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Bridging Gaps and Advancing Care in Sickle Cell Disease in the Context of Drug Therapy

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Learning Objective 1

Identify the importance of comprehensive team-based therapeutic and supportive care in preventing end-organ damage and improving QoL in patients with SCD.

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Learning Objective 2

Assess the effectiveness and challenges of current therapies to address the burden of disease in patients with SCD.

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Learning Objective 3

Evaluate future directions in SCD treatment including combination therapies, long-term efficacy and safety studies of new interventions, and investigational agents.

Existing Unmet Needs in SCD Care: Beyond Pain Crisis

Maya Bloomberg, MSN, APRN

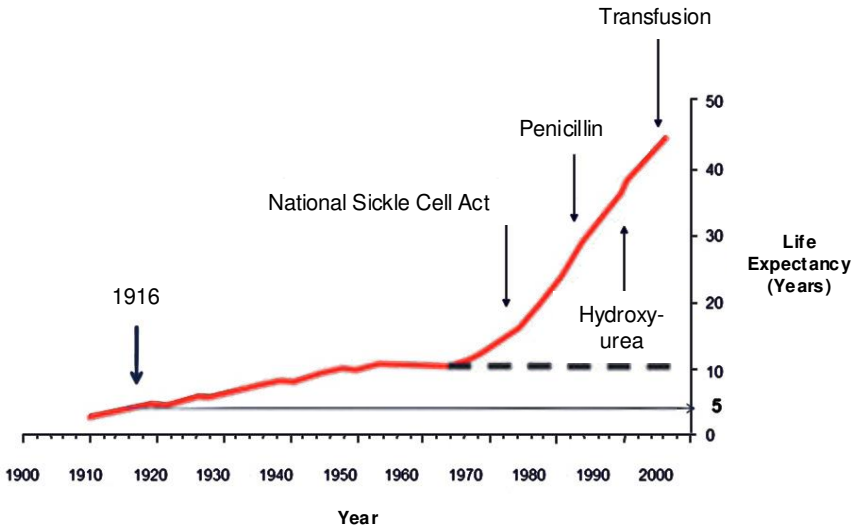
ARS Question

What measure beyond acute pain crisis do you consider most important when determining severity of SCD?

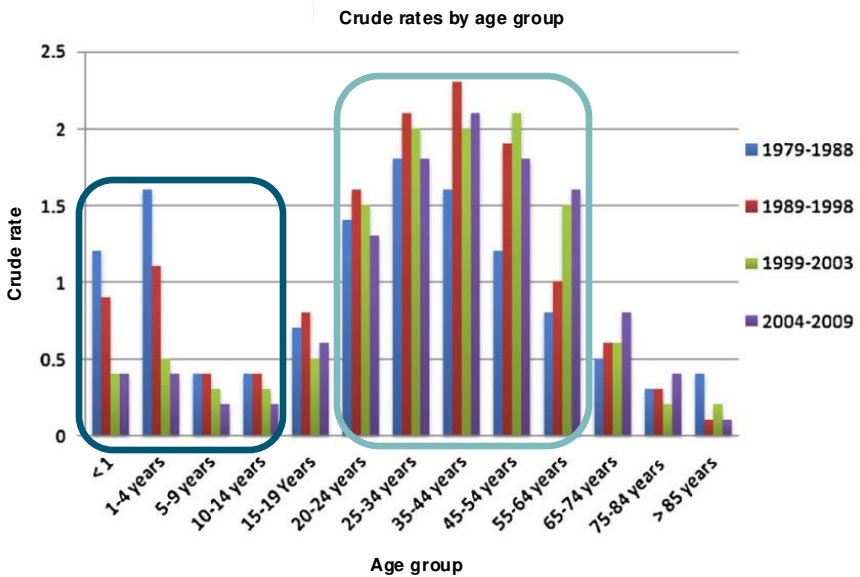
A. Frequency of acute care visits
B. Patient quality of life
C. End-organ damage
D. Chronic pain

Morbidity & Mortality of SCD

- ≥ 95% of **children** with SCD expected to **survive into adulthood** in high-resource countries
- **Median survival of 48 years** adjusting for left truncation bias (42 & 48 years for men & women in 1994)



Wailoo K, et al.

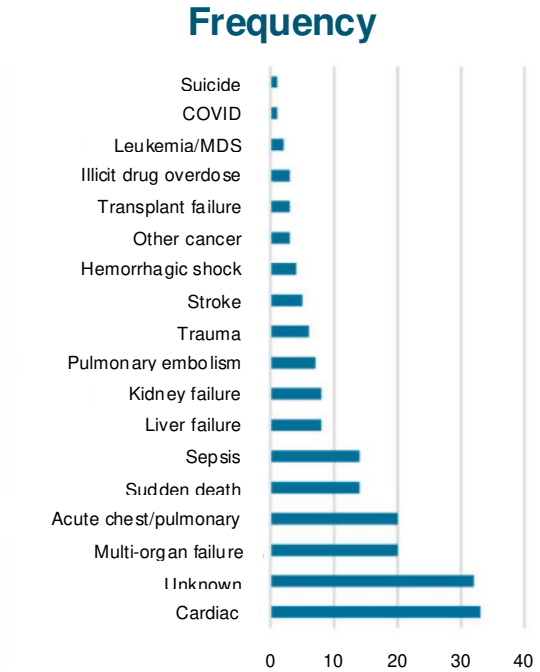


Hamideh D, et al.

Telfer P, et al. *Haematologica.* 2007;92(7):905-912. Quinn CT, et al. *Blood.* 2010;115(17):3447-3452. Couque N, et al. *Br J Haematol.* 2016;173(6):927-937. Platt O, et al. *N Engl J Med.* 1994;330(23):1639-1644. DeBaun MR, et al. *Blood.* 2019;133(6):615-617. Wailoo K, et al. *N Engl J Med.* 2017;376(9):805-807. Hamideh D, et al. *Pedate Blood Cancer.* 2013;60(9):1482-1486.

Causes of Mortality in SCD: SCDIC Registry

Complications Associated With Death

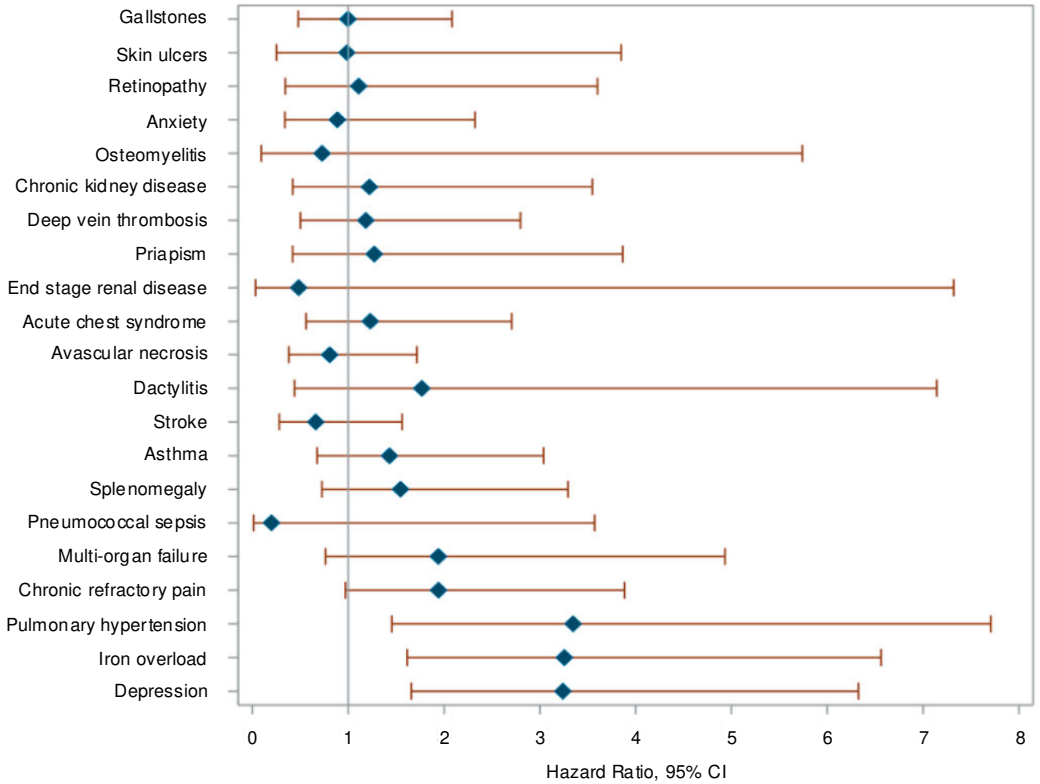


Patients age 25 to 34 with **two or more** SCD-related complications were **more likely to die** than those with one or less SCD-related complications

SCDIC = Sickle Cell Disease Implementation Consortium; MDS = myelodysplastic syndrome.

Njoku F, et al. *Am J Hematol.* 2024;99(5):900-909.

Association Between Comorbid Conditions and Death: SCDIC Registry



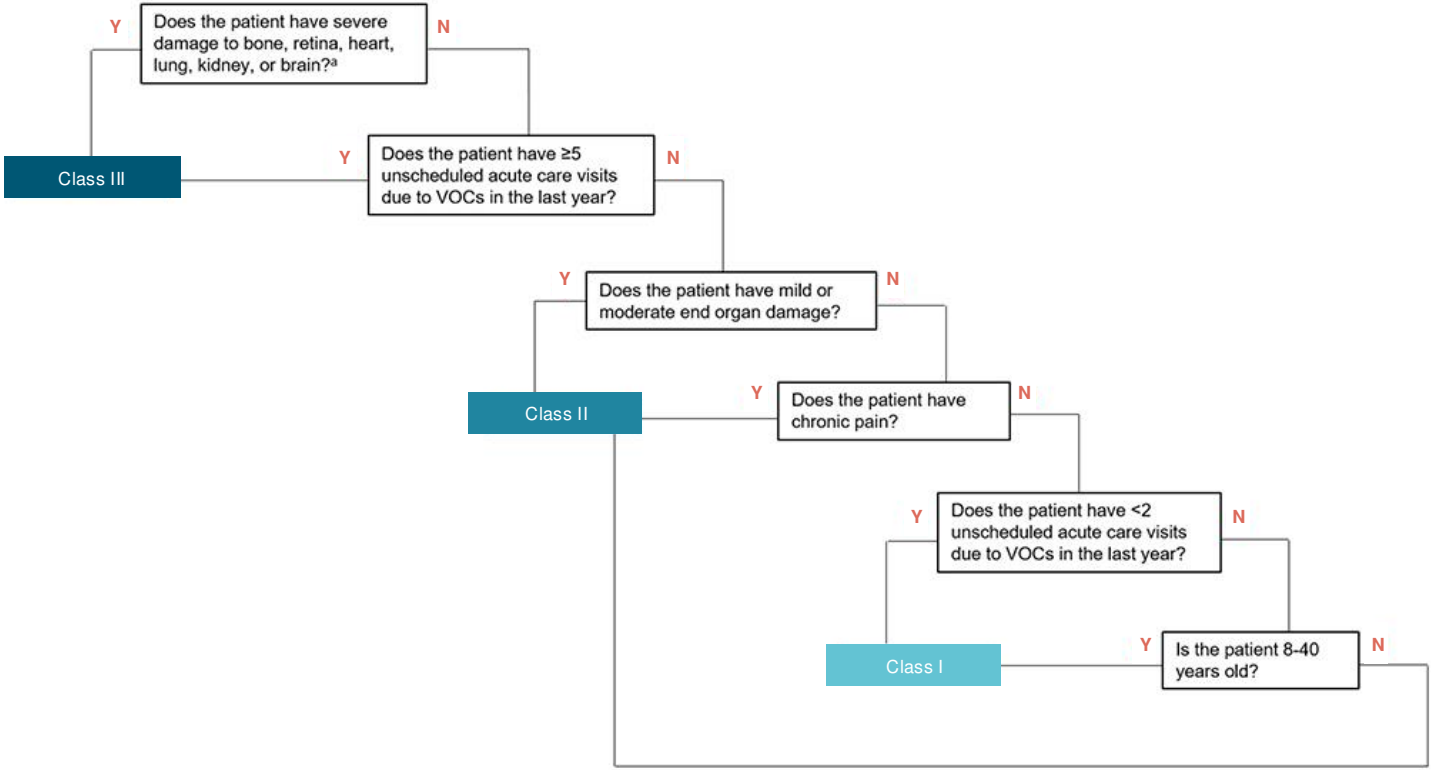
Njoku F, et al. *Am J Hematol.* 2024;99(5):900-909.

Severity in SCD: More Than Just Pain

- Number of **painful episodes** and **frequency** of acute care visits for VOC are both key measures for assessing severity of SCD
- Other **measures**, including organ damage, patient QoL, and type of pain (acute vs chronic) are also **important to consider**

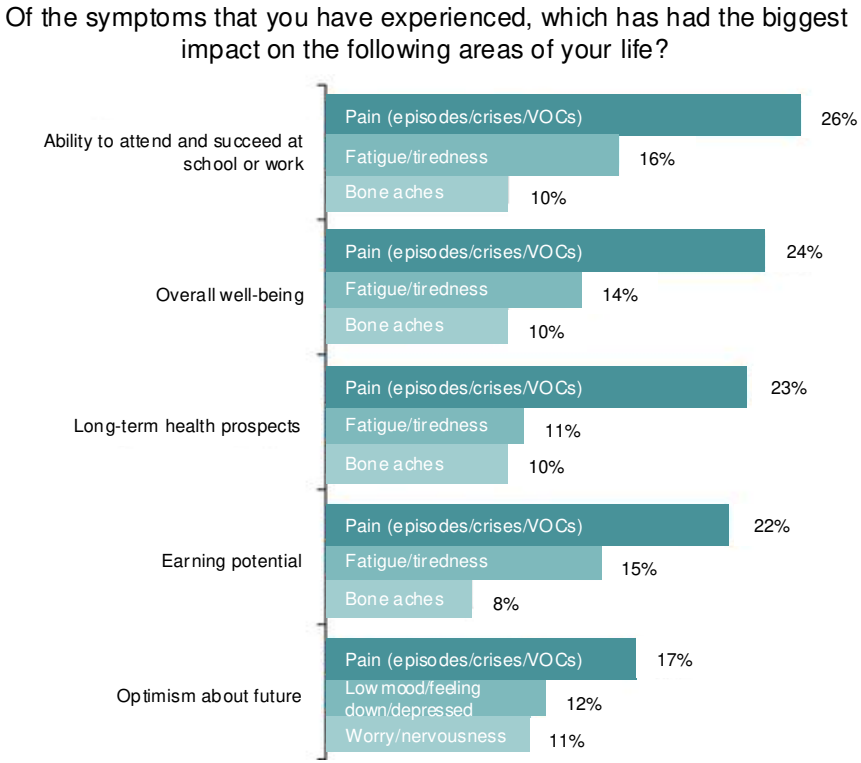
VOC = vaso-occlusive crisis; QoL = quality of life.
Shah N, et al. *Clinicoecon Outcomes Res.* 2020;12:625-633.

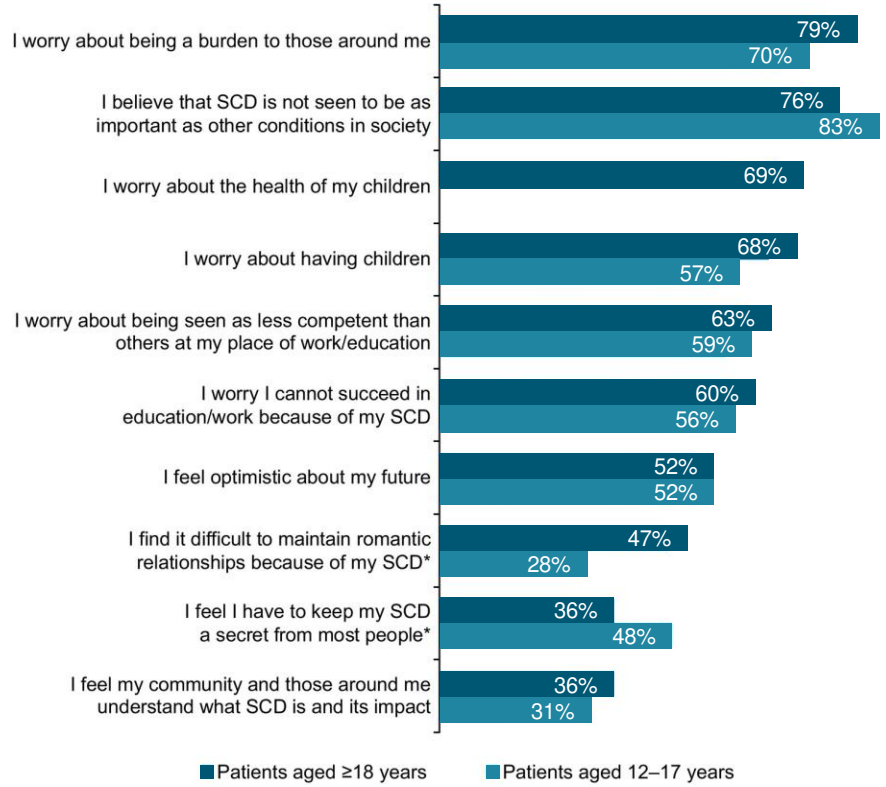
A Model for Classifying Disease Severity in SCD



Shah N, et al. *Clinicoecon Outcomes Res.* 2020;12:625-633.

SHAPE Survey of Patients Living with SCD





SHAPE = Sickle Cell Health Awareness, Perspectives, and Experiences.
De Montalembert M, et al. *Eur J Hematol.* 2024;113(2):172-182.

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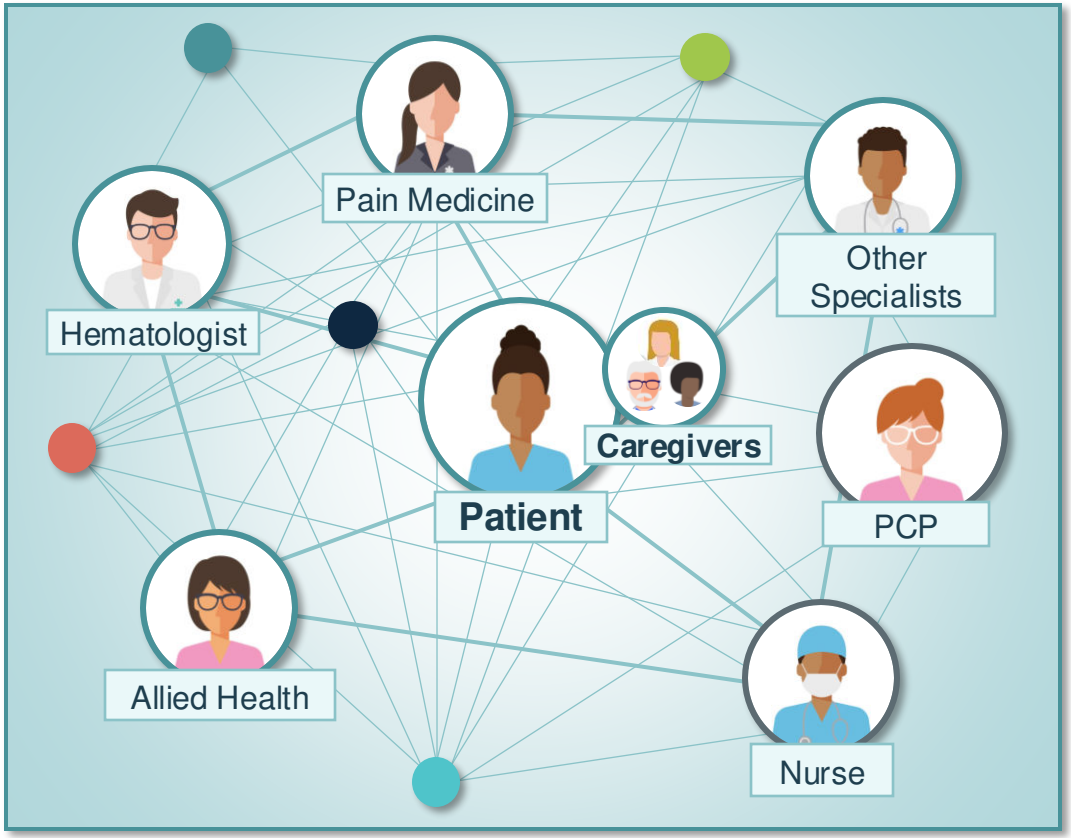
Importance of a Team-Based Approach to SCD



Patient Story:

How does SCD impact patients?

Faculty Discussion

Where Are We Now? Treatment of SCD

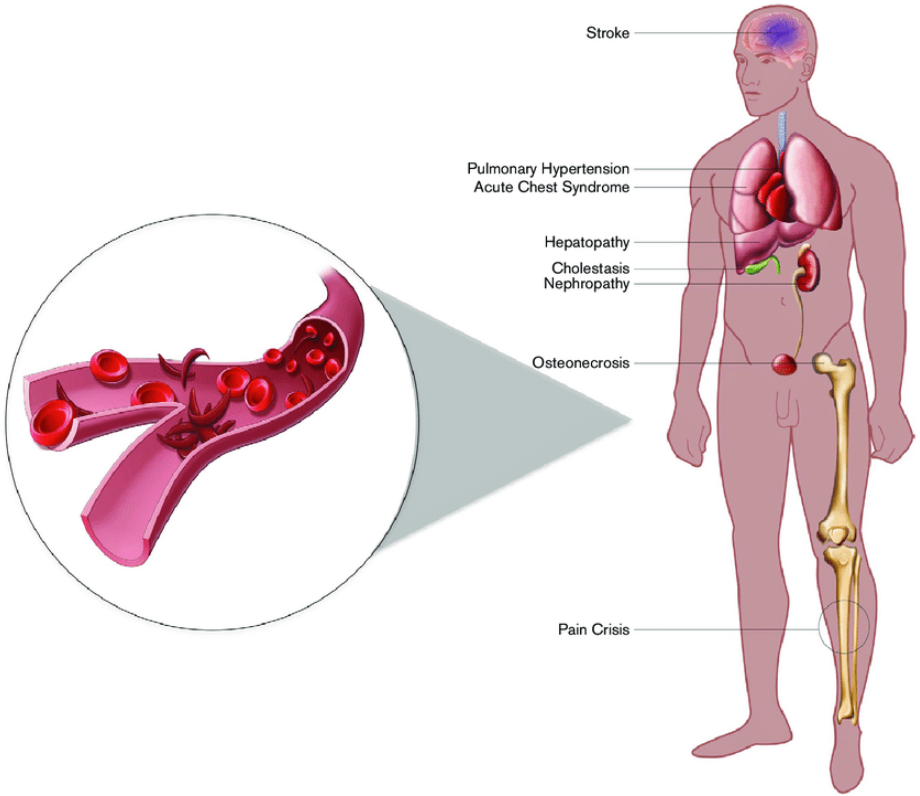
Laura M. De Castro, MD, MHSc

ARS Question

Of the 5 American Society of Hematology (ASH) Treatment Guidelines for SCD, which do you reference most often in your clinical practice?

A. Acute and chronic pain management
B. Cardiopulmonary and kidney disease
C. Cerebrovascular disease
D. Stem cell transplantation
E. Transfusion support

Multi-Organ Complications of SCD



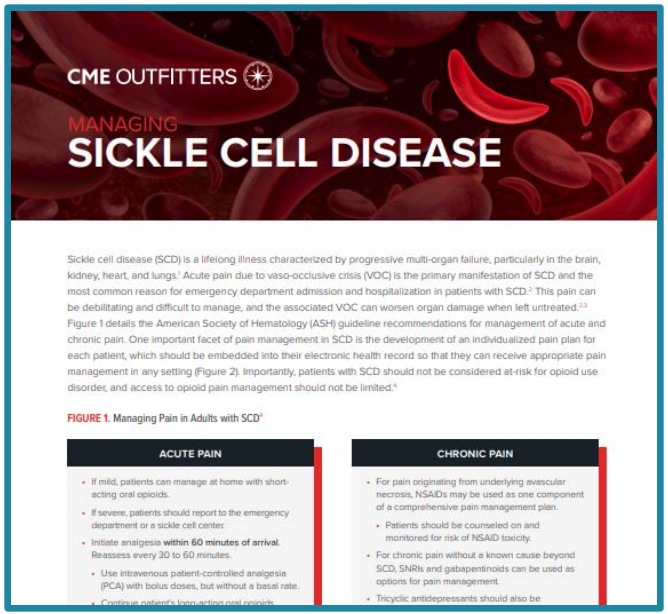
Much of SCD treatment focuses on managing **pain** and addressing **complications** associated with end-organ damage

Hosoya H, et al. *Blood Adv.* 2018;2(5):575-585.

ASH Treatment Guidelines

- ASH has released several treatment guidelines for SCD
  - Cardiopulmonary and kidney disease
  - Transfusion support
  - Cerebrovascular disease
  - Management of acute and chronic pain
  - Stem cell transplantation
- Full guidelines are available at hematology.org

CMEO Point-of-Care Toolkit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MANAGING
SICKLE CELL DISEASE

Sickle cell disease (SCD) is a lifelong illness characterized by progressive multi-organ failure, particularly in the brain, kidney, heart, and lungs.[1] Acute pain due to vaso-occlusive crisis (VOC) is the primary manifestation of SCD and the most common reason for emergency department admission and hospitalization in patients with SCD.[2] This pain can be debilitating and difficult to manage, and the associated VOC can worsen organ damage when left untreated.[2,3] Figure 1 details the American Society of Hematology (ASH) guideline recommendations for management of acute and chronic pain. One important facet of pain management in SCD is the development of an individualized pain plan for each patient, which should be embedded into their electronic health record so that they can receive appropriate pain management in any setting (Figure 2). Importantly, patients with SCD should not be considered at-risk for opioid use disorder, and access to opioid pain management should not be limited.[4]

FIGURE 1. Managing Pain in Adults with SCD[2]

ACUTE PAIN

- If mild, patients can manage at home with short-acting oral opioids.
- If severe, patients should report to the emergency department or a sickle cell center.
- Initiate analgesia **within 60 minutes of arrival.** Reassess every 30 to 60 minutes.
  - Use intravenous patient-controlled analgesia (PCA) with bolus doses, but without a basal rate.
- Continue patient's long-acting oral opioids.

CHRONIC PAIN

- For pain originating from underlying avascular necrosis, NSAIDs may be used as one component of a comprehensive pain management plan.
  - Patients should be counseled on and monitored for risk of NSAID toxicity.
- For chronic pain without a known cause beyond SCD, SNRIs and gabapentinoids can be used as options for pain management.
- Tricyclic antidepressants should also be

ASH. https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/sickle-cell-disease-guidelines.

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Primary Pharmacotherapy for SCD

Drug	Mechanism	Clinical effect
Hydroxyurea	Stimulation of HbF production	Reduced frequency of VOC
L-glutamine	Mechanism unclear but uptake is increased in sickle cells and may reduce adherence of sickle cells to endothelium	Reduced frequency of VOC
Crizanlizumab	Humanized monoclonal antibody to P-selectin; inhibits adherence of sickle cells and development of VOCs	Reduced frequency of VOC
Voxelotor	Inhibitor of HbS polymerization by reversibly binding hemoglobin and stabilizing its oxygenated state	Increased hemoglobin levels and reduced hemolysis

Hydroxyurea, L-glutamine, and crizanlizumab are approved for prevention of VOC and disease complications in adult and pediatric patients with SCD. The indication for voxelotor in SCD has been withdrawn by the manufacturer.

HbF = fetal hemoglobin; HbS = sickle cell hemoglobin.

Tang MS, et al. *Vox Sang.* 2024;119(6):521-528.

Primary Pharmacotherapy for SCD

Drug	Mechanism	Clinical effect
Hydroxyurea		duced frequency of VOC
L-glutamine	Mecha sick	duced frequency of VOC
Crizanlizumab	Huma inhibit develop	Reduced frequency of VOC
Voxelotor	Inhibitor of HbS polymerization by reversibly binding hemoglobin and stabilizing its oxygenated state	Increased hemoglobin levels and reduced hemolysis

In September 2024, voxelotor was voluntarily withdrawn from the market by the manufacturer due to safety concerns that arose during post-marketing trials.

The indication for voxelotor in SCD has been withdrawn by the manufacturer.

U.S. Food and Drug Administration [FDA]. 2024. https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerting-patients-and-health-care-professionals-about-voluntary-withdrawal-oxbryta-market-due.

Curative Therapies: Allogeneic HSCT*

2,853 SCD recipients HLA & haplo-matched donors (up to 11/2019)

- All patients: **96% OS, 95% stable engraftment; 20% aGVHD, 10% cGVHD**
- Adults (n = 88): **98% OS, 86% stable engraftment; 7% aGVHD, 1% cGVHD**

Regimen Type	aGVHD (≥ Gr 2)	cGVHD	Stable Engraftment	Overall Survival
HLA-Matched/Myeloablative	12%	20%	91%	91%
HLA-Matched/Non-Myeloablative	4%	0%	87%	93%
Haploidentical/Reduced Intensity	10%	10%	89%	94%

*Common indications = stroke, recurrent VOC, or acute chest syndrome despite hydroxyurea (high-risk SCD).

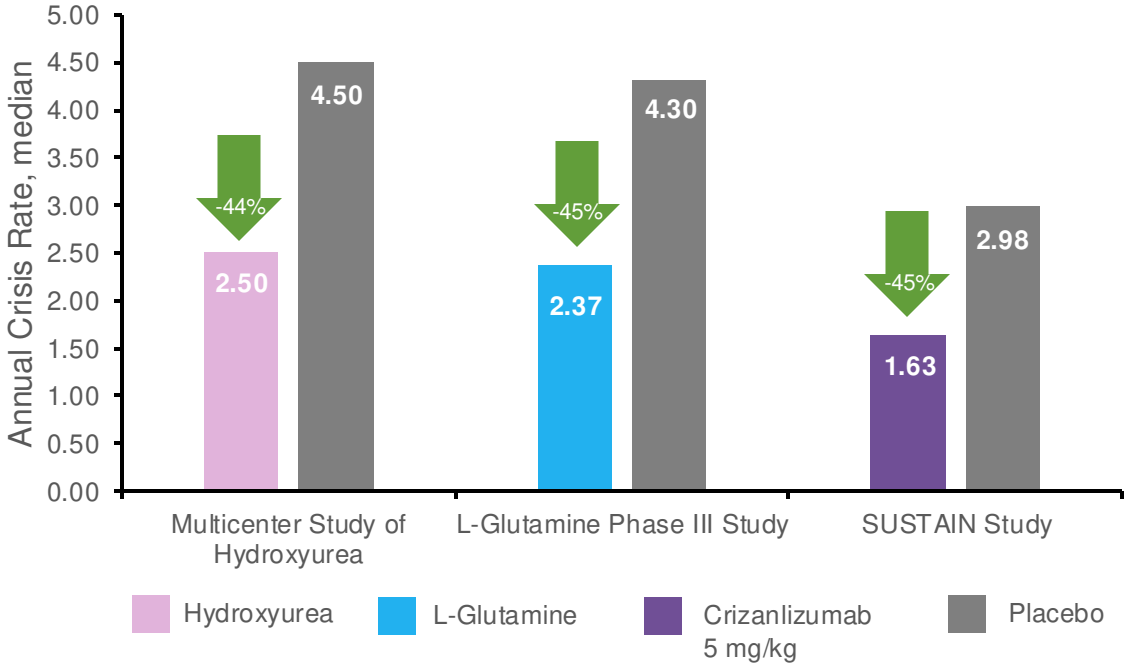
HLA = human leukocyte antigen; OS = overall survival; aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease.

Iqbal M, et al. *Transplant Cell Ther.* 2021;27(2):167-e1. Eapen M, et al. *Lancet Haematol.* 2019;6(11):e585-e596. Alzahrani M, et al. *Br J Haematol.* 2021;192(4):761-768. Kassim AA, et al. *Blood.* 2024;143(25):2654-2665.

Treatment Sequencing in SCD

1. Hydroxyurea
2. Optimize hydroxyurea dose
3. + L-glutamine (oral) or crizanlizumab (IV infusion)

- Clinical trial
- Allogeneic hematopoietic stem cell transplantation (HSCT)
- Gene therapy?



Hydroxyurea, L-glutamine, and crizanlizumab are approved for prevention of VOC and disease complications in adult and pediatric patients with SCD.

Zaidi AU, et al. *Contemp Clin Trials.* 2021;110:106546.

Various Treatment Challenges in SCD

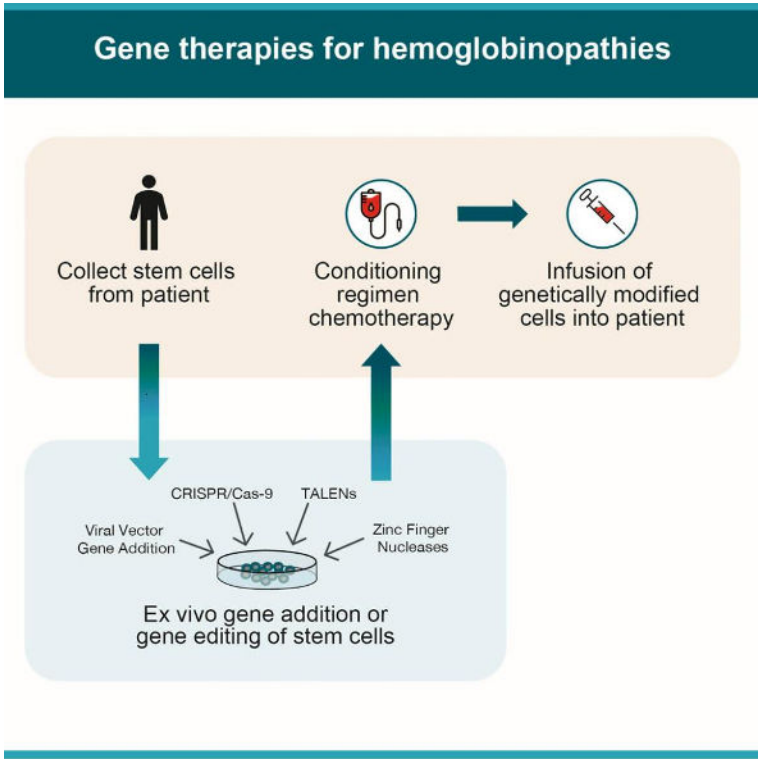
- **Limited access to curative therapies**
  - HSCT: limited by donor availability
  - Gene therapy: limited by cost, distance to a center, insurance
- **Underutilization of disease-modifying treatments**
  - Variations in access to care by location, age, gender
  - Prior authorization
  - Patient fear/mistrust of treatments
- **Social drivers of health**
  - Ability to afford treatment
  - Access to transportation
  - Provider bias/ assumptions
- **Specific agent-related challenges**
  - Hydroxyurea: high discontinuation rates and questions about efficacy
  - Crizanlizumab: mixed results in clinical settings; side effects

Lee LT, et al. *Public Health Rep.* 2019;134(6):599-607. Alan S, et al. *Ann Blood.* 2024;9.

Moving to Long-Term Disease Management in SCD

Santosh L. Saraf, MD

Newly Approved Treatment Approach: Gene Therapy

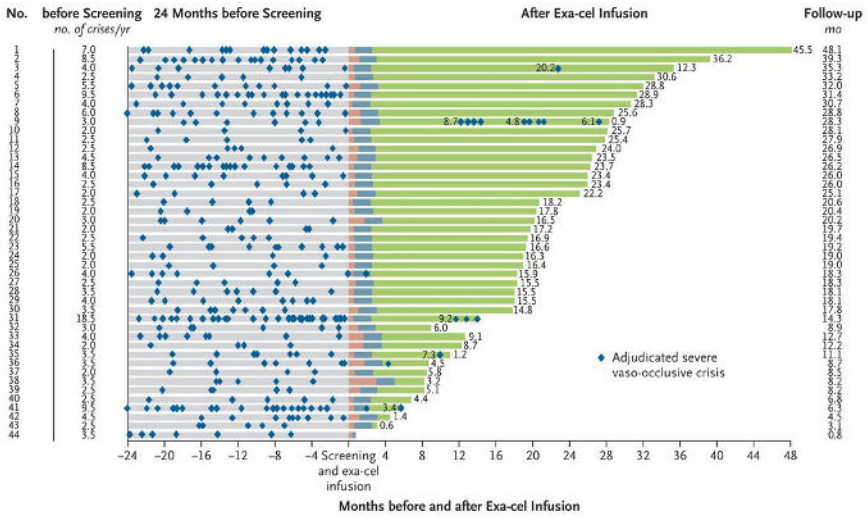


- Two approved gene therapies for SCD in patients age ≥ 12 with VOC
  - **Exagamglogene autotemcel:** CRISPR gene editing to increase production of fetal hemoglobin
  - **Lovotibeglogene autotemcel:** Lentiviral vector introduces modified β-globin gene to replace mutated β-globin gene
- Major benefit: potentially curative
- Challenges: difficult to access, expensive

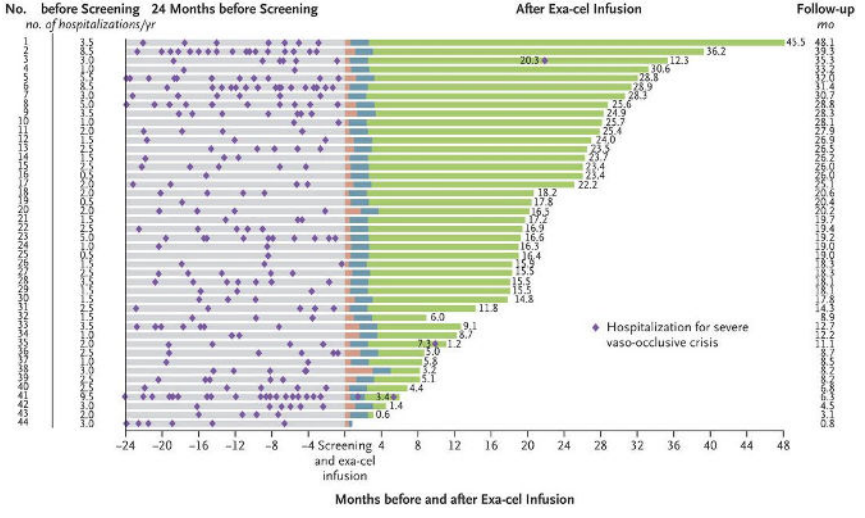
CRISPR = clustered regularly interspaced short palindromic repeats.
Locatelli F, et al. *Mol Ther.* 2024;32(5):1202-1218.

Exagamglogene Autotemcel (Exa-cel) Phase III Trial: Vaso-Occlusive Crisis

Freedom from Severe VOC



Freedom from Hospitalization for Severe VOC



Exa-cel is FDA approved for the treatment of SCD in patients age ≥ 12 with recurrent vaso-occlusive crises.

Frangoul H, et al. *N Engl J Med.* 2024;390:1649-1662.

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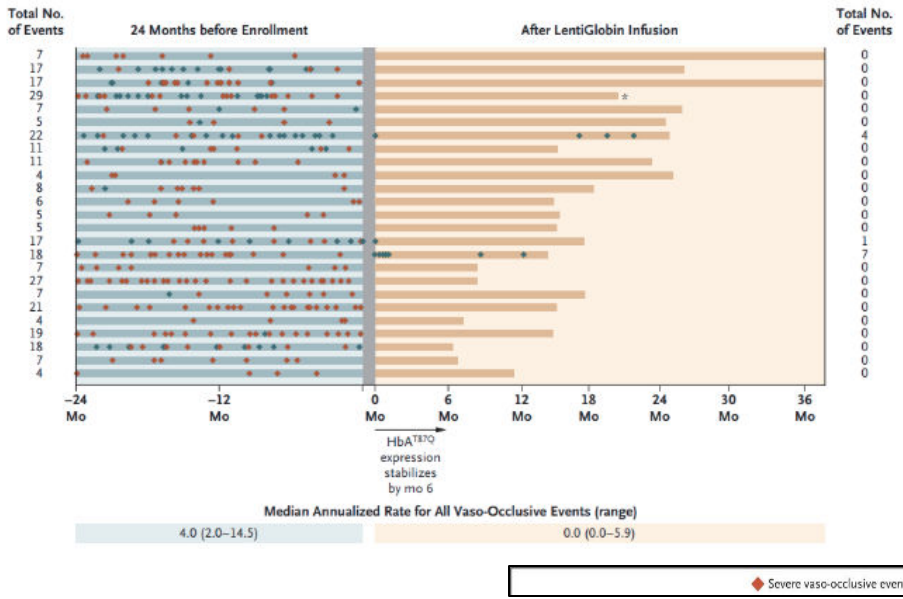
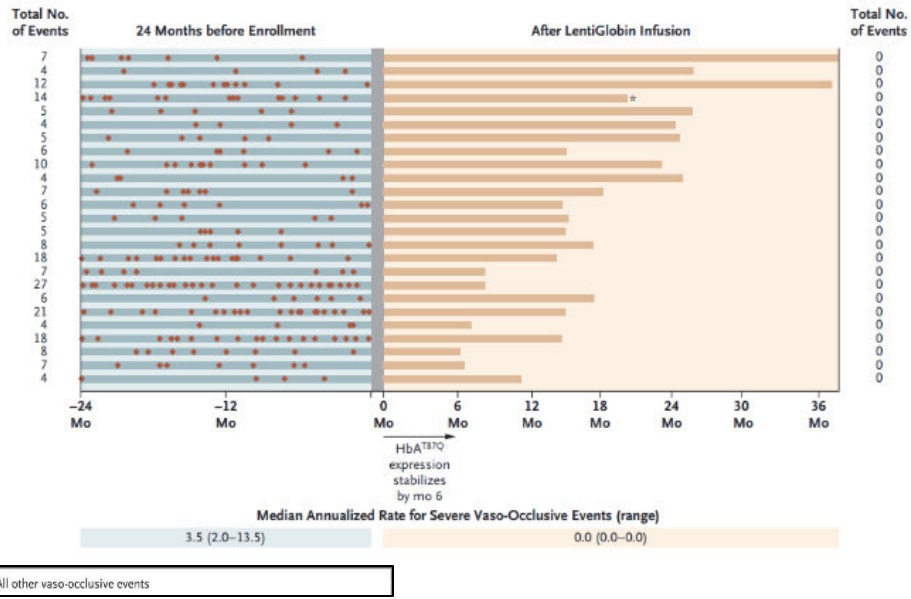
Lovotibeglogene Autotemcel (Lovo-cel) Phase I/II Trial: Vaso-Occlusive Events (VOEs)

All VOEs



Severe VOEs



Lovo-cel is FDA approved for the treatment of SCD in in patients age ≥ 12 with a history of vaso-occlusive events.

Kanter J, et al. *N Engl J Med.* 2022;386:617-628.

ARS Question

Which of these investigational approaches to SCD treatment do you find most interesting?

A. HbF inducers (decitabine/THU, pociredir)
B. Pyruvate kinase activators (etavopivat, mitapivat)
C. HbS-oxygen stabilizers (osivelotir)
D. Downstream targets such as arginine and hemopexin
E. I am not familiar with these treatments

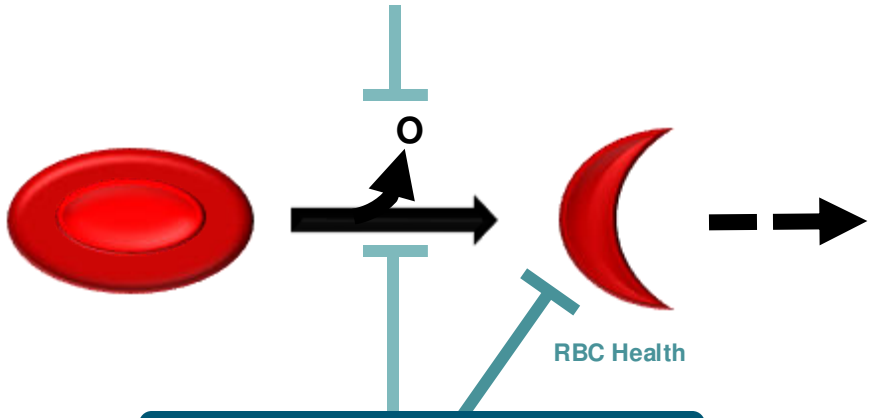
Investigational Therapeutic Targets in SCD

HbS-Oxygen Stabilizers

- Osivelotir

HbS → HbF

- Decitabine + THU
- Pociredir



Downstream Targets

- Selectin inhibitors
- Arginine
- Riociguat
- Citrulline
- Hemopexin
- Anti-C5 (crovalimab)
- rADAMTS13
- ω-3 fatty acids (epileuton)
- Anti-IL6 (tocilizumab)

Pyruvate Kinase Activators

- Mitapivat
- Etavopivat

These agents are **investigational** and **not approved** by the FDA.

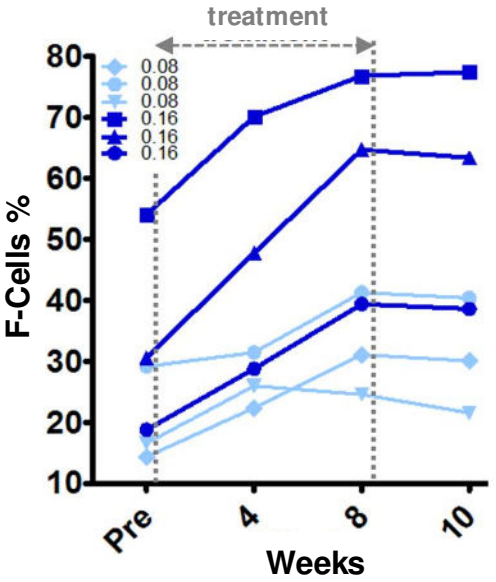
RBC = red blood cell.

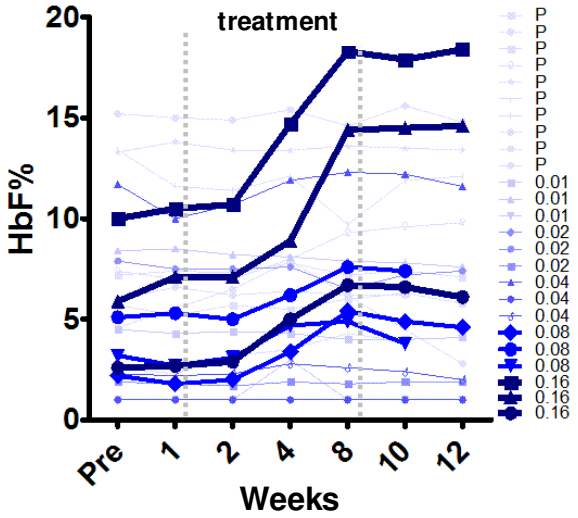
Gibson JS, et al. *Expert Opin Ther Targets.* 2023;27(2):133-149.

HbF Inducers: Decitabine/THU

Phase I Study of Decitabine/THU in Patients with SCD

- 5 adults with SCD per dose level (3 treatment, 2 placebo)
  - Median age: 34 (23-56) years
  - 21/25 were female
- Treated 2x/week for 8 weeks





Decitabine is not currently FDA approved for SCD.

F-cells are defined as the proportion of RBCs producing high levels of HbF.

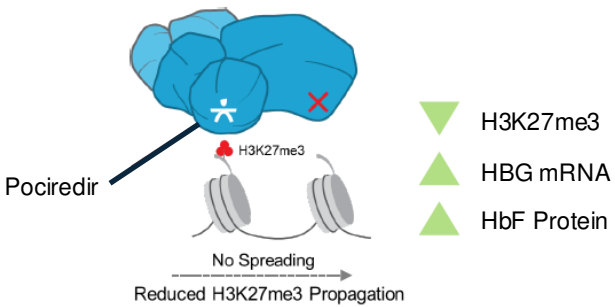
Molokie R, et al. *PLoS Med.* 2017;14(9):e1002382.

HbF Inducers: Pociredir

Oral small molecular inhibitor of embryonic ectoderm development protein

- ↓ Polycomb repressor complex 2 (PRC2)
- ↓ Histone methylation used to transcriptionally silence chromatin

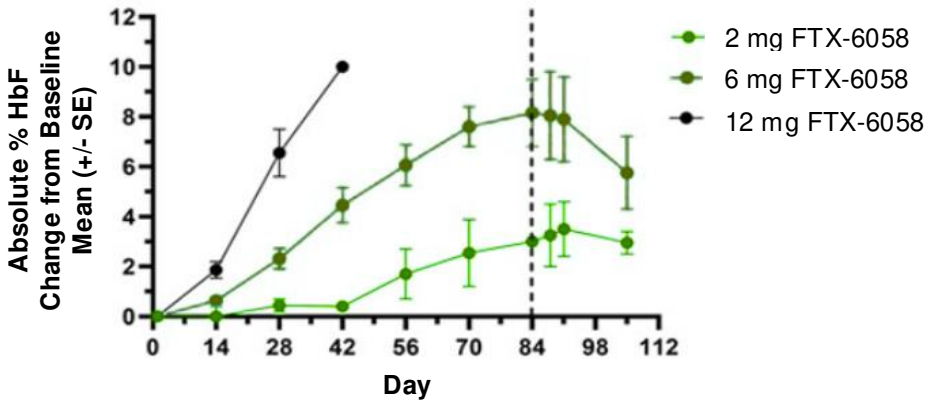
Pociredir Inhibits the PRC2 Complex and Induces HbF Expression



Pociredir Phase Ib Study Design

(dose escalation with 10 patients per cohort)

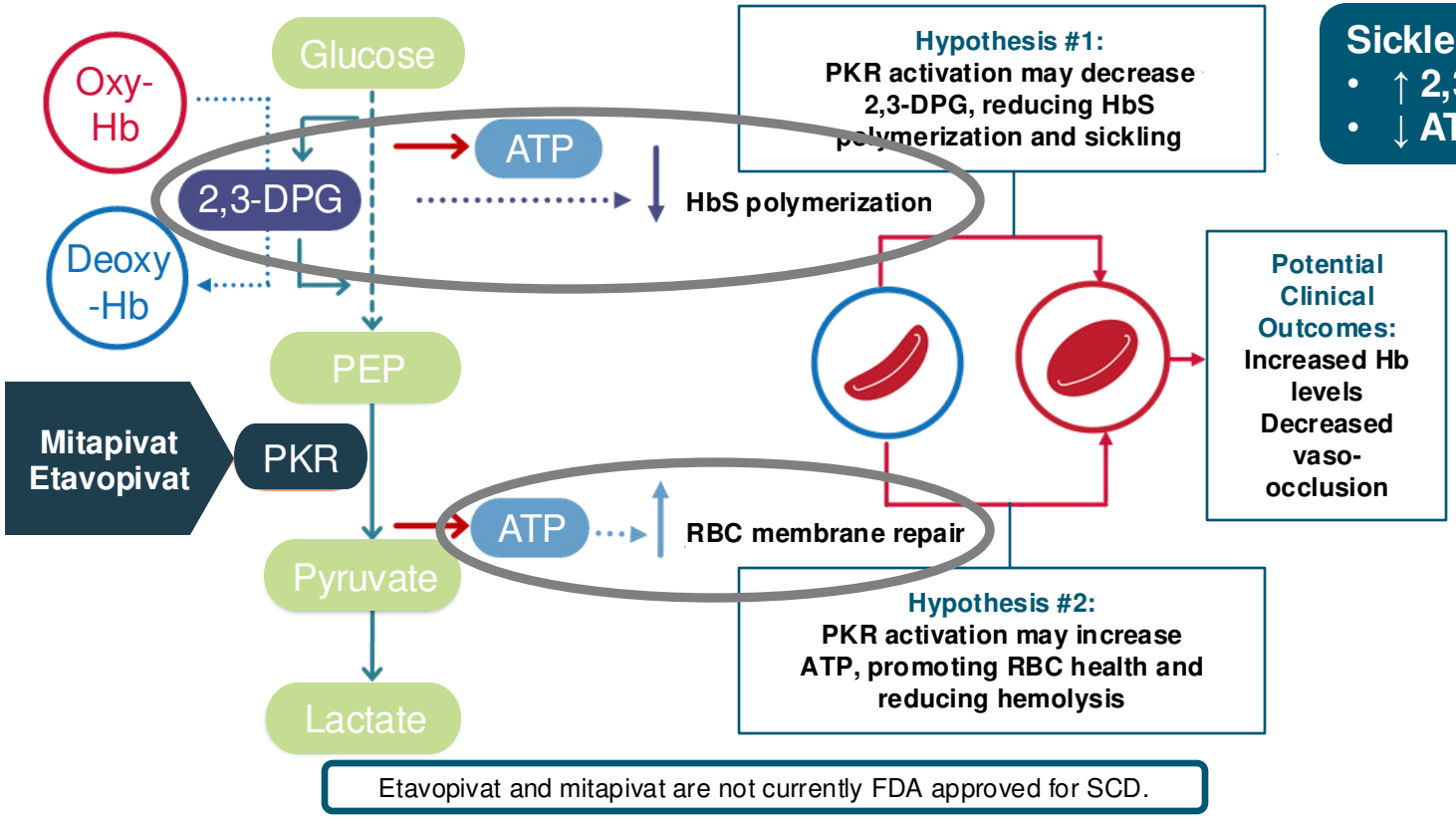
Screening Period	Treatment Period (once daily capsule)	Follow-up Period
4 Weeks (Day -28 to Day -1)	12 Weeks (Day 1 to Day 84)	4 Weeks (Day 85 to Day 112)* **+3-day visit window*



Pociredir is not currently FDA approved for SCD.

Minniti C, et al. European Hematology Association Congress; 2024. Abstract No. S294. https://library.ehaweb.org/eha/2024/eha2024-congress/422398/caterina.minniti.interim.results.of.a.phase.1b.study.28pioneer29.of.an.oral.hbf.html.

Pyruvate Kinase (PK) Activators (Etavopivat, Mitapivat)



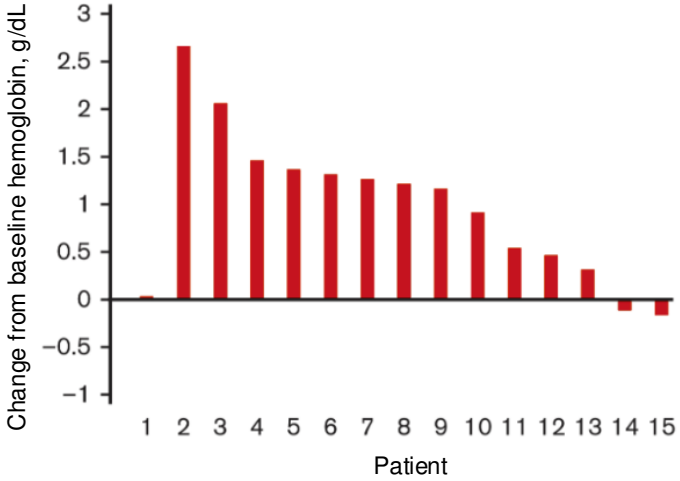
DPG = diphosphoglycerate; PEP = phosphoenolpyruvate; PKR = pyruvate kinase receptor; ATP = adenosine triphosphate.

Glenthoj A. *Haematologica*. 2024;109(8):2398-2400.

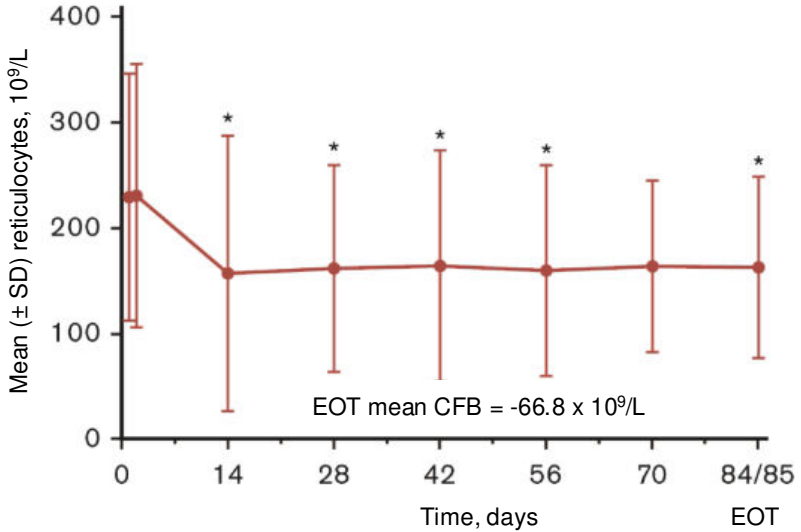
PK Activators: Etavopivat Impact on Hemolytic Anemia

Etavopivat Phase I

↑ Hgb



↓ Retic



Etavopivat is not currently FDA approved for SCD.

Hgb = hemoglobin; EOT = end of treatment; CFB = change from baseline.
Saraf SL, et al. *Blood Adv.* 2024;8(16):4459-4475.

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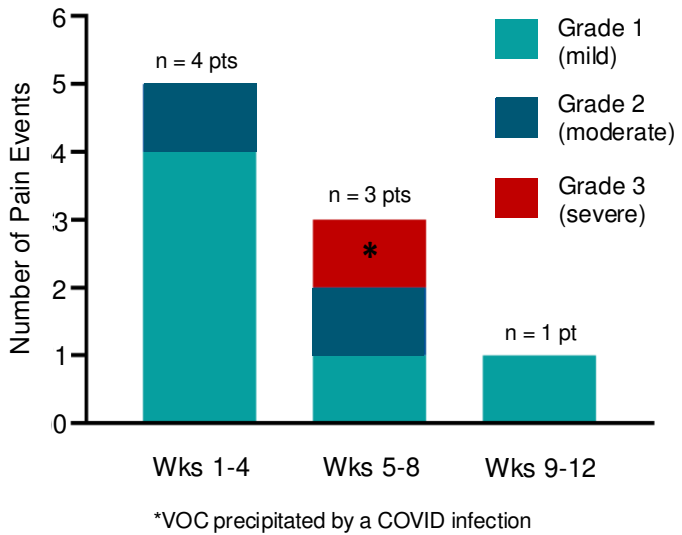
PK Activators: Etavopivat Impact on VOC

Etavopivat Phase I[1]



*VOC precipitated by a COVID infection

Etavopivat is not currently FDA approved for SCD.

Etavopivat Phase II/III HIBISCUS Trial VOC Outcomes vs Placebo:[2]

- 46% reduction in annualized VOC rate in ITT group (non-significant)
- Significant improvement in annualized VOC rate in per-protocol group**
  - (0.66 in 200 mg cohort vs 1.77 with placebo)
- Increased length of time to first VOC (34 weeks vs 17 weeks)

**Per-protocol group defined as ≥ 80% protocol compliance and completion of the double-blind period with no major protocol deviations

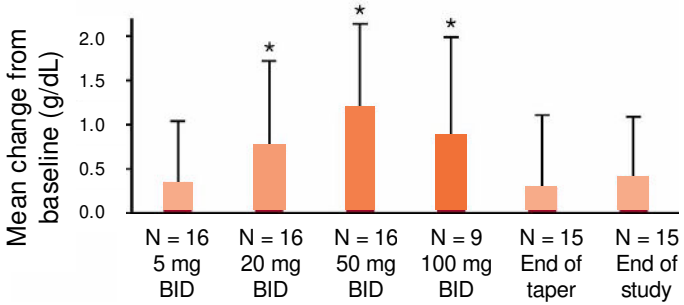
1. Saraf SL, et al. *Blood Adv*. 2024;8(16):4459-4475. 2. Delicou S, et al. 66th Annual ASH Meeting and Exposition; 2024. Abstract No. 179. https://ash.confex.com/ash/2024/webprogram/Paper204962.html.

PK Activators: Mitapivat Impact on Hemolytic Anemia

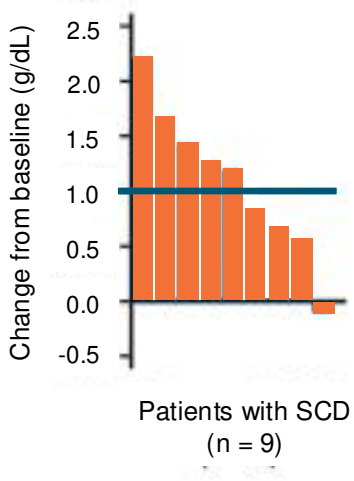
Mitapivat

↑ Hgb

Phase I

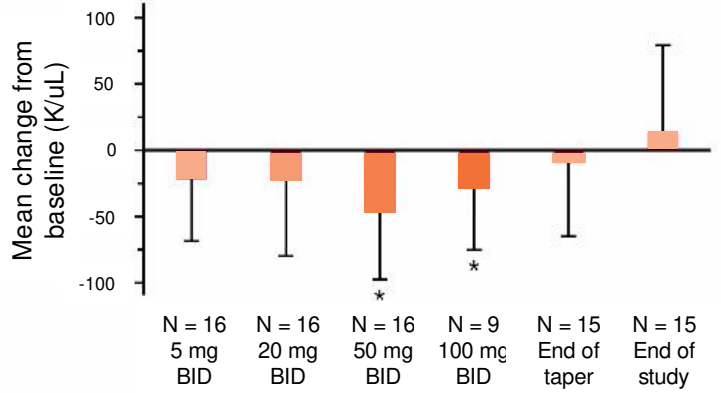


Phase II



↓ Retic

Phase I



Mitapivat is not currently FDA approved for SCD.

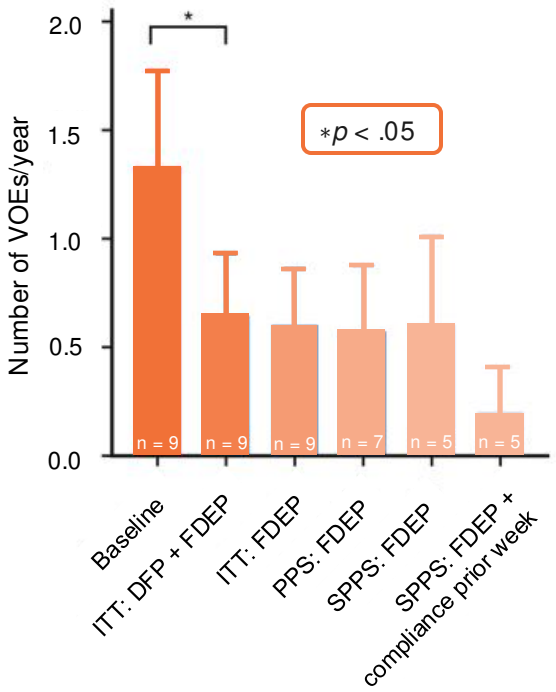
BID = twice daily.

Xu JZ, et al. *Blood.* 140(19):2053-2062. van Dijk MJ, et al. *Blood Adv.* 2023;7(24):7539-7550.

CME OUTFITTERS

PK Activators: Mitapivat Impact on VOC

Phase II

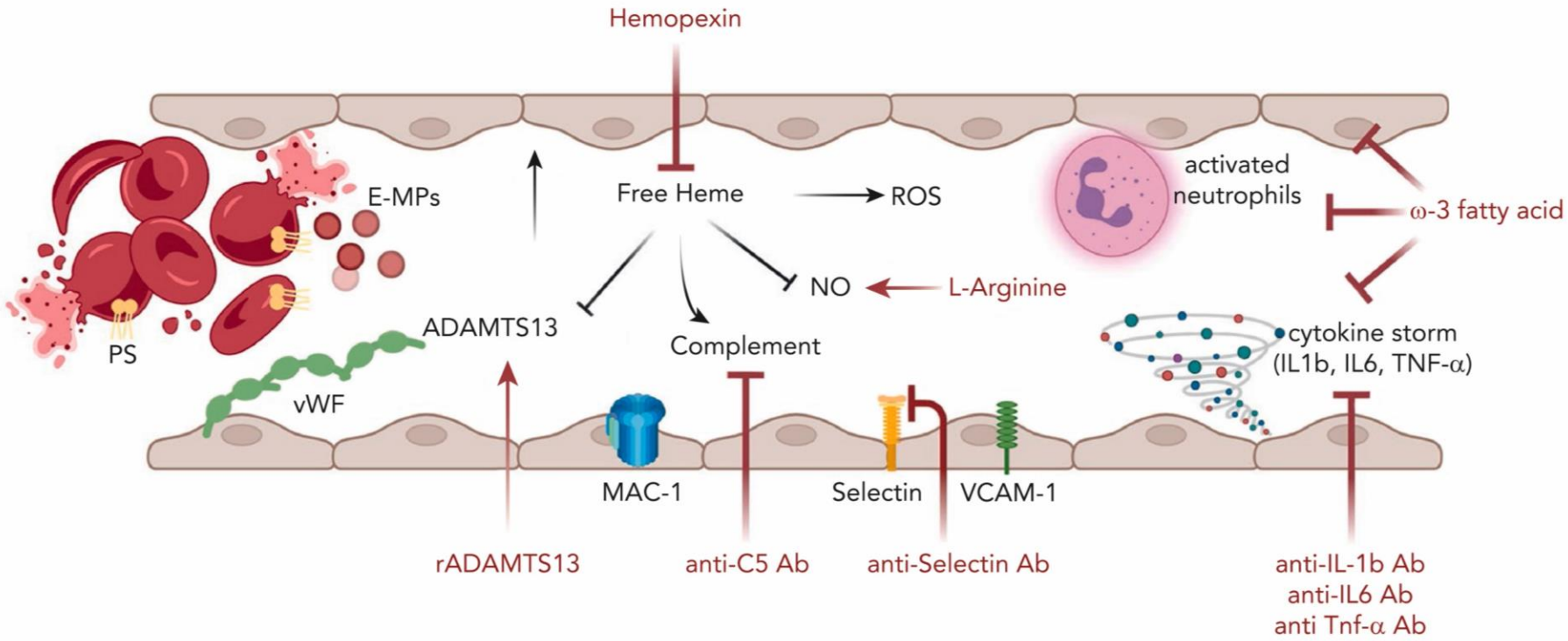


Mitapivat is not currently FDA approved for SCD.

DFP = dose-finding period; FDEP = fixed-dose extension period; ITT = intention to treat; PPS = per-protocol set; SPPS = strict per-protocol set.

van Dijk MJ, et al. *Blood Adv.* 2023;7(24):7539-7550.

Downstream Targets



Pinto VM, et al. *Blood.* 2024;144(8):853-866.

Key Ongoing Studies in SCD

Mechanism	Agent	NCT & Study Population	Phase & Primary End Points
Pyruvate Kinase Activators	Mitapivat	• RISE UP; NCT 05031780 • RESIST; NCT06286046	• Phase II/III; Δ Hgb & VOE • Phase II, open-label; % patients ↓ uACR by 30%
	Etavopivat	• HIBISCUS; NCT04624659 • HIBISCUS-2; NCT04624659	• Phase II/III; Δ Hgb & VOE • Phase III; Δ VOE, 6-minute walk, PROMIS fatigue
HbF Inducers	Decitabine/THU	• ASCENT-1; NCT05405114	• Phase II; Δ Hgb
	Pociredir	• FTX-6058; NCT05169580	• Phase I; Safety, tolerability, PK/PD
HbS Stabilizer	Osivelotor	• NCT05431088	• Phase II/III; Δ Hgb & VOE
Increase Nitric Oxide Pathway	L-Arginine	• STArT; NCT04839354	• Phase III; Δ Time time-to-crisis resolution
	Citrulline	• CONQUER SCD; NCT06635902	• Phase II; Δ Time time-to-crisis resolution
ω-3 Fatty Acids	Epileuton	• NCT05861453	• Phase I; Safety, tolerability, PK/PD
P-selectin Inhibitors	Crizanlizumab	• SPARKLE; NCT	• Phase III; Δ VOE
	Inclacumab	• THRIVE 131/133;	• Phase II/III; Δ VOE
Ferroportin Inhibitor	Vamifeport	• NCT04817670	• Phase II; Δ Hemolytic biomarkers

These agents are **investigational** and **not approved** by the FDA.

uACR = urine albumin-creatinine ratio; PK/PD = pharmacokinetics and pharmacodynamics.
Clinicaltrials.gov. https://clinicaltrials.gov/.

ARS Question

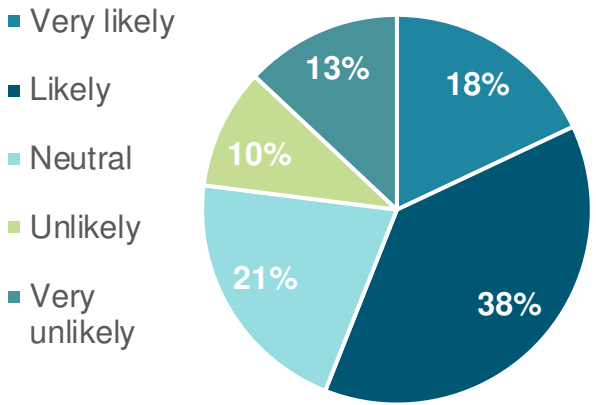
How often do you enroll your patients with SCD in clinical trials for SCD treatment?

A. Always
B. Regularly
C. Sometimes
D. Rarely
E. Never

Patient Perspectives on Clinical Trial Participation

Global LISTEN Survey: 1,145 patients with SCD from 17 countries

How likely are you to participate in a **clinical trial** if invited?



56% of patients are **likely** or **very likely** to participate in a clinical trial if offered

Key Reasons for Participating in Clinical Trials

- Support development of new treatments (62%)
- Increase self-knowledge about SCD (63%)
- Opportunity to receive their own data (51%)
- Possibility of receiving treatment regularly after the trial (47%)

LISTEN = Learning and Insights into Sickle Cell Trial Experiences.

Andemariam B, et al. ASH Annual Meeting and Exhibition; 2024. Abstract No. 1137. https://ash.confex.com/ash/2024/webprogram/Paper200009.html.

Faculty Discussion

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Consider factors beyond pain when assessing disease severity and identifying treatment options
- Educate patients on available treatment options to help make informed treatment decisions
- Select treatments that address underlying disease pathology rather than just symptoms when possible
- Identify patients who might be appropriate for clinical trial enrollment

To Ask a Question

Please select the *Ask Question* tab below the slide viewer.

Please include the faculty member's name if the question is specifically for them.

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