **Les experts recommandent désormais souvent de ne stopper l'hydroxyurée qu'après confirmation de la grossesse, surtout dans les pays où la transfusion reste limitée ou risquée.**
- **Il est nécessaire de développer une approche individualisée, notamment en fonction du potentiel d'allo-immunisation, des antécédents transfusionnels et de la sévérité de la maladie.**
- De nouveaux essais cliniques sont nécessaires pour confirmer ces résultats et renforcer le niveau de preuves.



Et si l'on pouvait prédire les complications maternelles durant la grossesse ?



# Modèle de prédiction des complications maternelles durant la grossesse chez les patientes atteintes de drépanocytose

- ▶ **Objectif de l'étude :**
- ▶ Développer et valider un modèle de prédiction des complications maternelles durant grossesse chez les patientes atteintes de drépanocytose, à partir de données cliniques et biologiques simples, obtenues avant ou au début de la grossesse.



# Modèle de prédiction des complications maternelles en grossesse chez les patientes atteintes de drépanocytose

- **Matériels et Méthode :**

- **étude de cohorte rétrospective d'adultes enceintes atteintes de SCD**

- Population étudiée : cohorte constituée à partir de deux grands systèmes hospitaliers américains — Mass General Brigham et Penn Medicine

- Variables retenues :

- le génotype,

- l'hémoglobine de base,

- le nombre d'épisodes vaso-occlusifs nécessitant une hospitalisation dans l'année avant la grossesse,

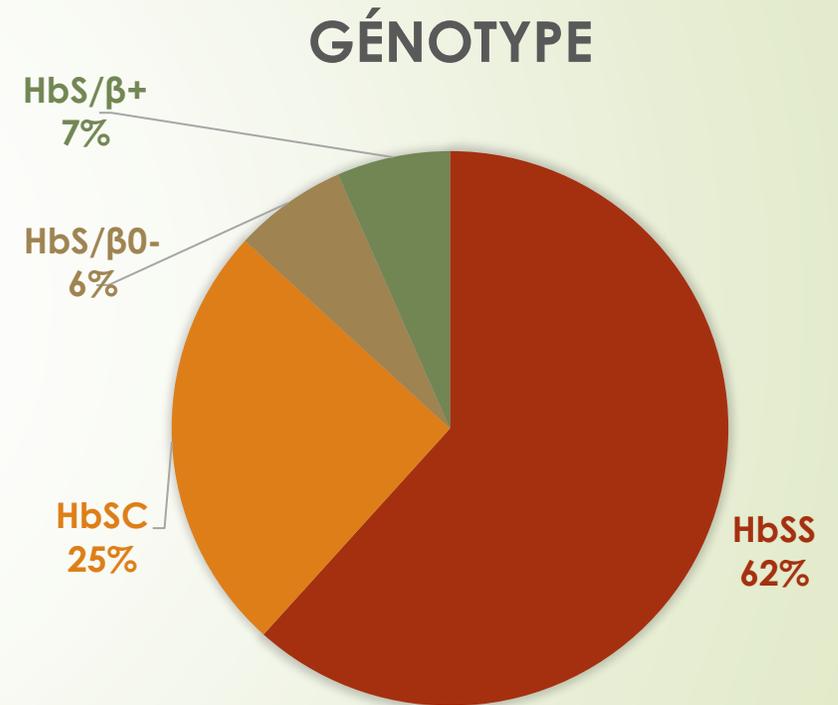
- les antécédents de syndrome thoracique aigu, l'hypertension pulmonaire,

- une variable d'interaction entre l'hémoglobine et le nombre d'épisodes vaso-occlusifs.

# Modèle de prédiction des complications maternelles en grossesse chez les patientes atteintes de drépanocytose

## ➤ Résultats :

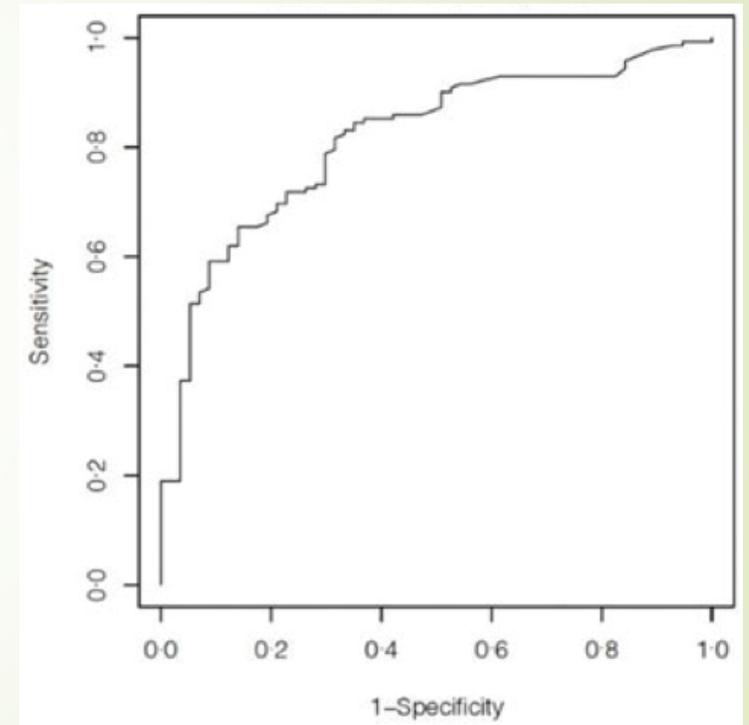
- **167 patientes** ont été retenues, représentant **231 grossesses**
- La plupart des patients (n=119, 71 %) ont contribué à une seule grossesse ; d'autres ont contribué jusqu'à quatre
- La répartition génotypique comprenait majoritairement des patientes HbSS, mais incluait aussi des patientes HbSC et HbS bêta-thalassémie.
- Transfusions préventives de CGR ont été initiées pour 36 grossesses (15,6 %).
- Une complication maternelle grave a été rencontrée dans 153 des 231 grossesses (66,2 %).



# Modèle de prédiction des complications maternelles en grossesse chez les patientes atteintes de drépanocytose

## ➤ Résultats :

- Le modèle a obtenu une AUC corrigée de 0,819.
- Le graphique de calibration a montré une pente de 0,9, proche de la valeur idéale (1), démontrant une bonne adéquation entre risques prédits et observés.





# Modèle de prédiction des complications maternelles en grossesse chez les patientes atteintes de drépanocytose

## ► Limites et points d'attention :

- Ce modèle n'est pas un outil d'inférence causale, mais bien **prédictif**. Ne permet pas d'établir des relations de cause à effet.
- Les données incluent peu ou pas d'informations sur les fausses couches précoces ou les avortements : limite partiellement la représentativité.
- Biais de sélection : cohorte suivie en centre expert



# Modèle de prédiction des complications maternelles en grossesse chez les patientes atteintes de drépanocytose

## ➤ Conclusion et perspectives

- Première étude multi-institutionnelle développant un modèle prédictif fiable, utilisant des données cliniques et biologiques facilement mesurables, pour anticiper les complications maternelles chez les femmes drépanocytaires.
- Excellente performance prédictive

## ➤ Étapes futures :

- Validation externe en cours via l'exploration d'autres bases de données, essentielle avant implémentation clinique large.
- Développement d'un calculateur de risque clinique :
  - - Identification des patientes à haut risque pouvant bénéficier d'interventions spécifiques (transfusions prophylactiques, inclusion dans essais cliniques...)
  - Identification des patientes à faible risque pouvant être suivies plus simplement, limitant les interventions inutiles.



# Iron Deficiency Limits Hydroxyurea-Induced Fetal Hemoglobin and Clinical Efficacy in Sickle Cell Disease

**Anoosha HABIBI**, Vincent de Pierrefeu, Laura Bencheikh, Elena Properzi, Fatima Bensiradj, Geoffroy Volle, Anais Bourguignon d'Herbigny, Yosr Zaouali, Stephane Moutereau, Nicolas Herbert, Marie Cambot, Gonzalo De Luna, Frédéric Galacteros, Pablo Bartolucci.

# Carence en fer / HU / Drépanocytose

## Hydroxyurea

**Reduces the mortality and VOC complications**

**Indication:**

- Anemia
- Vaso-occlusive complications
- Priapism
- Organ damage

**Polymorphism of response in the increase of HbF%**

**Biological response**

Hb , MCV MCH increase  
HbF% increase in some patients

**Dosage:**20-30 mg/kg/day

## Iron Deficiency

**Ferritin < 30 ng/ml ( µg/L)**

Transferrin saturation coef <20%

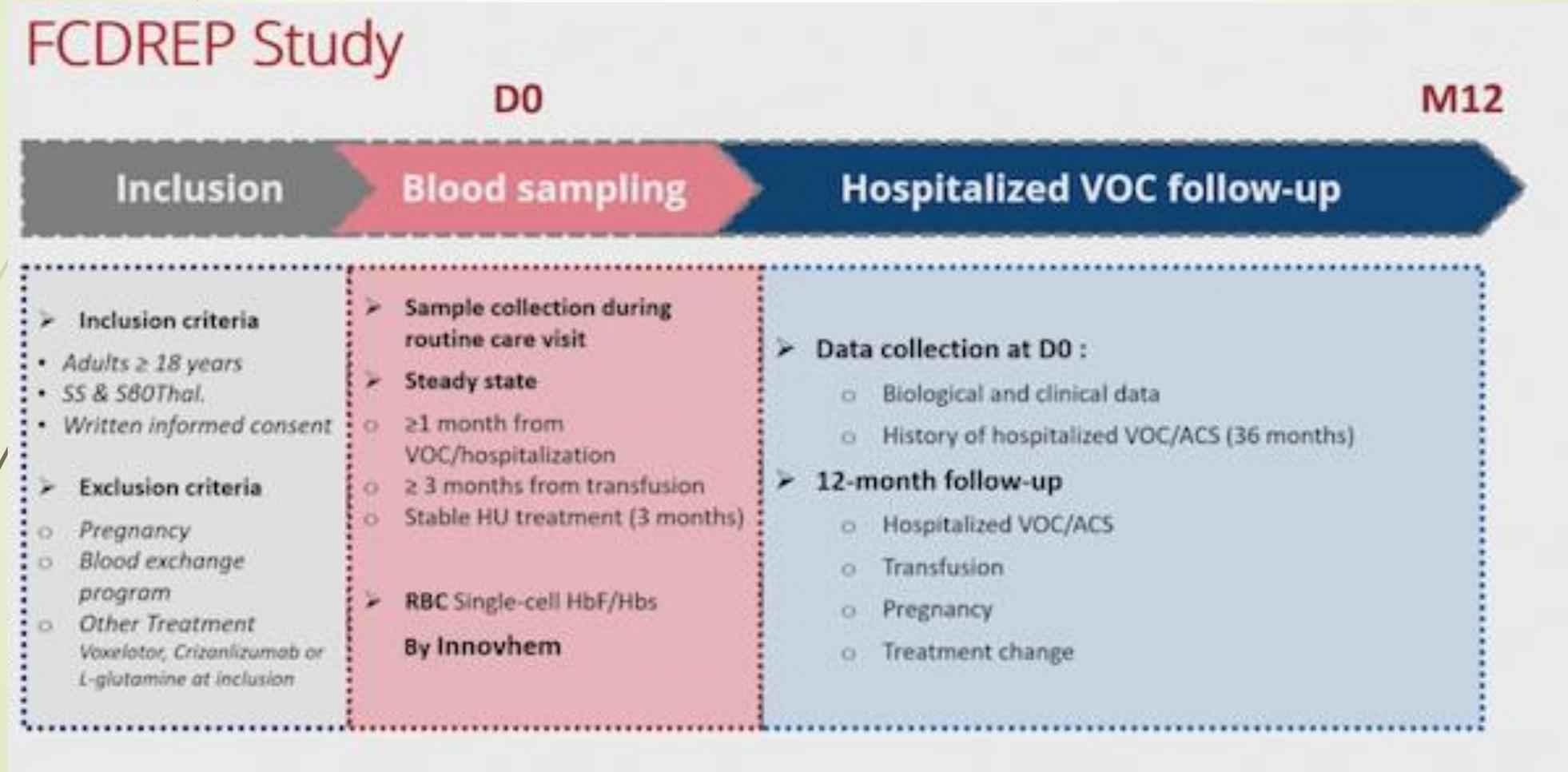
In Cardiac and Kidney Injury

Ferritin < 100 – 300 ng/ml +

Transferrin saturation coef <20%

**How to Evaluate Iron Status in SCA?**

# Carence en fer / HU / Drépanocytose

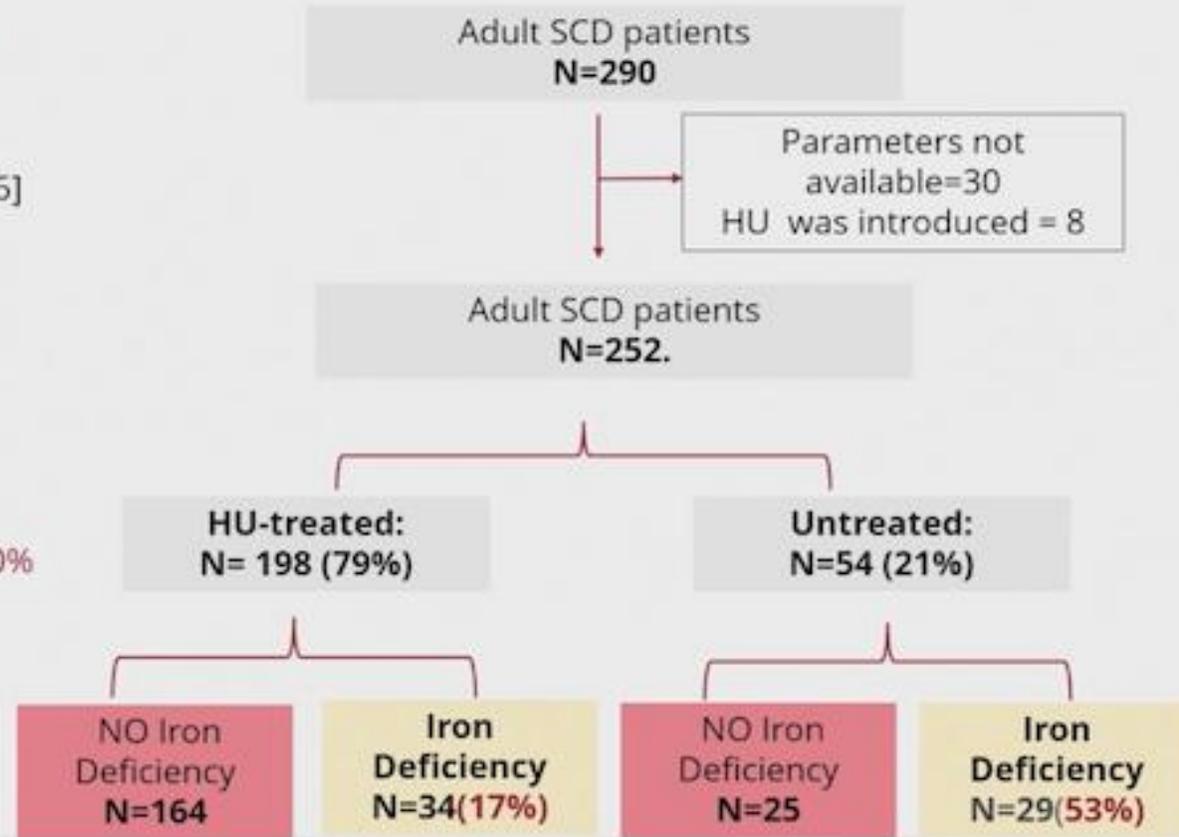


# Carence en fer / HU / Drépanocytose

## FCDREP Study

- **Median age:** 39 years [31–47.6]
- **Female:** 57.6%
- **Median HU dose:** 17.6 mg/kg/day [14.1–20.8]

**Iron Deficiency defined by:**  
Transferrin saturation Coef < 20%



# Carence en fer / HU / Drépanocytose

## Baseline clinical and biological variables

stratified by HU treatment and iron deficiency (ID), Median [IQR]

Variables	no HU			HU		
	No Iron Deficient (n=25)	Iron Deficient (n=29)	p-value	no Iron Deficient (n=164)	Iron Deficient (n=34)	p-value
Hb (g/dL)	8.6 [7.9-9.8]	8.7 [7.4-9.6]	0,744	9.1 [8.3-10.1]	8.4 [7.4-9.1]	0,002
WBC (G/L)	10.2 [7.6-12]	8.7 [7.3-10.6]	0,155	6.4 [4.9-8.3]	9.1 [7.2-11.3]	<0.0001
Platelets (G/L)	278 [214.5-365]	334 [267-420]	0,073	298 [238.3-382.5]	368 [273.5-477.5]	0,024
MCV (fL)	85 [77.5-96.5]	75 [69-80]	0,001	105 [93.5-117.5]	86 [79-96]	<0.0001
MCH (pg)	29 [25.3-34.8]	26 [23-28]	0,007	36 [32-41]	29 [27-33]	<0.0001
Reticulocytes (G/L)	267 [187.5-305]	221 [168-279.5]	0,386	122 [88-190.5]	180 [139-256.5]	0,0002
HbF (%)	10.3 [5.7-14.3]	2.9 [0.8-3.9]	<0.0001	18.1 [11-26.3]	8.2 [4.3-13.6]	<0.0001
CRP (mg/L)	5.4 [3.1-11.1]	2.9 [1.7-5.7]	0,111	4 [1.9-7.1]	3.8 [2.1-11]	0,365
LDH (U/L)	433 [330.3-642]	326 [293.5-564.5]	0,103	392 [306-518]	435.5 [357-528.8]	0,324
Total Bilirubin (µM)	30.5 [25.9-59.3]	39.8 [19.9-49.7]	0,567	39.8 [17.4-49.9]	39.8 [19.9-49.7]	0,739
Hospitalized VOCs (1 year after)	0 [0-0]	0 [0-1]	0,530			

In both groups, iron deficiency decreased significantly the Hb mass by MCH, MCV and the % of HbF

# Carence en fer / HU / Drépanocytose

## Iron Status

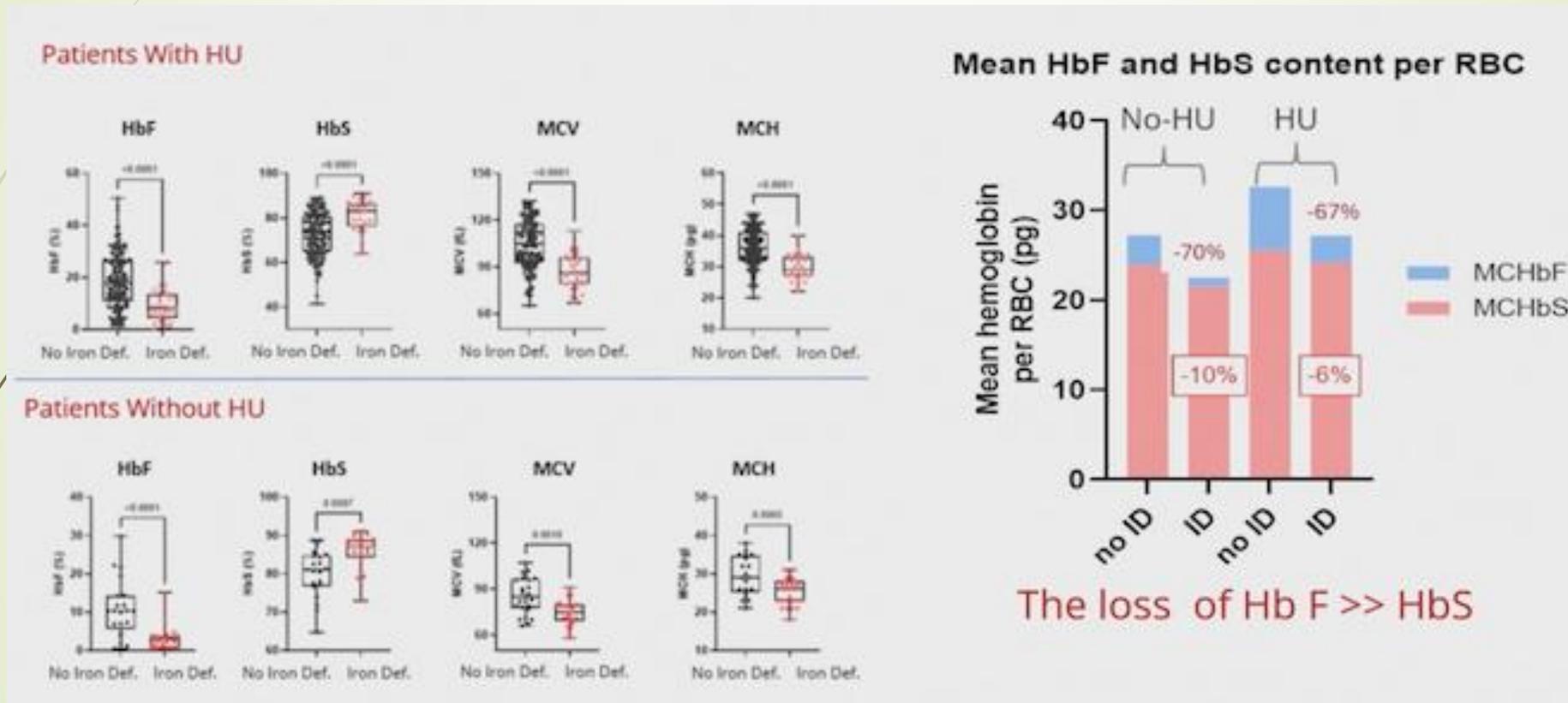
Baseline clinical and biological variables in SCD patients stratified by HU treatment and iron deficiency (ID), Median [IQR]

Variables	no HU			HU		
	No Iron Deficient (n=25)	Iron Deficient (n=29)	p-value	no Iron Deficient (n=164)	Iron Deficient (n=34)	p-value
Women, n (%)	15 (60)	10 (34.5)	0.100	100 (61)	15 (44.1)	0.086
Ferritin (µg/L)	<b>245</b> [120-431]	<b>91</b> [45.5-111.5]	<b>&lt;0.0001</b>	<b>306</b> [153.5-588.5]	<b>62</b> [44.5-180.8]	<b>&lt;0.0001</b>
Serum iron (µM)	18 [13.6-22.1]	8.9 [6.8-10.5]	<b>&lt;0.0001</b>	19.4 [14.7-26.3]	9.2 [6.4-10.5]	<b>&lt;0.0001</b>
Transferrin (g/L)	2.3 [2.1-2.5]	2.6 [2.4-3]	<b>0.002</b>	2.3 [2-2.5]	2.7 [2.4-3]	<b>&lt;0.0001</b>
Transferrin saturation (%)	29 [25.5-38.5]	14 [11.5-17]	<b>&lt;0.0001</b>	32 [26-47.8]	14 [11-16]	<b>&lt;0.0001</b>
CRP (mg/L)	5.4 [3.1-11.1]	2.9 [1.7-5.7]	0.111	4 [1.9-7.1]	3.8 [2.1-11]	0.365

**New definition of Iron deficiency in SCA is required**

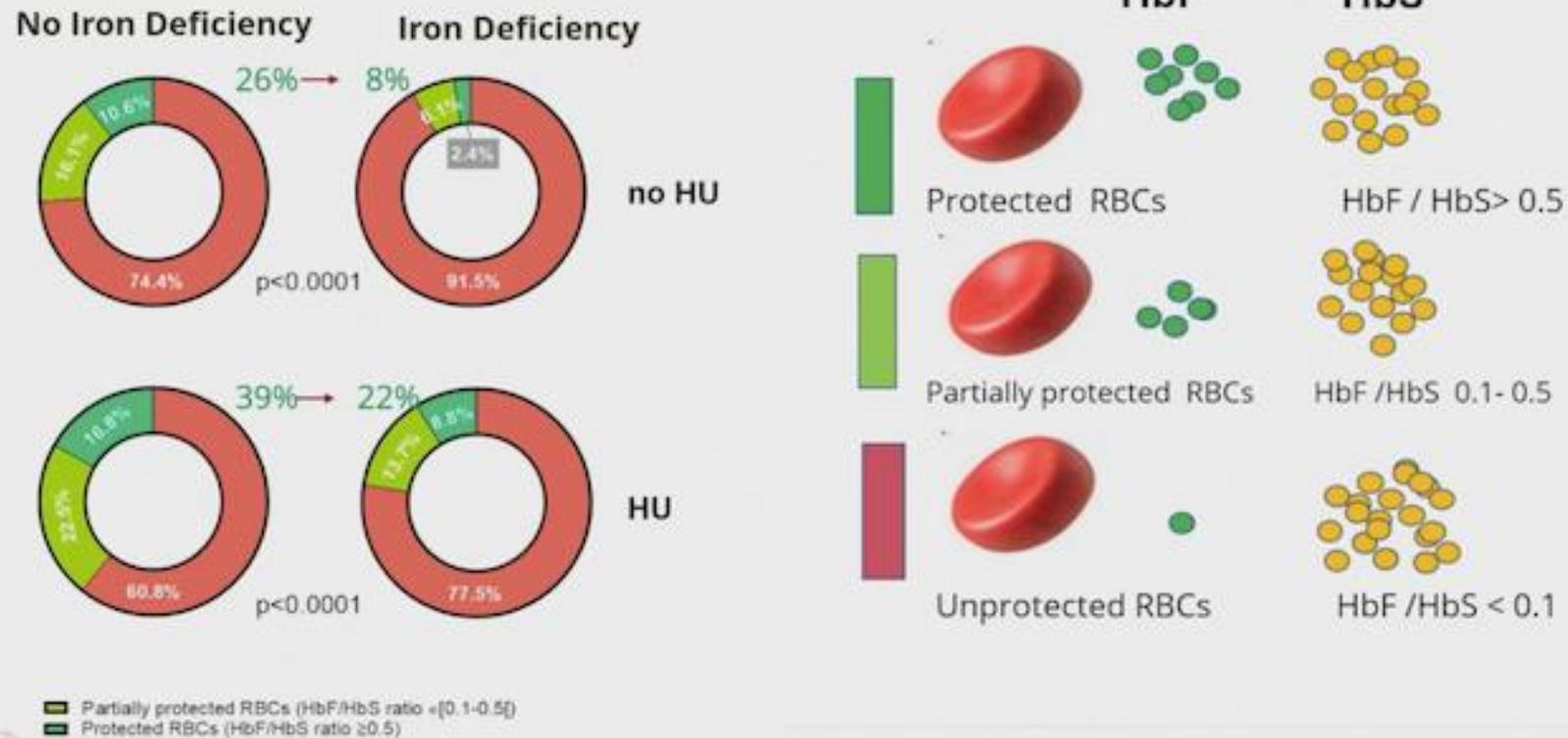
**Ferritin < 200 µg/L + Transferrin Sat Coef < 20% ?**

# Carence en fer / HU / Drépanocytose



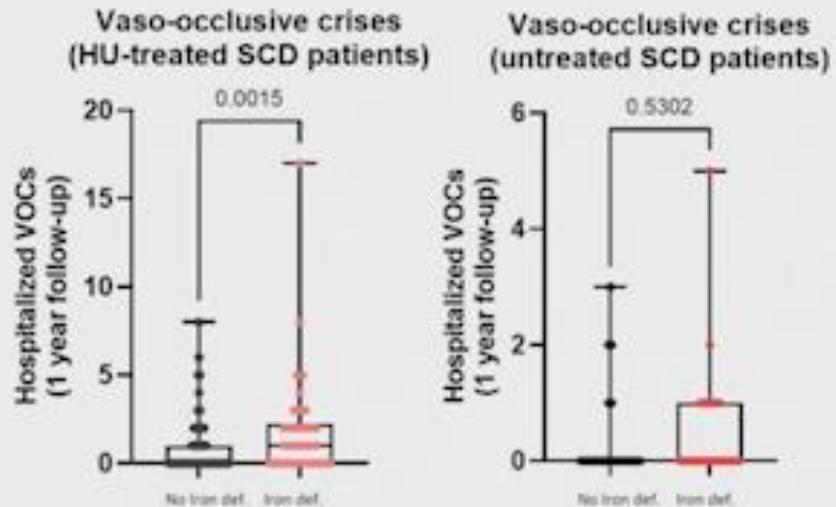
# Carence en fer / HU / Drépanocytose

## HbF Distribution in RBCs at a single level

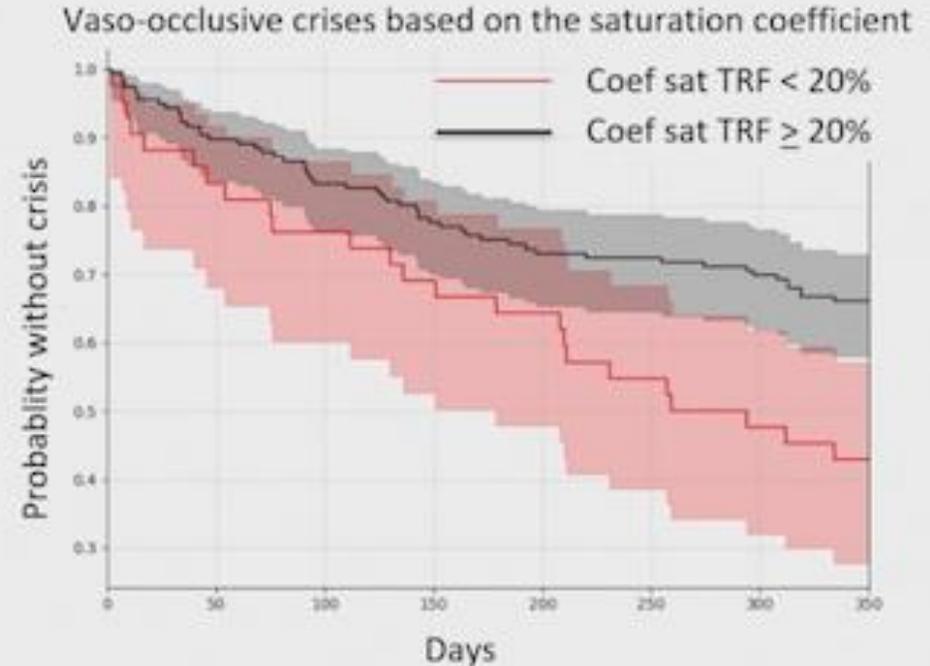


# Carence en fer / HU / Drépanocytose

## Vaso-occlusive crisis and iron deficiency



### HU Group Patients



# Carence en fer / HU / Drépanocytose

## Conclusion

- Dépister la carence en fer chez les patients traités par HU
- Nouvelle définition de la carence en fer dans la drépanocytose ?

**Ferritine < 200 + CST < 20%**

- Perte d'efficacité de l'HU lors d'une carence en fer
- Attention lors de la supplémentation



American Society of Hematology

Advancing Hematology Research and Patient Care



# Intégration de la génétique dans la médecine transfusionnelle

Stella T. Chou, MD

Divisions of Hematology and Transfusion Medicine

The Children's Hospital of Philadelphia



# Contexte physiopathologique et transfusionnel

- Inflammation chronique
- Dysrégulation immunitaire accrue
- Discordance entre le phénotype des donneurs et des receveurs
- Diversité génétique du système RH notamment chez les patients d'origine africaine

**=> Augmentation du risque d'allo immunisation**

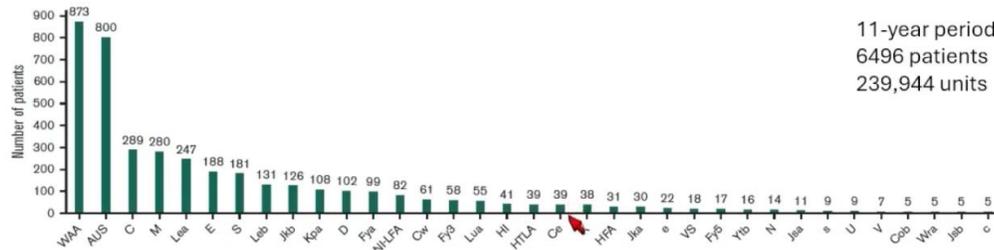


# Objectifs

- Discuter des défis immuno-hématologiques liés aux transfusions chez les patients drépanocytaires.
- Discuter du rôle des diagnostics moléculaires dans la transfusion .
- Découvrir les stratégies actuelles pour optimiser la sélection des unités transfusées.

# Le système RH

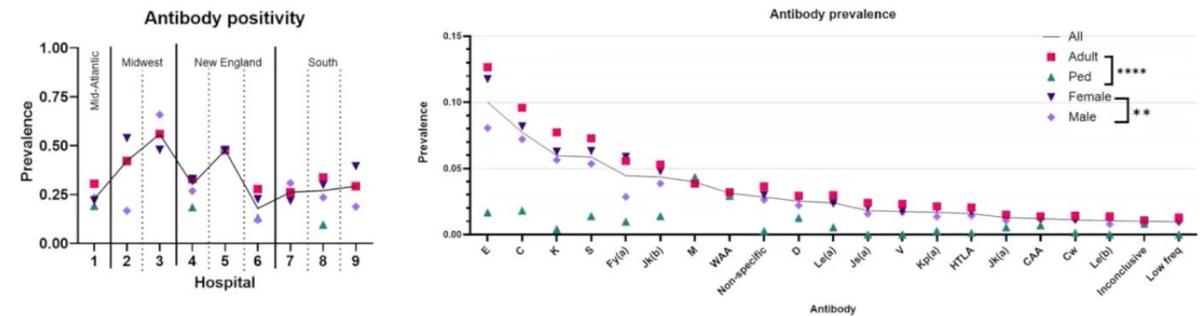
## Antibody formation with prophylactic Rh and K- matched units from European donors



11-year period  
6496 patients  
239,944 units

- 29.8% of individuals were alloimmunized
- Patients who made any antibody were more likely to make additional abs
- Rh antibodies are among most common specificities

## Antibody formation with prophylactic Rh and K- matched units from US donors

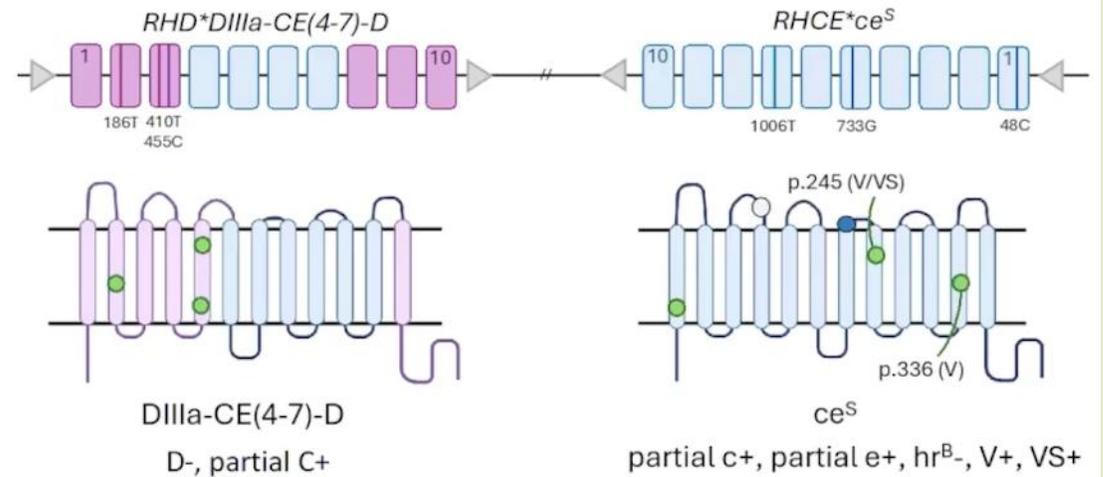
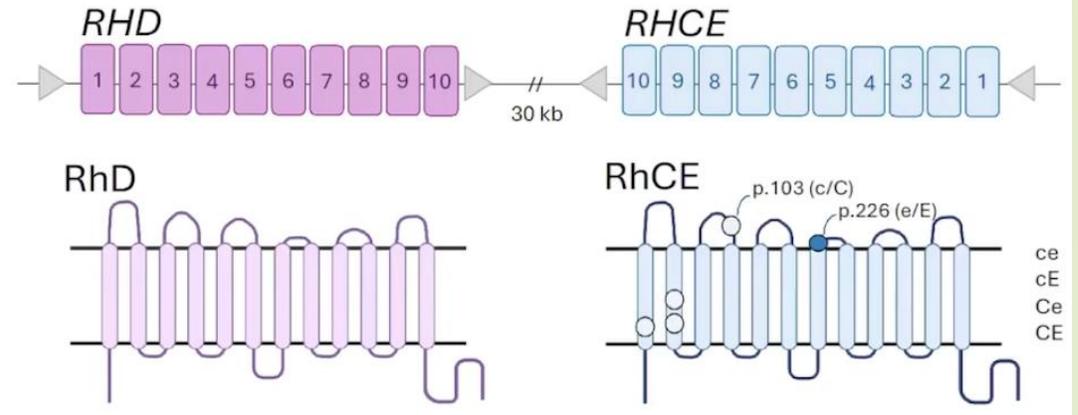


- Multi-institutional retrospective study of 2965 patients, 3:1 adult:peds
- 29.7% of individuals were alloimmunized
- Rh antibodies are among most common specificities



# Le système RH : un système complexe

- ➔ Très polymorphe avec >500 allèles RHD et >150 allèles RHCE



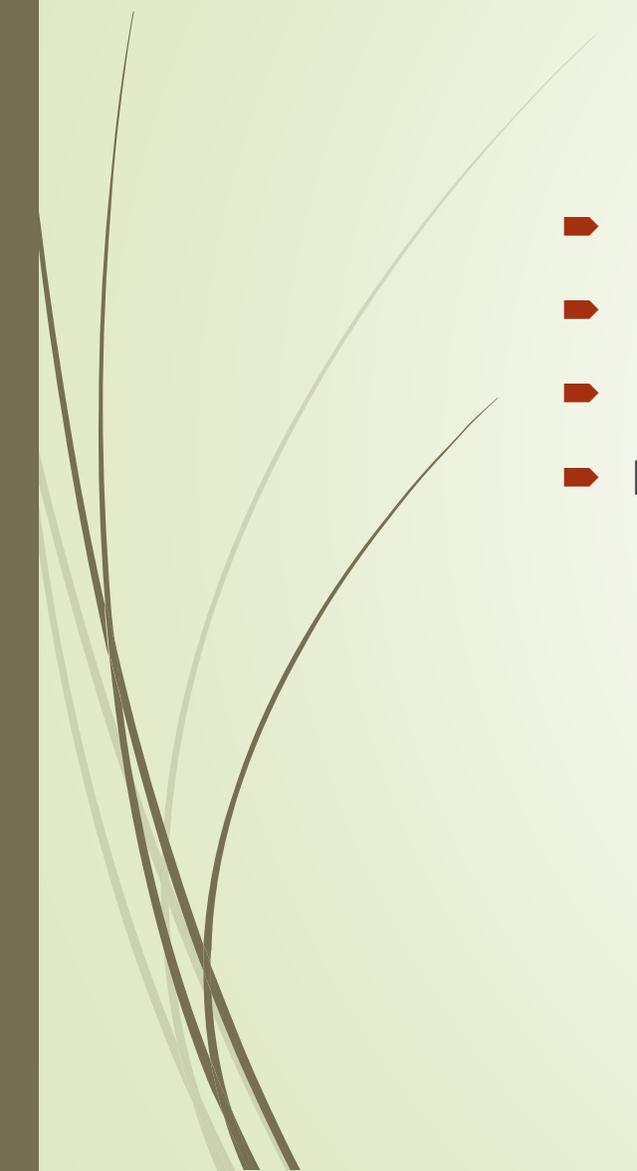


# Méthodes de typage des antigènes sanguins

- **Typage sérologique classique** : basé sur l'utilisation d'anticorps spécifiques
- **Phénotype sérologique peut être insuffisant pour détecter certains variants.**
- **Génotypage moléculaire** : permet d'identifier précisément la présence d'allèles et variants RH.



# Avantages du génotypage

- **Meilleure prédiction du phénotype antigénique réel.**
  - **Orientation précise de la sélection des poches compatibles.**
  - **Facilite l'évaluation rapide des anticorps.**
  - **Information partageable entre établissements.**
- 

# Approches cliniques et de prise en charge

- Réalisation du génotypage systématique dès le diagnostic ou à la première consultation.
- Identification précoce des variants
- - Adaptation de la transfusion selon les résultats : choix d'unités négatives pour les antigènes présents sous forme partielle ou variant.



## Current paradigm

Serologic phenotyping  
Prophylactic Rh (C,E or C/c, E/e)  
and K serologic matching  
Antigen negative RBCs for those  
immunized against



## Future paradigm

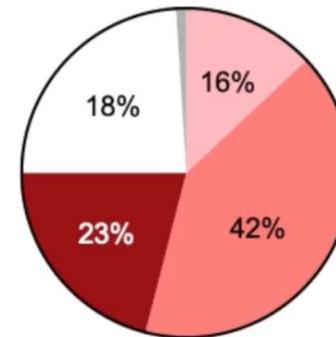
Extended RBC antigen genotype &  
Comprehensive RH analysis  
Genotype guides donor selection  
Prophylactic *RH* genotype-matched  
RBC units



# Perspective

- Essai clinique prospectif , phase 2
- Patients drépanocytaires > 6 mois nécessitant un programme de transfusion chronique
- Patients appariés avec des CGR de donneurs dont les génotypes RH et Kell sont compatibles
- Objectifs:
  - démontrer la faisabilité pratique
  - démontrer la réduction de l'allo-immunisation.

## Prospective RH genotype matching



Exact  
Haplotype  
Allele  
Permissive  
Off Study

- 30 subjects to date
- 717 units transfused
  - 100% RH genotype matched
  - 24% permissive match
- No transfusion delay due to inability to identify genotype matched units





# Conclusion

- Gestion transfusionnelle des patients drépanocytaires :
  - variants génétiques RH
  - Risque d'allo-immunisation
- Le génotypage étendu (allèles RH) : améliorer la compatibilité transfusionnelle.
- Proposition : génotypage systématique
- => **Réduction du risque d'allo immunisation**
- Limites : mobilisations des donneurs



# STArT

## Sickle Cell Disease Treatment with Arginine Therapy: *Results of a Phase-3 Randomized Controlled Trial*

CLAUDIA R. MORRIS MD

**PROFESSOR OF PEDIATRICS & EMERGENCY MEDICINE**



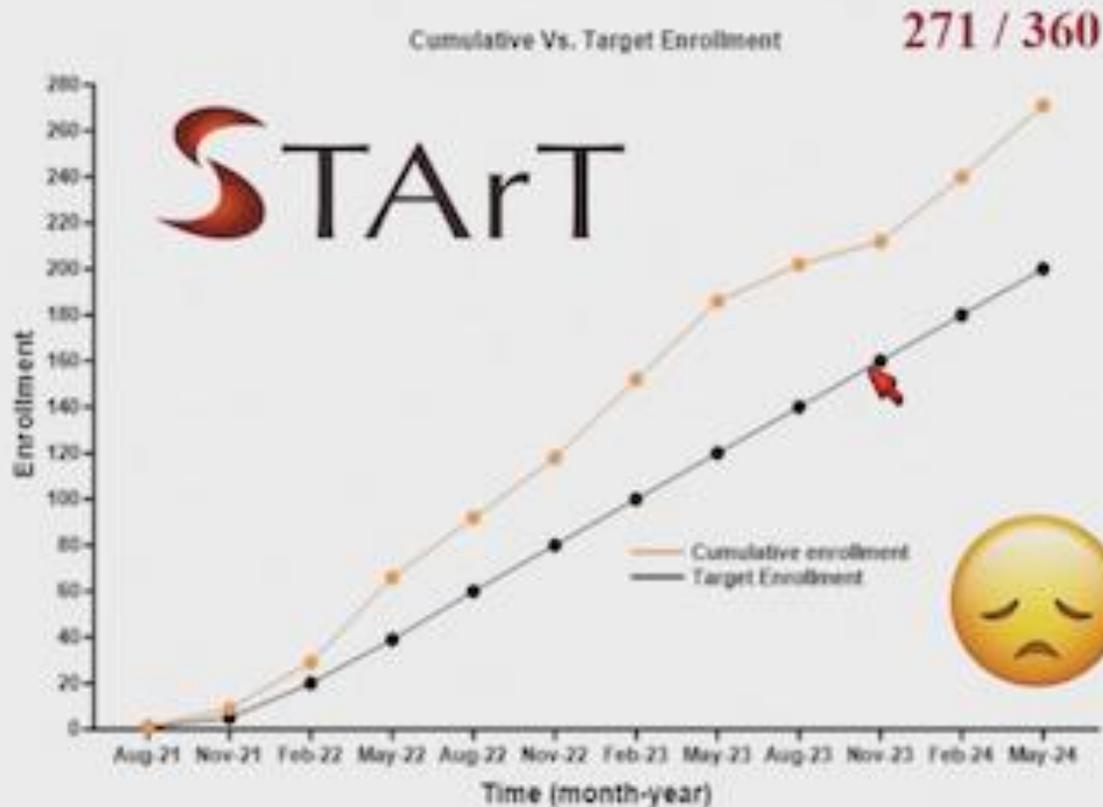




# Design

- Essai randomisé contrôlé contre placebo
- Phase III
- Multicentrique
- Patients drépanocytaires 3-21 ans (tout génotype)
- Hospitalisés pour CVO

# Enrollment Milestones



(Rees et al. STArT: Study protocol for a phase 3 RCT. *Trials*, 2023)

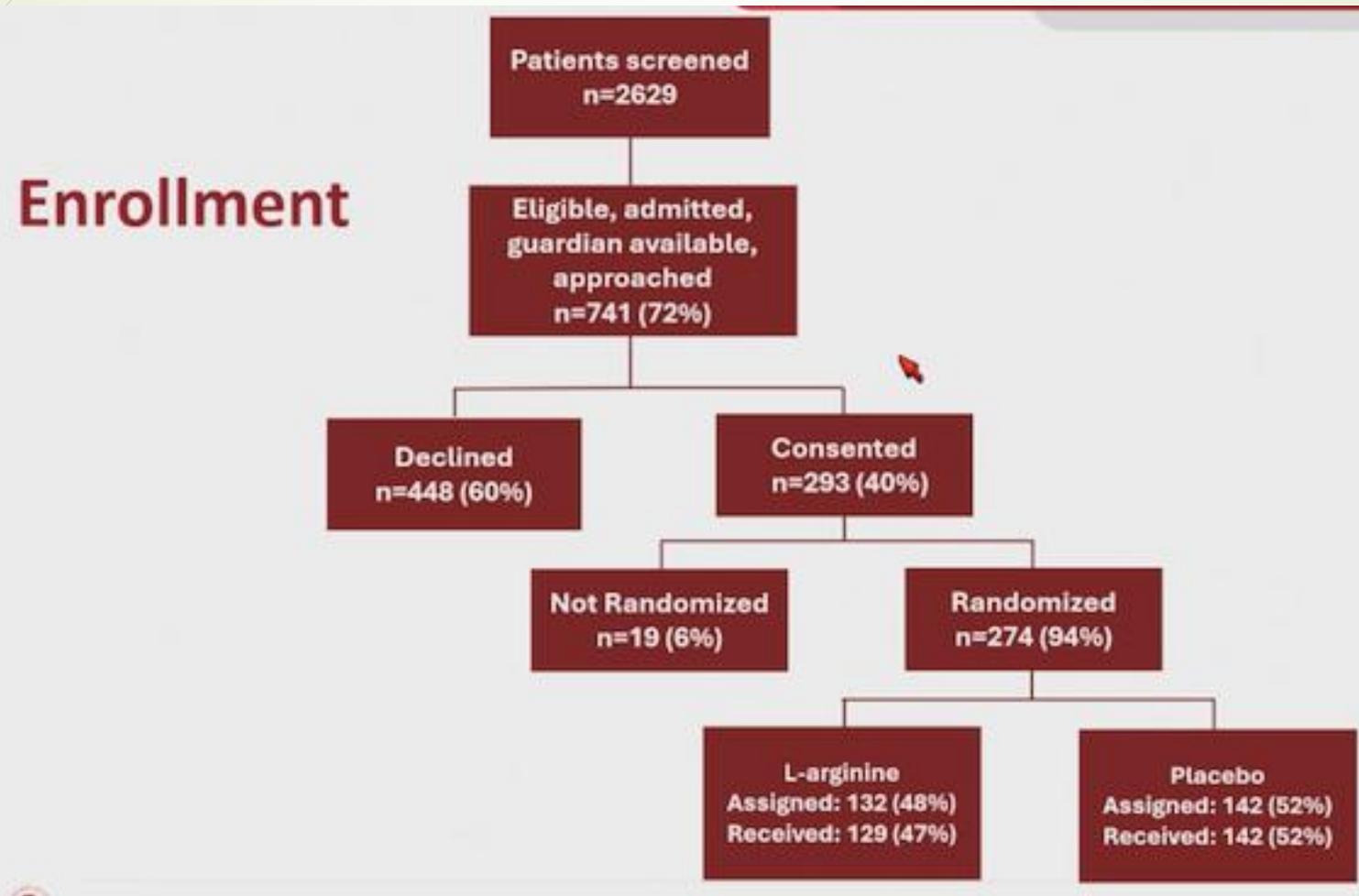


### STArT PEGARN Sites:

- Emory – Children’s Healthcare of Atlanta
  - Egleston
  - Hughes Spalding
- Children’s Hospital Los Angeles
- Children’s Hospital of Philadelphia
- Children’s National Medical Center
- Children’s Hospital of Wisconsin
- Nationwide Children’s Hospital
- Texas Children’s Hospital - Baylor
- Benioff Children’s Hospital – Oakland
- Washington University – St. Louis

**Halted early by DSMB  
for futility to meet  
primary outcome of  
Time-to-crisis-  
resolution**

# Flowchart



# Résultats

	Treatment		Overall (N = 271)
	L-Arginine (N = 129)	Placebo (N = 142)	
<b>Race</b>			
Black or African American	115 (89.1%)	134 (94.4%)	249 (91.9%)
American Indian/Alaskan Native	2 (1.6%)	0 (0.0%)	2 (0.7%)
White	3 (2.3%)	5 (3.5%)	8 (3.0%)
Multiple	2 (1.6%)	0 (0.0%)	2 (0.7%)
Unknown	7 (5.4%)	3 (2.1%)	10 (3.7%)
<b>Ethnicity:</b>			
Hispanic or Latino	13 (10.1%)	7 (4.9%)	20 (7.4%)
Not Hispanic or Latino	115 (89.1%)	135 (95.1%)	250 (92.3%)
Unknown or Not reported	1 (0.8%)	0 (0.0%)	1 (0.4%)
<b>Sex at birth:</b>			
Male	59 (45.7%)	80 (56.3%)	139 (51.3%)
Female	70 (54.3%)	62 (43.7%)	132 (48.7%)
<b>Age (years)</b>	14.8 [11.6, 18.1]	15.2 [10.7, 17.7]	15.1 [11.2, 17.7]
<b>Age group:</b>			
Under 12 years old	36 (27.9%)	42 (29.6%)	78 (28.8%)
12-21 years old	93 (72.1%)	100 (70.4%)	193 (71.2%)
<b>Weight (kg):</b>	53.1 [36.7, 63.0]	50.9 [35.4, 64.2]	52.4 [35.5, 63.5]
<b>Genotype:</b>			
Hb-SS	95 (73.6%)	96 (67.6%)	191 (70.5%)
Hb-SC	23 (17.8%)	38 (26.8%)	61 (22.5%)
S-Beta Zero Thal	7 (5.4%)	2 (1.4%)	9 (3.3%)
Hb S Beta + Thal/Other	4 (3.1%)	6 (4.2%)	10 (3.7%)

## Subject Characteristics: *Demographics*

# Résultats

	Treatment		Overall (N = 271)
	L-Arginine (N = 129)	Placebo (N = 142)	
Prescribed Hydroxyurea	99 (76.7%)	107 (75.4%)	206 (76.0%)
History of Acute Chest Syndrome	87 (68.0%)	107 (76.4%)	194 (72.4%)
ACS at presentation	12 (9.3%)	6 (4.2%)	18 (6.6%)
History of Asthma	62 (50.0%)	68 (47.9%)	130 (48.9%)
Bronchodilator Use	78 (62.4%)	90 (63.4%)	168 (62.9%)
Experienced SCD-related pain for $\geq 15$ days of the month for the last 6 months ( <i>chronic pain</i> )	50 (39.4%)	60 (42.6%)	110 (41.0%)
Experienced SCD- pain on at least half the days for the last 6 months ( <i>chronic pain</i> )	54 (42.5%)	67 (47.5%)	121 (45.1%)
Number of ED visits that did <b>not</b> result in hospitalization in past 12 months			
0	46 (35.7%)	46 (32.4%)	92 (33.9%)
1-2	47 (36.4%)	48 (33.8%)	95 (35.1%)
$\geq 3$	36 (27.9%)	48 (33.8%)	84 (31.0%)
Number of hospitalizations in the past 12 months			
0	27 (20.9%)	20 (14.1%)	47 (17.3%)
1-2	45 (34.9%)	61 (43.0%)	106 (39.1%)
$\geq 3$	57 (44.2%)	61 (43.0%)	118 (43.5%)

**Subject  
Characteristics:**

**Past Medical Hx**

# Résultats

STArT

	Treatment		Overall (N = 271)
	L-Arginine (N = 129)	Placebo (N = 142)	
<b>Duration of current pain crisis*</b>			
Today	18 (14.1%)	24 (16.9%)	42 (15.6%)
Yesterday (1 day ago)	50 (39.1%)	44 (31.0%)	94 (34.8%)
2-6 days ago	50 (39.1%)	47 (33.1%)	97 (35.9%)
1 week or longer	10 (7.8%)	27 (19.0%)	37 (13.7%)
<b>Time from 1<sup>st</sup> IV Opioid to First Study Drug Infusion (hours)</b>	8.3 [5.8, 11.6]	7.8 [5.2, 11.2]	8.0 [5.3, 11.4]
<b>IV Morphine Equivalents (mg/kg) prior to first study drug infusion</b>	0.4 [0.3, 0.5]	0.4 [0.3, 0.5]	0.4 [0.3, 0.5]

## Subject Characteristics:

- Duration of Pain
- Time to study drug
- IV morphine Equiv

# Résultats

Outcome	Treatment			P-Value*
	Overall (N = 271)	L-Arginine (N = 129)	Placebo (N = 142)	
<b>Primary Outcome</b>				
<b>Time to Crisis Resolution</b> <i>(study drug infusion to last IV opioid in hours)</i>	85.2 (123.0) 63.2 [31.6, 111.1]	81.5 (79.6) 60.8 [34.8, 109.0]	88.6 (152.2) 65.8 [31.1, 111.1]	0.983
<b>Time from first study drug infusion to discharge (hours)<sup>†</sup></b>	148.9 (806.4) 82.0 [46.9, 134.7]	102.6 (81.5) 81.9 [49.3, 134.5]	191.0 (1111.5) 82.6 [45.9, 135.3]	
	Shown as	Mean (SD) Median [IQR]		

**Primary Outcome**

# Résultats

Outcome	Treatment			P-Value*
	Overall (N = 271)	L-Arginine (N = 129)	Placebo (N = 142)	
<b>Secondary Outcomes</b>				
<b>Total IV Morphine Equivalents (mg/kg)</b>	2.2 (3.7) 1.2 [0.4, 2.7]	2.6 (4.5) 1.4 [0.5, 3.1]	1.9 (2.8) 1.0 [0.4, 2.3]	0.330

Shown as Mean (SD)  
Median [IQR]

**Secondary Outcome: Total IV Morphine Equivalents**

# Sécurité

## Safety Outcomes: Arginine is Safe!

Outcome	Overall (N = 271)	Treatment		P-Value*
		L-Arginine (N = 129)	Placebo (N = 142)	
Safety Outcomes				
Acute chest syndrome (present in ED/developed)	54 (19.9%)	29 (22.5%)	25 (17.6%)	0.298
Blood transfusion	63 (23.2%)	33 (25.6%)	30 (21.1%)	0.458
Oxygen use	84 (31.0%)	42 (32.6%)	42 (29.6%)	0.671
72 hour return to ED	17 (6.3%)	9 (7.0%)	8 (5.6%)	0.499
28 day return to ED	81 (29.9%)	35 (27.1%)	46 (32.4%)	0.412
Clinical Deterioration	11 (4.1%)	4 (3.1%)	7 (4.9%)	0.469
Any Adverse Event	164 (60.5%)	81 (62.8%)	83 (58.5%)	0.358
Serious AE	47 (17.3%)	22 (17.1%)	25 (17.6%)	0.644



# Conclusion

- ▶ Arginine est SAFE !
- ▶ STArt rejoint les autres essais de phase III n'ayant pas atteints leur CJP
- ▶ Variabilité des résultats (démographique, ATCD, site...)



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# Prospective hydroxyurea impact on cerebral magnetic resonance imaging from a 30-month trial of children with sickle cell anemia in Uganda

**Nancy S. Green, MD, Columbia University**

on behalf of:

**Idro R, Wambaka B, Mboizi V, Kalibbala D, Nambatya G, Ssenkusu J,  
Lubowa S, Kawooya M, Munube D, Kasirye P, Lipton M, Minja F**



 COLUMBIA | COLUMBIA UNIVERSITY  
IRVING MEDICAL CENTER



# Contexte

- ▶ Enfants drépanocytaires peuvent développer très tôt une vasculopathie cérébrale
- ▶ AVC, Silent cerebral infarcts, sténose artérielle, doppler pathologique
- ▶ BRAIN Safe (Idro 2022) : Prévalence 28% infarctus IRM en Uganda
- ▶ BRAIN safe 2 : étude prospective ouverte sur 30 mois avec HU à dose croissante

# Design

## BRAIN SAFE-2 Trial (2.5 years)

### Enrollment criteria:

- Aged 3-9 years; limited prior HU treatment
- Lack of prior stroke

### Primary Results

**Trial enrollment: N= 264, Completed: 95.5%**

- Initial HU dose:  $20.2 \pm 0.9$  mg/kg Escalated to  $25.9 \pm 2.7$
- 4 deaths, 4 non-fatal strokes
- Improved Neurocognitive Function and TCD ([Naggayi 2025](#)  
[Wambaka 2025](#))



# Method

## MRI-MRA Imaged Subset

- Randomly selected **N= 89**,  $\geq 5$  years of age
- MRI-MRA at trial Entry and Completion (2.5 yrs)
- Cerebral infarcts and stenoses
- Independent review by 2 neuro-radiologists with adjudication
- Analysis: ANOVA and Chi squared or Fisher exact test



### Overall:

- 83 of the 89 (93.3%) re-imaged:
- 4 reached premature endpoint: 1 death, 3 non-fatal strokes
  - None had initial abnormal TCD
- *Most MRI at trial exit: No change versus entry*
  - But some progressed

# Résultats

## MRI and MRA Findings at Trial Entry (month 0)

	Total N= 89 (%)	Initial SCI N= 62 (69.7%)	No SCI N= 27 (30.3%)	P-value +/- SCI
Mean age (yrs)	6.6 ±1.4	6.6 ±1.4	6.6 ±1.3	NS
Sex (male)	41 (46.1)	29 (46.8)	29 (44.4)	NS
Hb g/dL	7.7 ±1.1	7.7 ±1.0	7.8 ±1.3	NS
HbF%	11.4 ±6.6	9.9 ±7.7	11.4 ±6.6	NS
O2 saturation (%)	95.4 ±3.2	95.4 ±3.3	95.5 ±2.9	NS
BP systolic (mm Hg)	105.0 ±11.3	104.9 ±10.5	105.4 ±13.4	NS
TCD mean TAMV	150.1 ±31.4	155.1 ±33.4	137.0 ±21.9	0.06
Elevated TCD	20.2%	27.4%	3.7%	.03
Arterial Stenosis	8 (9.0)	8 (12.9)	0	*
Neurocognition				NS

### Initial Results:

1. SCI in 70%

2. Only TCD predicted SCI and stenosis at trial entry

3. No Neuro-cognitive Differences

# Résultats

## MRI and MRA Findings at Trial End (month 30)

	Total N= 83 (%)	Initial SCI (s) N= 56 (67.4%)	No SCI N= 27 (32.5%)	P- value
Mean age (yrs)	9.1 ±1.3			NS
Sex (male)				NS
Hb (g/dL)	8.5 ±1.2	8.6 ±1.2	8.5 ±1.2	NS
HbF%	19.7 ±10.4	17.7 ±9.0	20.1 ±10.7	NS
Elevated TCD	10.8%	16.1%	0	*
Arterial Stenosis	6 (7.2)	6	0	*
Progression: SCI	8 (9.6)	8 (14.3)	0	*
Progression: Stroke	3 (3.6)	3 (5.4)	0	*
Neurocognition	Improved		Higher Exec. Function	0.045

### Final results:

1. No SCI at entry:  
**No new SCI or stenosis**
2. SCI at entry:  
- **14% progressed**  
- **No differences if SCI progressed vs. stable**
3. Initial Stenosis:  
**2 had stroke**
3. No SCI vs. SCI:  
**Some higher neurocognition**



# Conclusion

- Confirmation d'une prévalence plus importante des SCI des enfants en Uganda vs pays à hauts revenus
- Initiation d'HU en prévention est protecteur de la survenue de SCI
- Débuter le plus tôt possible l'HU
- Étendre aux autres pays Africains



# Etavopivat in Adolescents with Sickle Cell Disease: Emerging Safety and Efficacy Findings from the First Cohort of the Ongoing Phase 1/2 HIBISCUS Kids Study

Adlette Inati,<sup>1</sup> Bernhards Ogutu,<sup>2,3</sup> E. Leila Jerome Clay,<sup>4</sup> Pavithra Dhayakar<sup>5</sup>, Kaming Lo,<sup>6</sup>  
and Miguel R. Abboud<sup>7</sup>

<sup>1</sup>Lebanese American University Gilbert and Rose-Marie Chagoury School of Medicine, Byblos and NINI Hospital, Tripoli, Lebanon; <sup>2</sup>KEMRI Kondele Children's Hospital, Kisumu, Kenya; <sup>3</sup>CREATES, Strathmore University, Nairobi, Kenya; <sup>4</sup>Novo Nordisk Inc., Princeton, NJ, USA; <sup>5</sup>Novo Nordisk, Bangalore, India; <sup>6</sup>Novo Nordisk Inc., Lexington, MA, USA; <sup>7</sup>American University of Beirut, Beirut, Lebanon

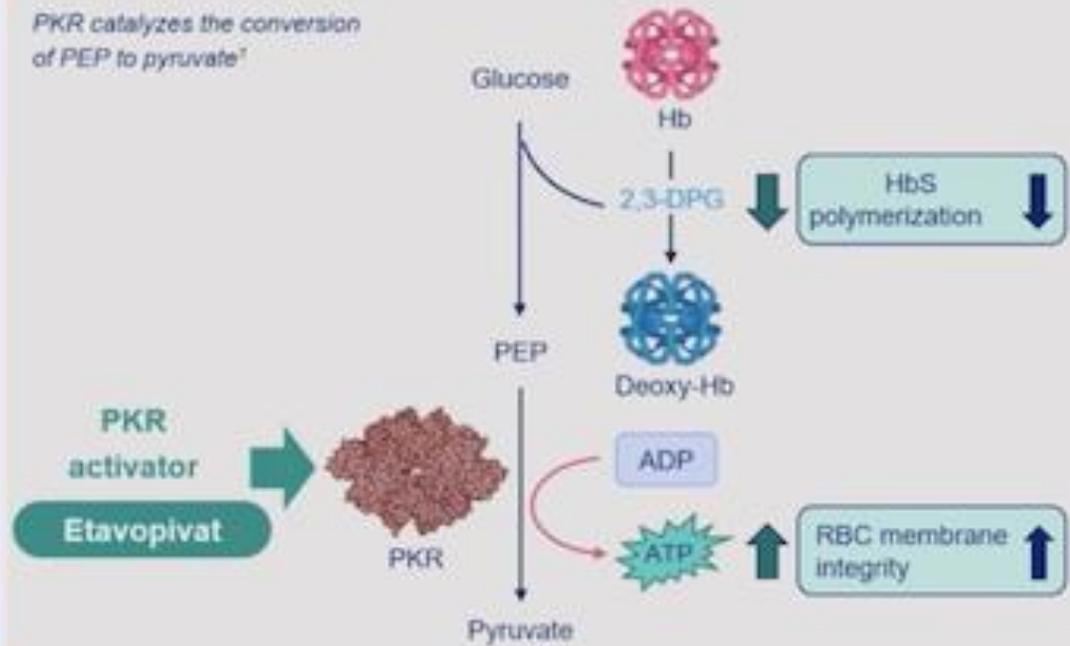
# Contexte

Multimodal effects of PKR activation by etavopivat lead to increased Hb, decreased VOC, and improved RBC health<sup>1-3</sup>



Etavopivat is a once-daily, orally bioavailable, small-molecule activator of the PKR, under investigation for the treatment of individuals with SCD<sup>1-3</sup>

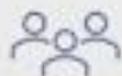
PKR catalyzes the conversion of PEP to pyruvate<sup>1</sup>



# Design

## HIBISCUS Kids: Study design<sup>1</sup>

Single-arm, four-cohort, open-label, ongoing phase 1/2 study investigating the pharmacokinetics and safety of etavopivat in children and adolescents with SCD (aged 6 months to <18 years)



25 adolescent patients treated with etavopivat 400 mg QD

### Key inclusion criteria:

- SCD diagnosis
- Hb  $\geq$ 5.5 to <10.5 g/dL
- Stable dose of HU (if applicable)\*
- Severe SCD<sup>1</sup>

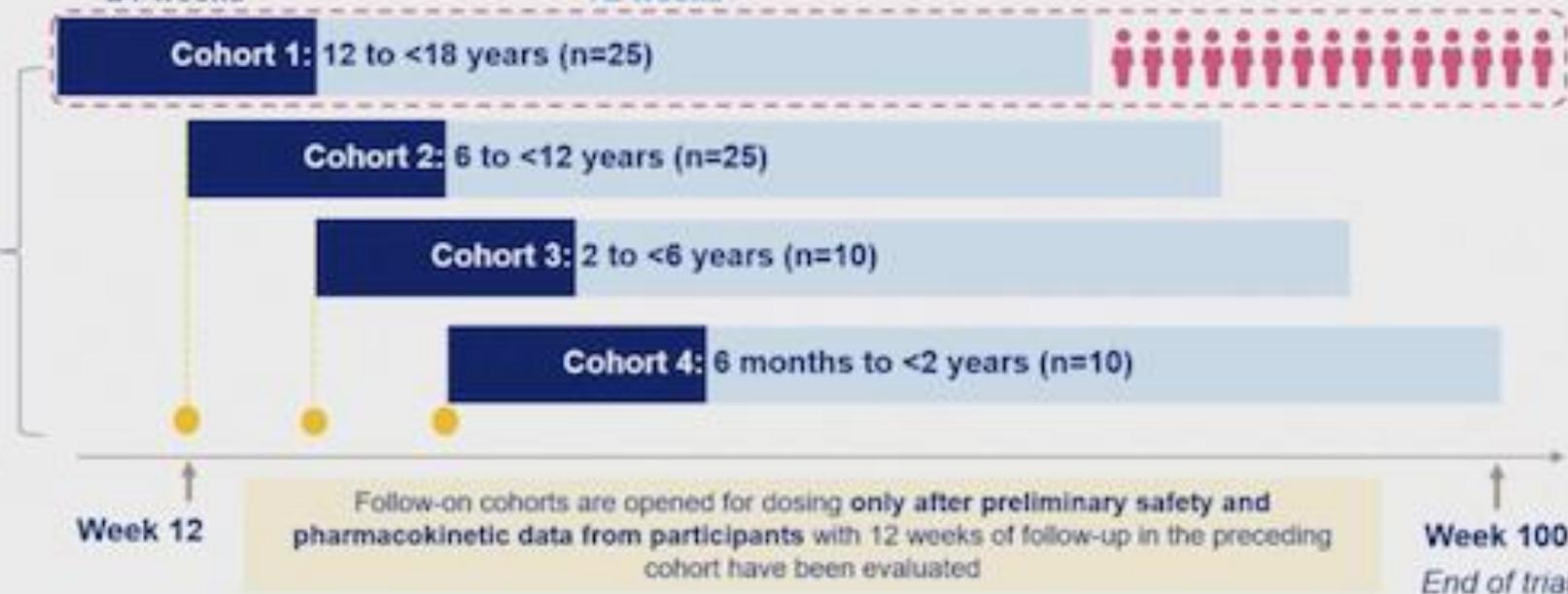
### Key exclusion criteria:

- >15 VOCs within 12 months
- Hospitalizations within 14 days prior to starting study treatment
- Abnormal TCD in the 12 months prior to starting study treatment

Open-label treatment  
24 weeks

Open-label extension  
72 weeks

Interim analysis of Cohort 1  
(n/N=15/25)



# Méthode

## Study objectives and endpoints



### Objective

To assess pharmacokinetics, safety, and tolerability of etavopivat in adolescent and pediatric patients during the 24-week primary treatment period and the 72-week treatment extension period

### Study objectives

#### Primary:

1. Pharmacokinetics of etavopivat
2. Safety and tolerability of etavopivat at week 24

#### Secondary:

1. Effect of etavopivat on Hb response
2. Occurrence of VOCs
3. Changes in fatigue
4. Changes in cerebral blood flow

#### *Not presented here*

5. Safety and tolerability of etavopivat during the 72-week treatment extension period

### Study endpoints

#### Primary:

1. Single-dose and steady-state etavopivat exposure profile
2. Incidence of AEs, serious AEs, etavopivat discontinuations, dosing interruptions, and dose reductions at week 24

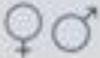
#### Secondary:

1. Hb response >1.0 g/dL increase from baseline at weeks 12 and 24
2. Number of VOCs during the 24-week treatment period
3. Change from baseline in PROMIS Fatigue T-score at week 24
4. Change from baseline in TAMMV by TCD at week 24

5. AEs, serious AEs, etavopivat discontinuations, dosing interruptions, and dose reductions

# Résultats

## Demographics and baseline characteristics

Demographics and baseline characteristics	Interim population (N=15)
 Age in years, mean (range)	14.5 (12–17)
 Sex, n (%) Female Male	10 (67) 5 (33)
 Race, n (%) Black or African American White*	10 (67) 5 (33)
 Hemoglobinopathy genotype†, n (%) HbSS HbSβ <sup>0</sup> -thalassemia	13 (87) 2 (13)
 Baseline Hb, mean (SD) g/dL	8.0 (1.13)
 Number of VOCs in the past 12 months, mean (SD)	2.5 (0.74)
 Number of VOCs leading to hospitalization in the past 12 months, mean (SD)	1.4 (1.06)
 Concomitant hydroxyurea use in the past 3 months, n (%)	12 (80)

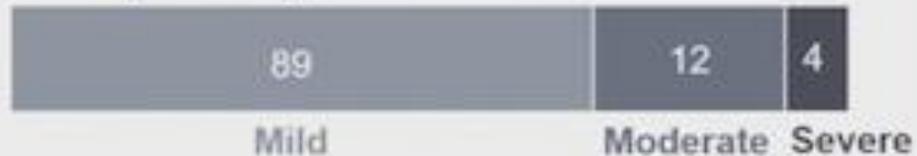
\*Please note that Arabic participants were classified as 'White' in the race category. †For hemoglobinopathy genotype, HbSC and HbSβ<sup>0</sup>-thalassemia were also recorded.  
Hb, hemoglobin; SD, standard deviation; VOC, vaso-occlusive crisis.

# Sécurité

Etavopivat was well tolerated, with safety findings consistent with underlying disease and no unexpected safety concerns

All 15 participants completed 24 weeks of treatment

TEAE by severity\*, # of events



- **No life-threatening events** or **deaths** reported
- **One serious drug-related TEAE** (cholestasis) was recorded
- **One drug interruption was recorded**, with no participants requiring a dose reduction or drug discontinuation

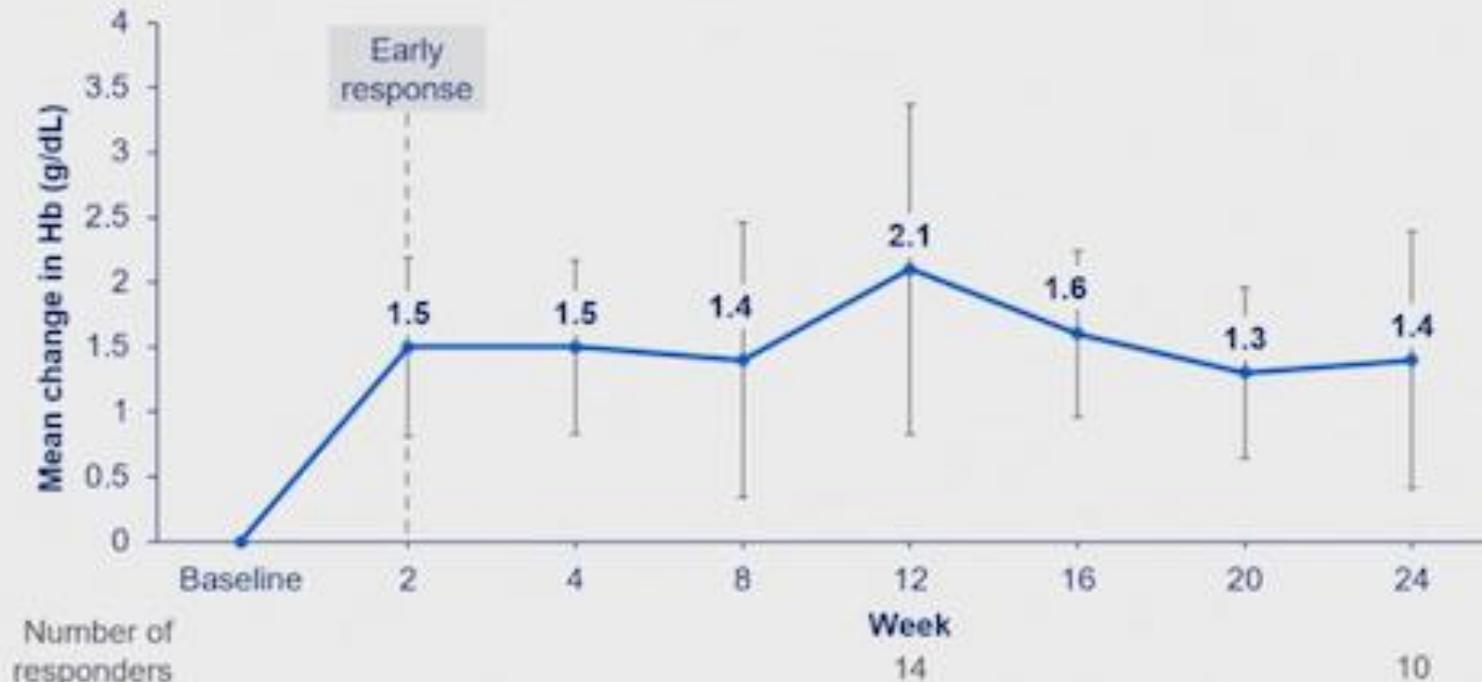
TEAEs with incidence  $\geq 20\%$ :

	n (%)	# of events
Sickle cell anemia with crisis	9 (60)	26
Malaria	4 (27)	5
Tonsillitis	4 (27)	4
Headache	4 (27)	5
Upper respiratory tract infection	3 (20)	4
Malaise	3 (20)	3
Back pain	3 (20)	3

# Résultats

Hemoglobin responses were achieved as early as week 2 and maintained through weeks 12 and 24

Mean Hb change from baseline [SD] through week 24 (N=15)



At week 24, 10 out of 15 participants demonstrated an Hb response\*

Over 24 weeks, the mean (SD) VOC was 1.8 (1.9) (total number of VOC was 27)

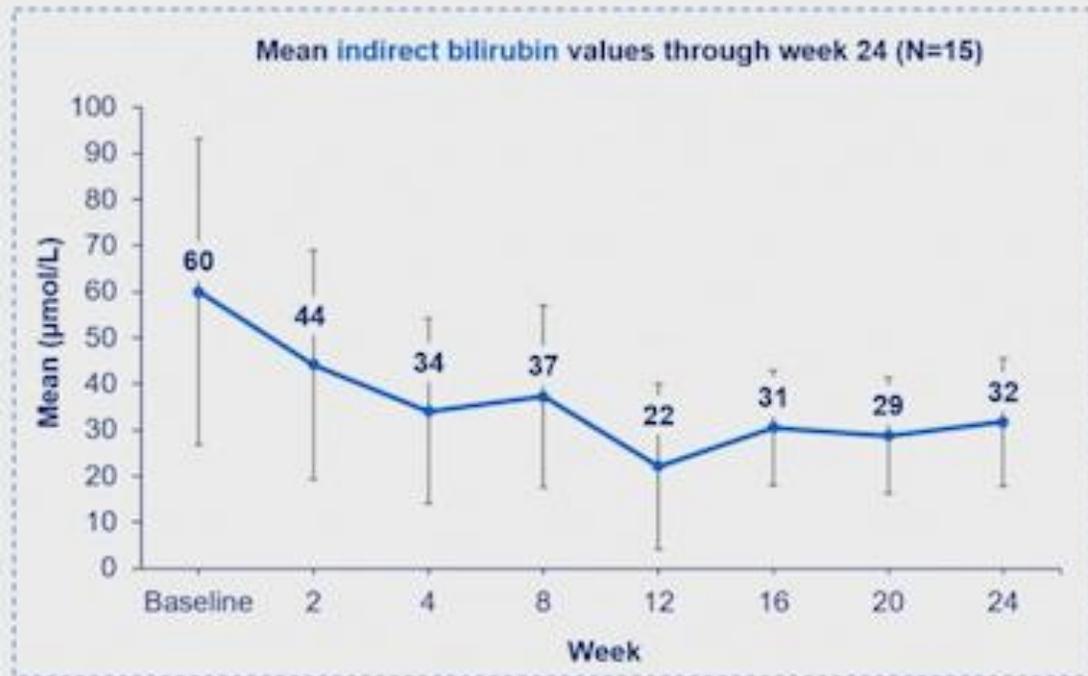
# Résultats

Observed trend towards improvement in fatigue over time as assessed by the PROMIS score



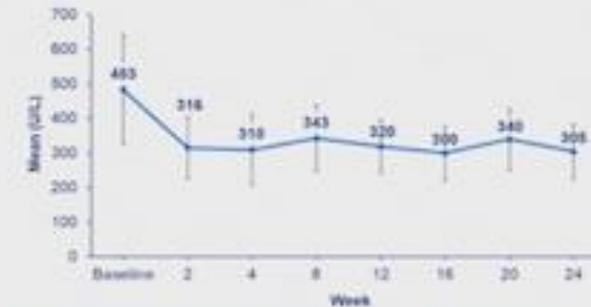
# Résultats

Sustained improvements in hemolysis markers were observed from baseline through week 24



Baseline was defined as the average of screening and day 1 measurement prior to first dose of etavopivat. Error bars represent standard deviation.

Mean lactate dehydrogenase values through week 24 (N=15)

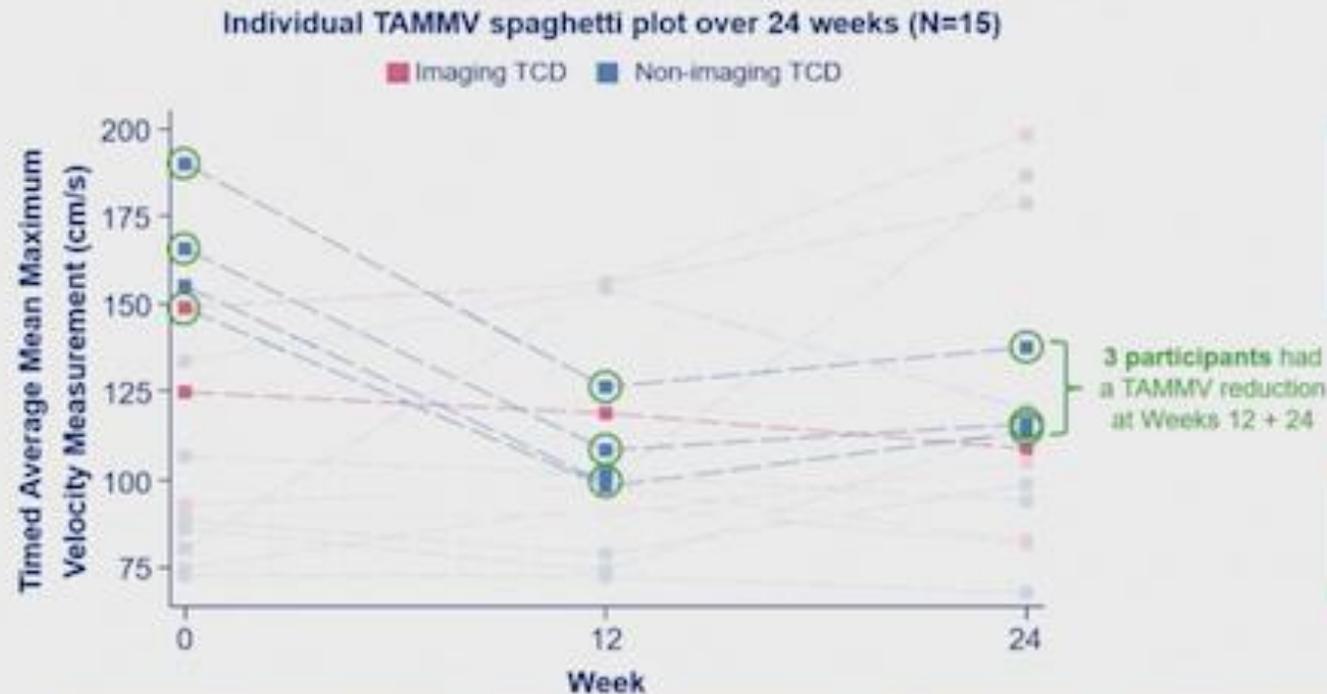


Mean absolute reticulocyte count values through week 24 (N=15)



# Résultats

Cerebral blood flow velocity improvement was observed at Weeks 12 and 24 in four participants\*



The one participant who had a conditional TCD (non-imaging TCD >170 cm/s) at baseline also demonstrated a TAMMV reduction

An improvement in TAMMV was defined as a TAMMV reduction of >15 cm/s from baseline

\*Cerebral blood flow velocity improvement (>15 cm/s from baseline) was observed in four participants at Week 12 and four participants at Week 24. Three participants achieved improvement at both Weeks 12 and 24; one patient only achieved improvement at Week 12 and one only at Week 24. TAMMV, time-averaged mean of the maximum velocity; TCD, transcranial doppler.

# Conclusion



In this first, dedicated study of a PKR activator in a pediatric population with SCD, etavopivat was found to be well tolerated by adolescents in this cohort, with safety findings consistent with underlying disease and no unexpected safety concerns



Observed clinical benefits included improvements in Hb levels and hemolytic markers, accompanied by a reduction in patient-reported fatigue scores



Cohort 1 enrollment (N=25) and dosing are now complete, and the weight-based dosing with a granule formulation has begun for Cohort 2, children aged 6 to <12 years



The study is expected to provide further insights into the safety, tolerability, and potential clinical benefits of etavopivat in younger children

These conclusions are drawn from emerging data collected from 15 of the 25 participants in Cohort 1.  
Hb, hemoglobin; PKR, pyruvate kinase red blood cell isozyme; SCD, sickle cell disease.

*Le stress oxydatif et la dénaturation de l'hémoglobine C à l'origine de la physiopathologie de la drépanocytose SC : effets des antioxydants et l'hydroxyurée.*



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ABSTRACT # abs25-12593

## **Oxidative stress and hemoglobin-C denaturation drive hemoglobin SC pathophysiology and can be ameliorated by antioxidants and hydroxyurea**

**Tahereh Setayesh**, PhD, Anifat Tijani, MSc, Harsimran Kaur, MD, Shristi Khanal, MSc, Zhenqi Zhu, PhD, Mengna Chi, PhD, Abigail Kincaid, Russell Ware, MD, PhD, Punam Malik, MD



# Introduction

## Etude PIVOT, Phase 2

- ▶ Ghana
- ▶ Enfants et adultes SC : 5-50 ans
- ▶ Hydroxyurée 20mg/kg/j vs Placebo durant 12 mois
- ▶ Objectif primaire : montrer la non-infériorité de l'HU vis-à-vis de la toxicité hématologique
- ▶ Objectifs secondaires: : modification des paramètres biologiques (HbF), hospitalisations et transfusions



# Introduction

## Etude PIVOT, Phase 2

- ▶ Objectif primaire : Non atteint
- ▶ Objectifs secondaires: HU associé à une réduction du nombre de CVO et d'hospitalisation chez l'enfant et l'adulte
- ▶ Augmentation modeste de l'HbF avec une forte variabilité



**Comment l'hydroxyurée peut-il  
apporter un bénéfice clinique  
aussi significatif avec une  
majoration seulement modeste  
de l'HbF ?**

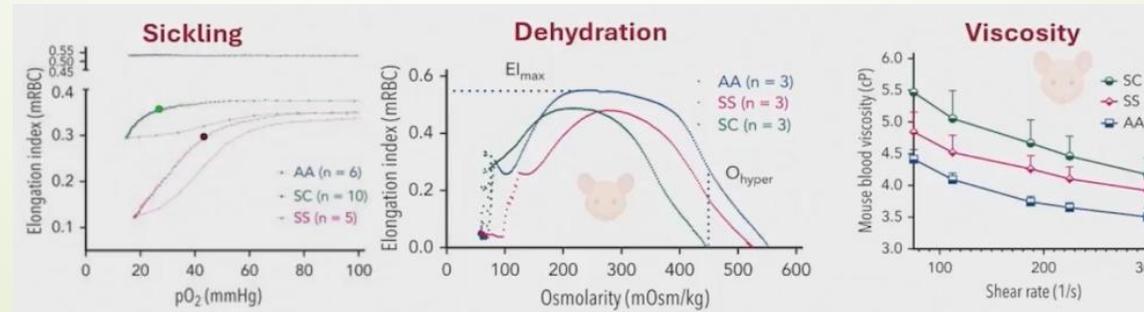


# Introduction

- Hypothèse : l'hémoglobine C est plus sujette aux dommages oxydatifs que l'HbS, ->  d'hémoglobine dénaturée -> endommage la membrane.
- HU -> réduction de l'oxydation de l'hémoglobine de manière indépendante de l'HbF.

# Matériels et Méthodes

- Modèle murin SC reprenant les caractéristiques de la drépanocytose SC
  - Xérocytose
  - Seuil de falciformation plus bas que chez les SS
  - Taux d'Hb plus élevée que chez la souris SS
  - Viscosité sanguine totale élevée
  - Rétinopathie plus fréquente que la souris SS
  - Cristallisation de l'HbC en condition désoxygénée
  - Dans ce modèle : absence d'hémoglobine F car l'expression des chaînes gamma s'estompe à J14 de vie



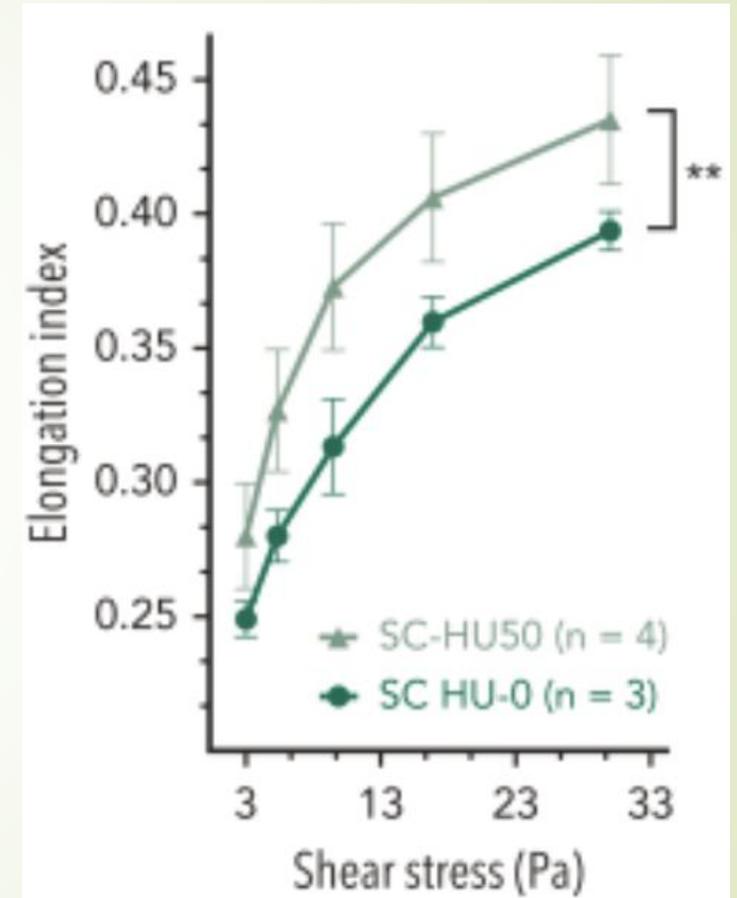


# Matériel et méthode

- ▶ Hydroxyurée (HU) administrée à 50 mg/kg, 3 fois par semaine pendant 4 semaines, dose optimisée pour limiter la toxicité.
- ▶ Quercétine (antioxydant naturel) administrée seule 0,2 mg/kg/j
- ▶ Groupes témoin : solution saline

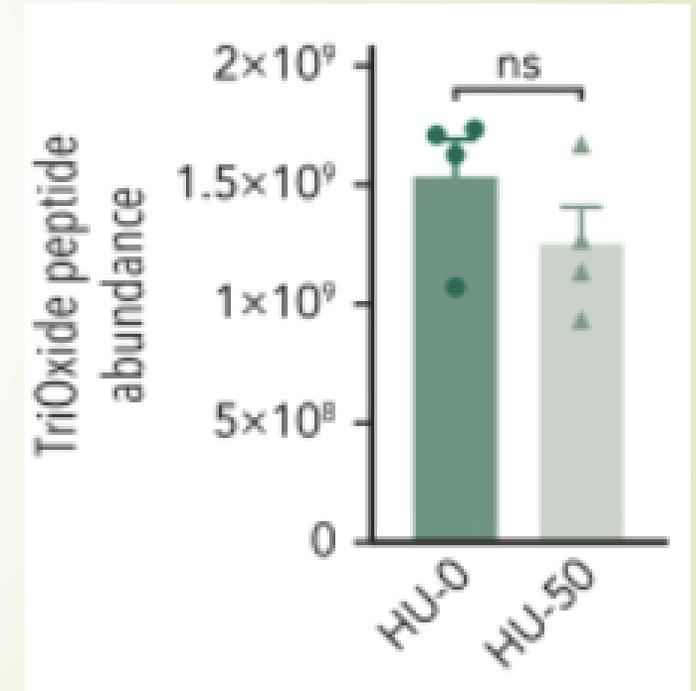
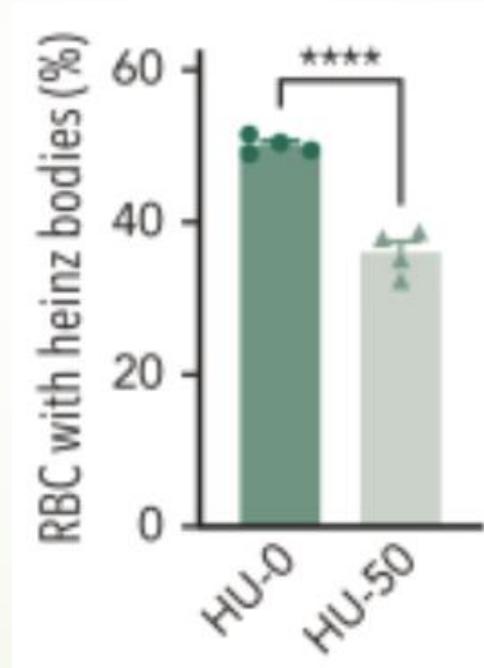
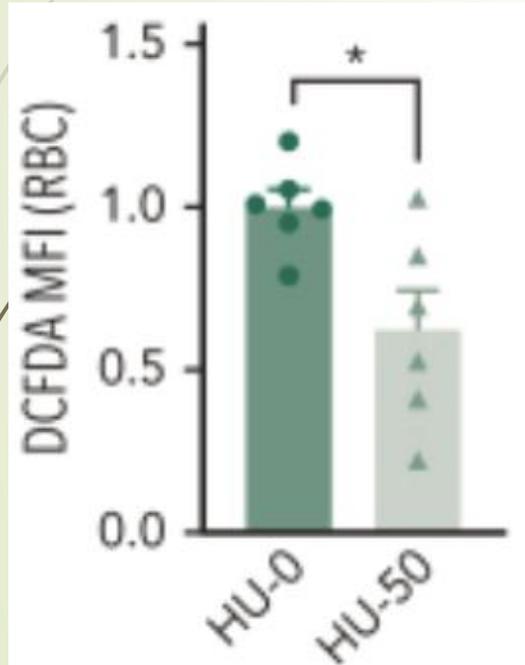
# Résultats

- Hydroxyurée chez la souris SC : déformabilité



# Résultats

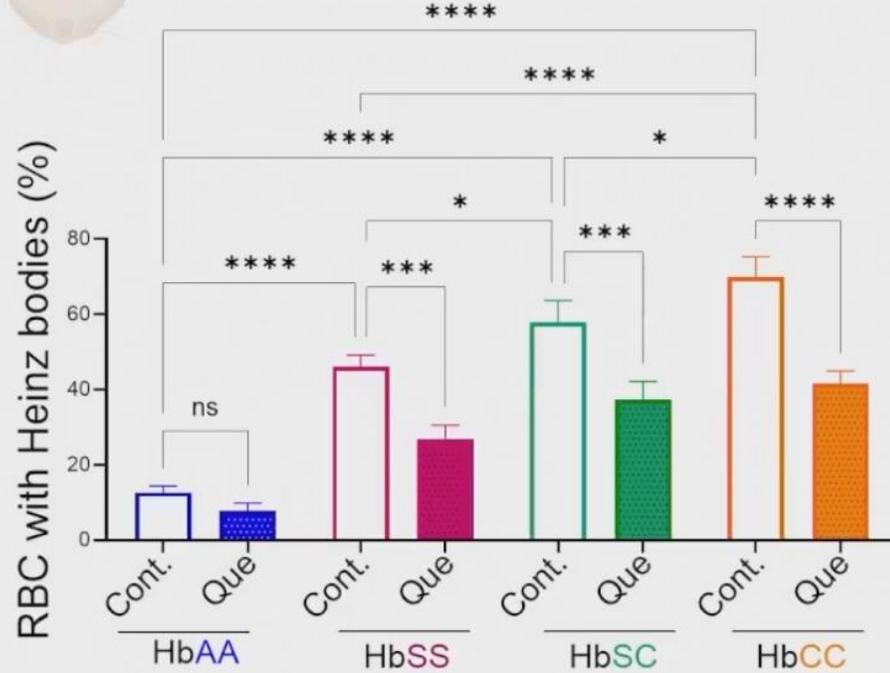
- Hydroxyurée chez la souris SC : stress oxydatif



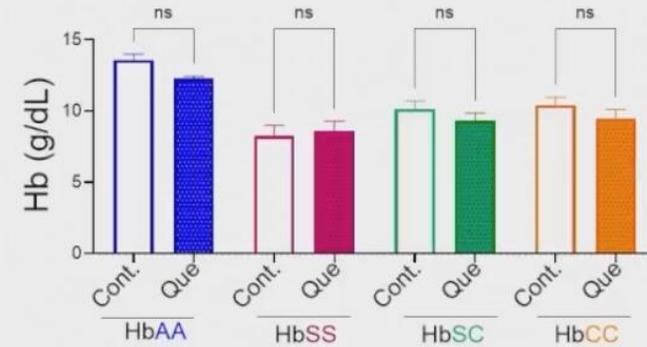
ROS

# Résultats

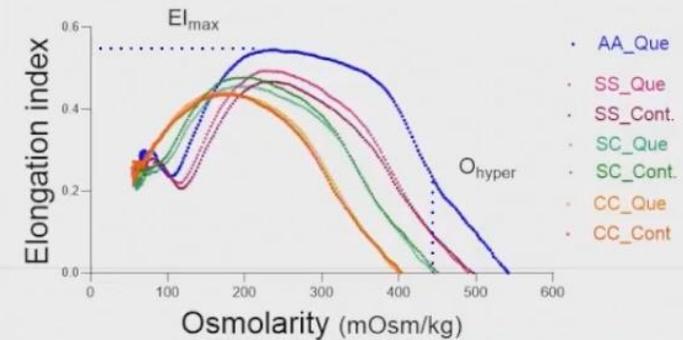
Quercetin improves membrane mechanics *without* altering RBC count, Hb, or hydration



Quercetin (Que) did not improve RBC count, hemoglobin concentration or cell Volume.

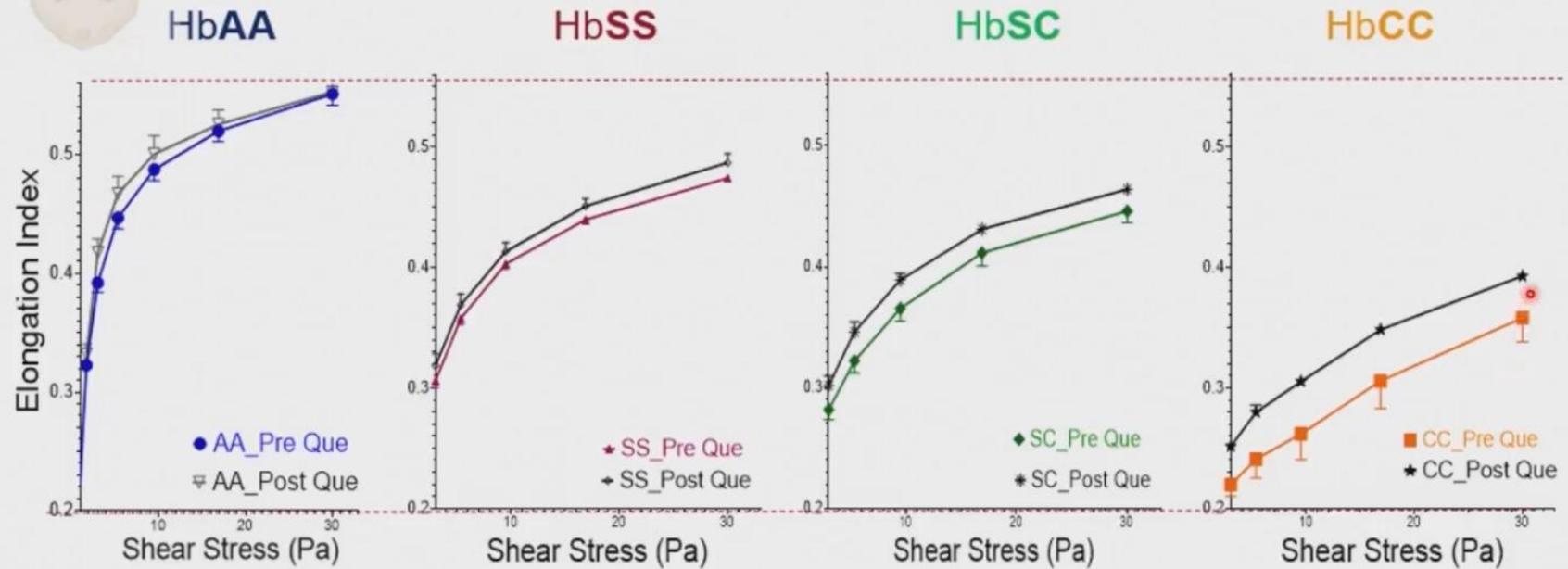


Quercetin (Que) did not improve RBC dehydration.



# Résultats

Antioxidant therapy improves membrane deformability in HbC-containing RBCs





# Conclusion

- ▶ Rôle majeur du stress oxydatif induit par l'hémoglobine C dans la physiopathologie de la drépanocytose SC : lésions membranaires des globules rouges, dysfonction biomécanique.
- ▶ HU : effet protecteur sur la membrane des globules rouges : réduction du stress oxydatif sans nécessité d'induire l'HbF
- ▶ Quercétine : améliore la déformabilité des membranes des GR soumis à un stress oxydatif, sans modifier le nombre de GR ni leur hydratation.
- ▶ Le modèle murin humanisé HbSC développé est une avancée majeure pour étudier ces mécanismes et tester de nouvelles approches.



Merci de votre attention

