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Sickle Cell Disease Education and Therapeutic Management

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SCD, sickle cell disease.

SCD Overview

SCD, sickle cell disease.

Overview

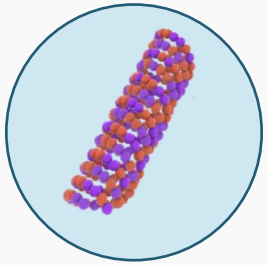
Sickle cell disease[1,2]

Group of inherited disorders

- Characterized by mutations in the β-globin gene, resulting in HbS production

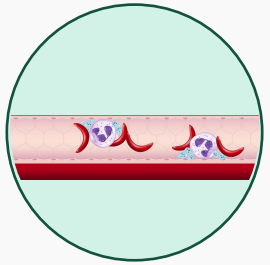
Autosomal-recessive inheritance

- Requiring one copy of the β^S gene and a second variant β-globin gene (e.g., β^S, β^C, β^D, β-thal)



HbS polymerization[1]

- Drives a cascade of pathologic processes involving abnormal RBC function
- Leads to the manifestation of characteristic clinical syndromes, including sickle cell anemia



Morphologic changes (e.g., RBC sickling)[1,3]

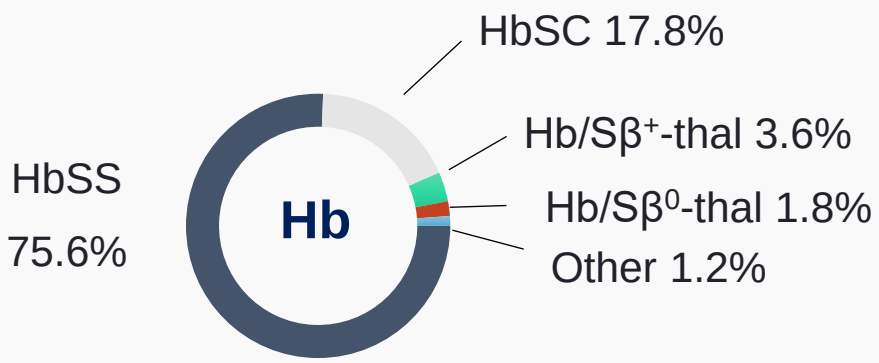
- Impair normal biorheology
- Drives the downstream pathogenesis of SCD-related symptoms, including vaso-occlusion

HbS, sickle hemoglobin; RBC, red blood cell; SCD, sickle cell disease.

1. Sedrak A, Kondamudi NP. *Sickle Cell Disease*. StatPearls Publishing; 2023. Updated August 12, 2023. Accessed December 7, 2023. https://www.ncbi.nlm.nih.gov/books/NBK482384/. 2. Rees DC, et al. *Lancet.* 2010;376(9757):2018-2031. 3. Sundd P, et al. *Annu Rev Pathol.* 2019;14:263-292.

SCD Is Among the Most Common Inherited Conditions Globally[1]

- SCD impacts ~100,000 individuals in the United States and >7,000,000 individuals globally[1,2]
  - It is more common in people descended from regions where malaria is or was endemic[1]
- Hemoglobin genotypes among individuals with SCD in the United States[3]:



- SCD incidence shows a wide range[4,*]:
  - 0.07 per 1000 in nonendemic areas
  - 10.68 per 1000 in African regions

SCD occurs in[1]:

out of 365

Black or African-American births

out of 16,300

Hispanic-American births

*Sickle-cell disorders include HbSS, HbSC, HbS/β thalassemia.[4] Hb, hemoglobin. HbS β, heterozygosity for hemoglobin S and β-thalassemia; Hb SC, heterozygosity for hemoglobin S and C; Hb SS, homozygosity for abnormal hemoglobin S; SCD, sickle cell disease.

1. CDC. Data & statistics on sickle cell disease. Updated July 7, 2023. Accessed November 13, 2023. https://www.cdc.gov/ncbddd/sicklecell/data.html/. 2. GBD 2021 Sickle Cell Disease Collaborators. *Lancet Haematol.* 2023;10(8):E585-E599. 3. Saraf SL, et al. *Paediatr Respir Rev.* 2014;15(1):4-12. 4. Modell B, et al. *Bull World Health Organ*. 2008;86(6):480-487.

Pathophysiology of SCD

SCD, sickle cell disease.

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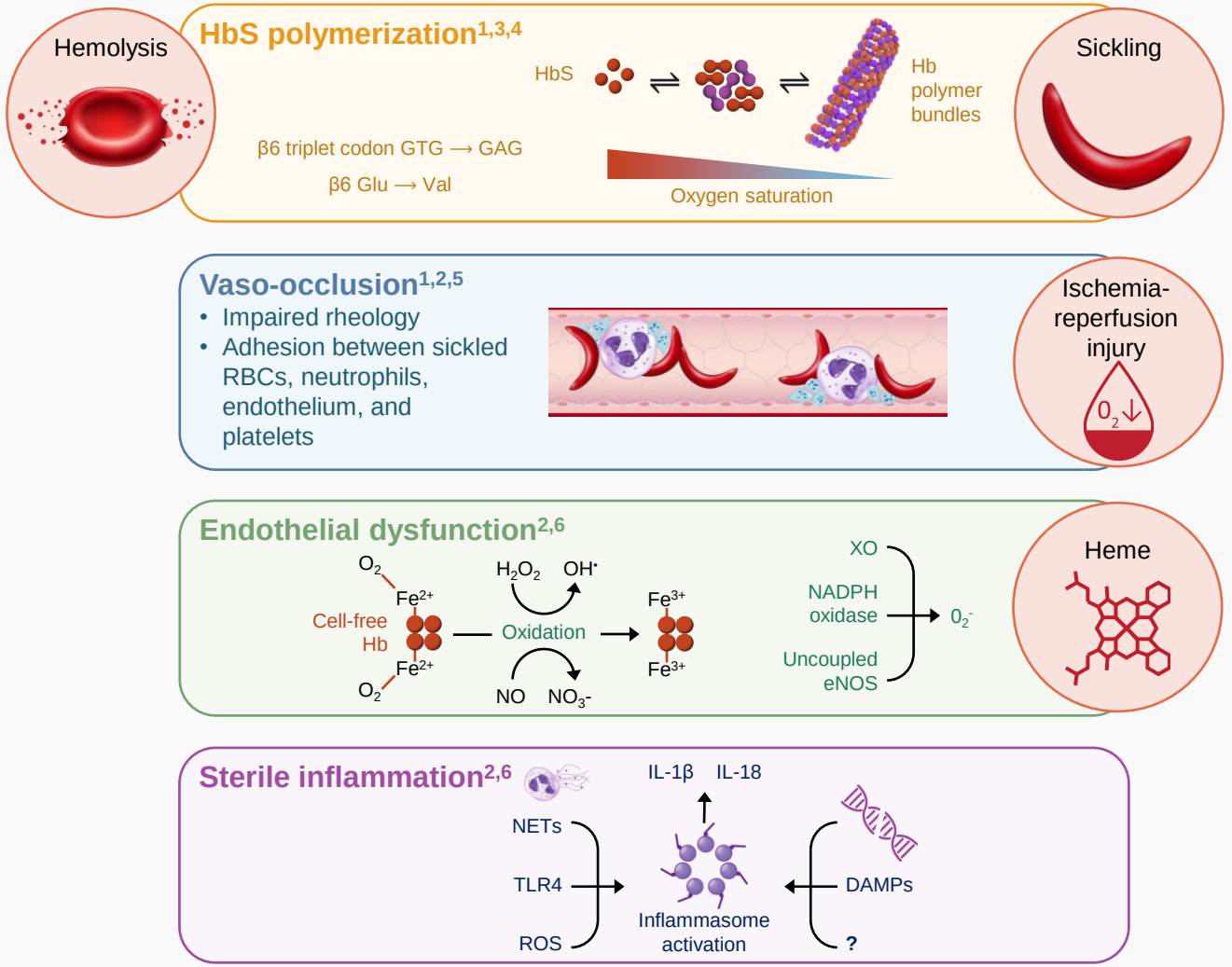
Key Pathophysiological Processes in SCD

- HbS mutation in β-globin chains results in multiple synergistic pathological processes[1,2]:
  - **a. HbS polymerization**
    HbS polymers are rigid and distort RBCs, causing sickling and hemolysis, and impair rheology
  - **b. Increased adhesion-mediated vaso-occlusion**
    Impaired rheology and aggregation of sickled RBCs with neutrophils, platelets, and endothelial cells lead to slowing or stoppage of blood flow
  - **c. Hemolysis-mediated endothelial dysfunction**
    Endothelial dysfunction caused by depleted endothelial NO reserves and the generation of oxygen free radicals
  - **d. Activation of sterile inflammation**
    Sterile inflammation, caused by the release of IL-1β, further promoting vaso-occlusion

We will explore the phenotypic features arising from each of these processes

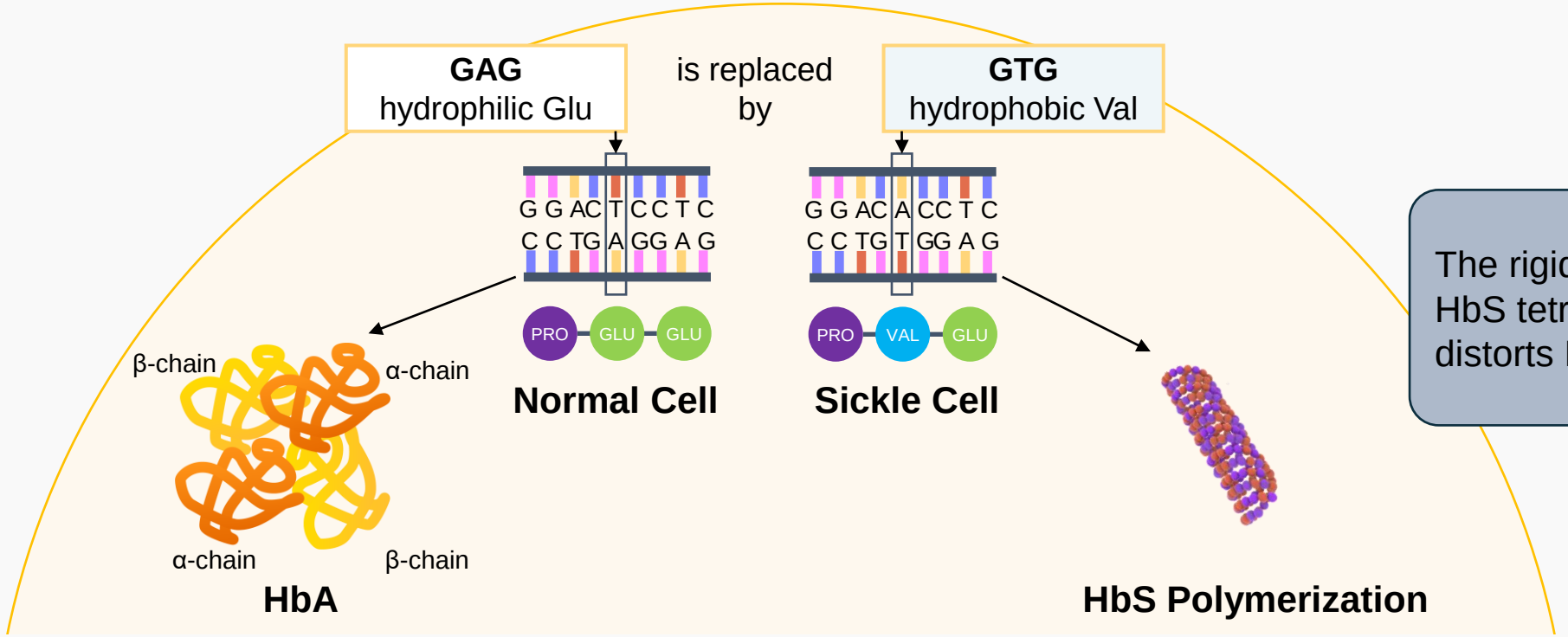


DAMP, danger-associated molecular pattern; eNOS, endothelial nitric oxide synthase; Fe, iron; Glu, glutamic acid; H_2O_2, hydrogen peroxide; Hb, hemoglobin; HbS, sickle hemoglobin; IL, interleukin; NADPH, nicotinamide adenine dinucleotide phosphate; NET, neutrophil extracellular trap; NO, nitric oxide; O, oxygen; $OH^{\bullet}$, hydroxyl free radical; RBC, red blood cell; ROS, reactive oxygen species; SCD, sickle cell disease; TLR4, toll-like receptor 4; XO, xanthine oxidase.

1. Sedrak A, Kondamudi NP. *Sickle Cell Disease*. StatPearls Publishing; 2023. Updated August 12, 2023. Accessed January 11, 2023. https://www.ncbi.nlm.nih.gov/books/NBK482384/.
2. Sundd P, et al. *Annu Rev Pathol.* 2019;14:263-292. 3. Hoban MD, et al. *Blood.* 2016;127(7):839-848. 4. Kato GJ, et al. *J Clin Invest*. 2017;127(3):750-760. 5. Hebbel RP, et al. *Blood.* 1990;76(5):1015-1020. 6. Gladwin MT, et al. *Blood.* 2014;123(24):3689-3690.

Polymerization of Deoxygenated HbS Tetramers Leads to RBC Sickling[1,2]

- The substitution of glutamic acid with valine at the 6th position of the β-globulin polypeptide chain (dbSNP identifier Rs334) drives hemoglobin polymerization in SCD[2,3]



The rigidity of polymerized HbS tetramers physically distorts RBCs[2,4]

- Hemoglobin S deoxygenation in tissues with high oxygen demand promotes exposure of hydrophobic motifs on individual HbS tetramers[2]
- Each hydrophobic valine is stabilized by binding a corresponding hydrophobic valine pocket[5,6]
  - This leads to HbS polymerization, precipitation, and hemolysis

dbSNP, The Single Nucleotide Polymorphism Database; Glu, glutamic acid; HbA, normal hemoglobin; HbS, sickle hemoglobin; Pro, proline; RBC, red blood cell; SCD, sickle cell disease; Val, valine.

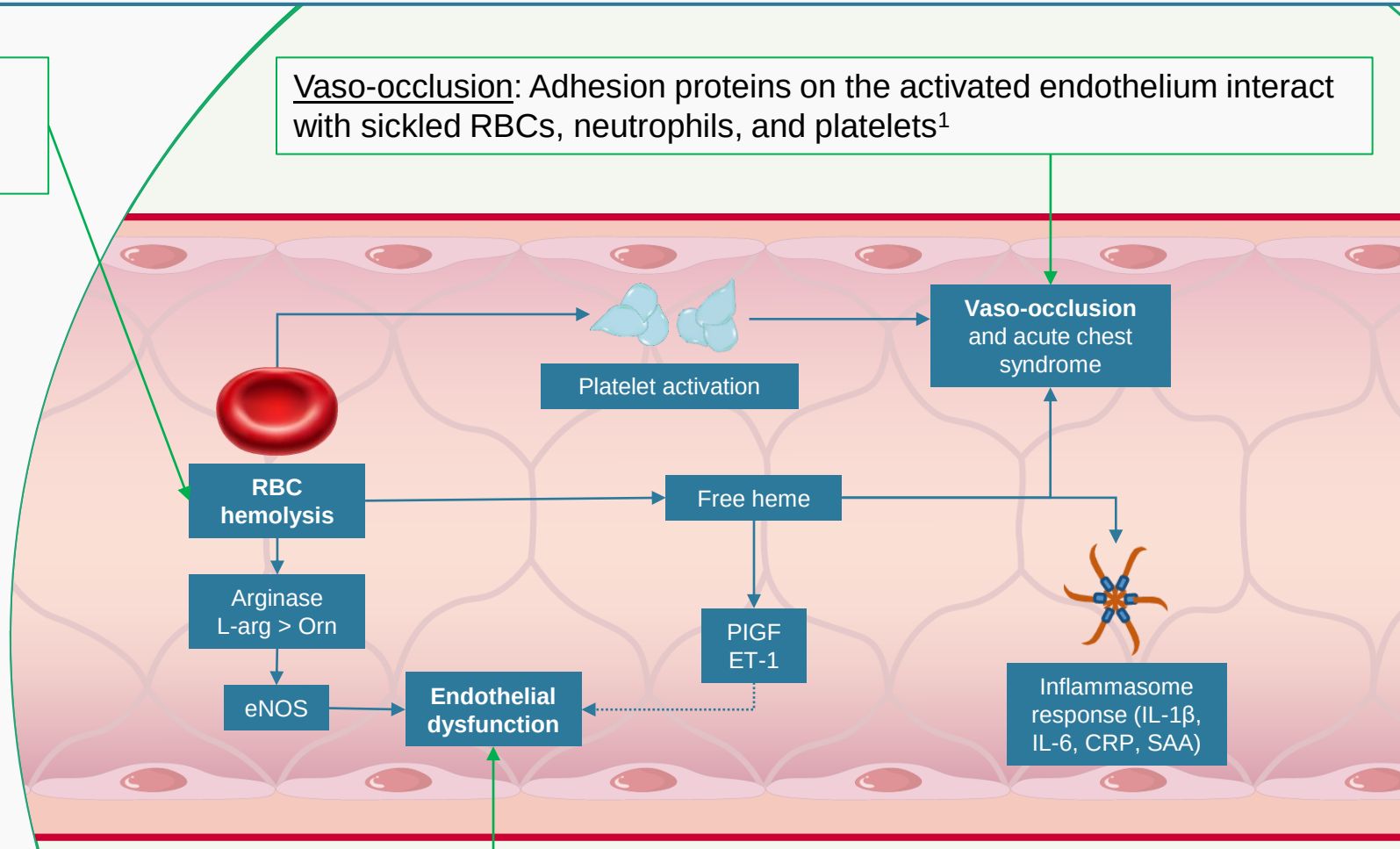
1. NIH. Evidence-based management of sickle cell disease. Accessed October 24, 2023. https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. 2. Sundd P, et al. *Annu Rev Pathol.* 2019;14:263-292. 3. McCune SL, et al. *Proc Natl Acad Sci U S A*. 1994;91(21):9852-9856. 4. Ramadas N, et al. *Front Med (Lausanne).* 2023;11:10:1141020. doi:10.3389/fmed.2023.1141020. 5. Gibson JS, Rees DC. *Expert Opin Ther Targets.* 2023;27(2):133-149. 6. Eaton WA, Hofrichter J. *Blood.* 70(5):1245-1266.

Intravascular Hemolysis Contributes to Vasculopathy, Endothelial Dysfunction, and Vaso-Occlusion in SCD

Intravascular hemolysis: Contributes to chronic vasculopathy, platelet activation, and pulmonary hypertension[1]

Intravascular hemolysis[1,2]:

- Inhibits NO signaling
  - NO dysregulation drives vasoconstriction, induces inflammation
- Amplifies ROS formation
- Disrupts redox balance
- Causes endothelial dysfunction

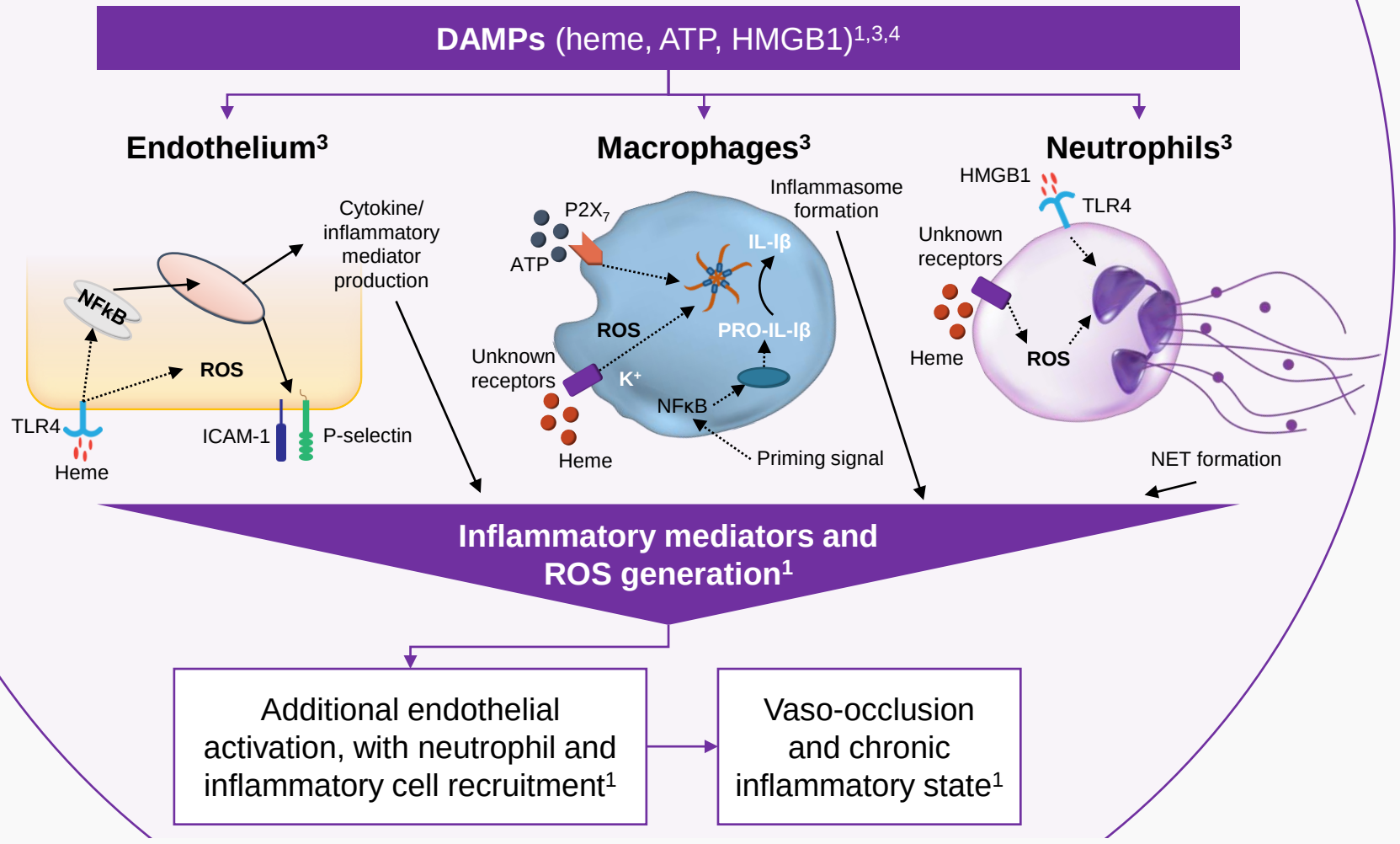


CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; IL, interleukin; L-arg, L-arginine; NO, nitric oxide; Orn, ornithine; PlGF, placental growth factor; RBC, red blood cell; ROS, reactive oxygen species; SAA, serum amyloid A; SCD, sickle cell disease.

1. Kato GJ, et al. *J Clin Invest*. 2017;127(3):750-760. 2. Sundd P, et al. *Annu Rev Pathol.* 2019;14:263-292.

Hemolysis Also Activates Danger-Associated Molecular Pattern Signaling and Sterile Inflammation

Sterile inflammation: Pathogen-free inflammation mediated by free heme and DAMPs[1,2]



- Heme activates TLR4 on endothelial cells and monocyte/ macrophages[5]
  - Extracellular ATP contributes to DAMP signaling in addition to ROS generation and NO inhibition[1]
- Inflammatory mediators, including TNF-α, can be secreted by expression of microparticles on the membrane surface of sickled RBCs and via free heme[5,6]

This contributes to the manifestations of vaso-occlusion and chronic inflammation in SCD

ATP, adenosine triphosphate; DAMPs, danger-associated molecular patterns; HMGB1, high mobility box B1 protein; ICAM, intercellular adhesion molecule; IL, interleukin; K^+, potassium; NET, neutrophil extracellular traps; NFκB, nuclear factor kappa B; NO, nitric oxide; $P2X_7$, PTX purinoreceptor 7; RBC, red blood cell; ROS, radical oxygen species; SCD, sickle cell disease; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha.

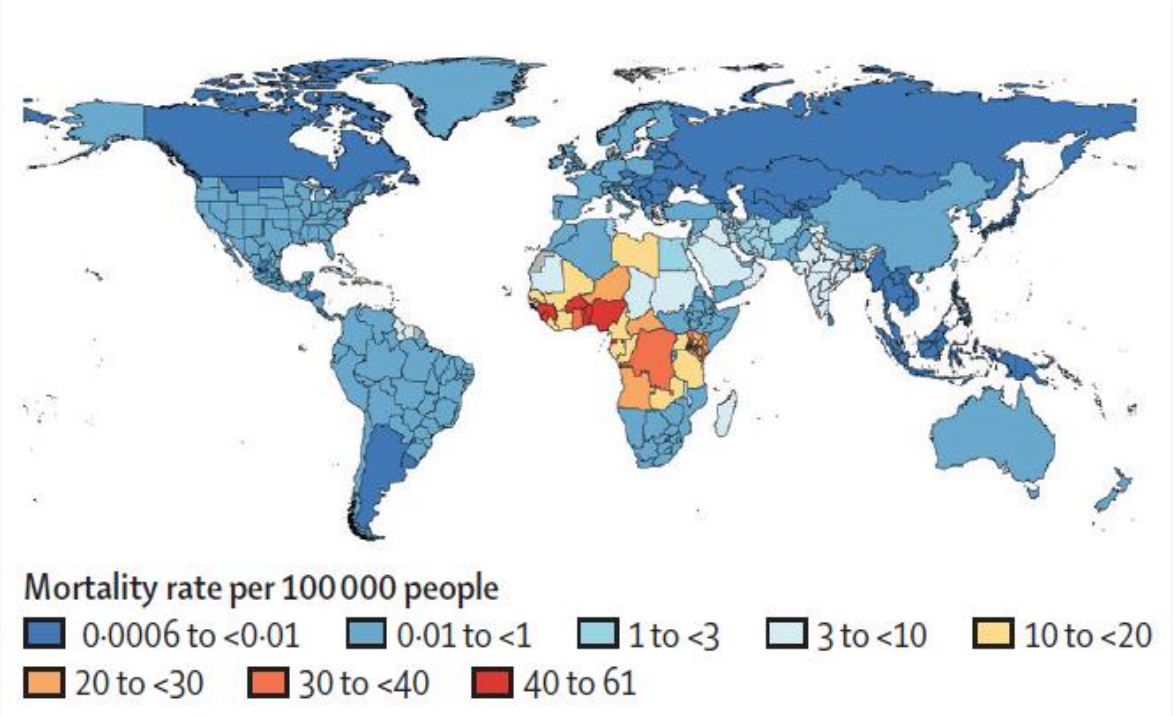
1. de Almeida CB, et al. Inflammation and sickle cell anemia. In: Costa FF, Conran N, eds. *Sickle Cell Anemia: From Basic Science to Clinical Practice.* 1st ed. Springer; 2016:177-211. 2. Wagener FA, et al. *Blood.* 2001;98(6):1802-1811. 3. Mendonça R, et al. *Inflamm Res.* 2016;65(9):665-678. 4. Chen Y, et al. *J Cell Mol Med.* 2015;19(12):2715-2727. 5. Figueiredo RT, et al. *J Biol Chem.* 2007;282(28):20221-20229. 6. Steinberg MH. Overview of sickle cell anemia pathophysiology. In: Costa FF, Conran N, eds. *Sickle Cell Anemia: From Basic Science to Clinical Practice.* 1st ed. Springer; 2016:49-73.

Patient Impact

SCD Is Associated With Increased Mortality

SCD Has an Annual Global Mortality Burden of 376,000 Individuals

All-age total sickle disease mortality rate, males and females, 2021[1]



In the United States, SCD continues to be a source of early mortality among African Americans[2]

75 ***years*** Average US life expectancy

40 ***years*** Average age of death with SCD

Reduced overall life expectancy in Black Americans (2016)

Global all-age SCD mortality rate[1]

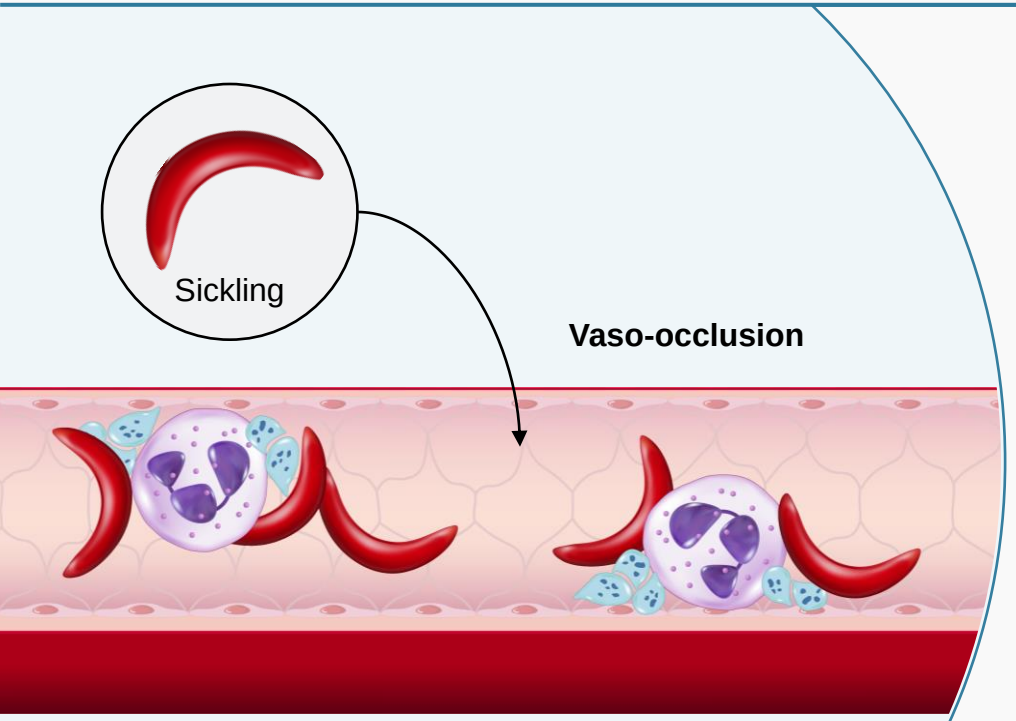
0.4 ***per 100K population***

SCD-related annual death rate among Black Americans[2]

1.91 ***per 100K population***

SCD, sickle cell disease.
Retrospective analysis of all deaths during 1979 to 2017, using National Center for Health Statistics all-cause mortality data, Centers for Disease Control and Prevention.
1. GBD 2021 Sickle Cell Disease Collaborators. *Lancet Haematol.* 2023;10(8):E585-E599. 2. Payne AB, et al. *Ann Emerg Med*. 2020;76(3S):S28-S36.

SCD-Associated Vaso-Occlusion Underlies the Phenotypic Features of SCD



Even after reperfusion, vasculopathy and endothelial dysfunction may persist

Vaso-occlusion → Acute pain; Acute chest syndrome; Hyposplenism; Osteonecrosis; Nephropathy

Inflammation
Increased VCAM-1 and adhesion molecule expression → Hypercoagulability

Hemolysis
Decreased NO bioavailability → Pulmonary hypertension; Priapism; Leg ulcers; Cerebrovascular disease

NO, nitric oxide; SCD, sickle cell disease; VCAM-1, vascular adhesion molecule

1. Rees DC, et al. *Lancet.* 2010;376(9757):2018-2031.

SCD Is Linked With Pain, Vaso-Occlusion, and Other Comorbidities

In a retrospective longitudinal cohort study of >7500 individuals with SCD, the most prevalent conditions by age were reported as[1,*]:

<18 and 18 to 45 years:
Vaso-occlusive pain and infection[1]

46 to 64 years:
Infection and cardiovascular disease[1]

Older adults vs. <18 years:
reduced rates of vaso-occlusive pain, fever, and ACS[1,†]

Across all ages of the prevalence analysis, vaso-occlusive pain, fever, and infection were the most common comorbidities among patients with SCD[1]

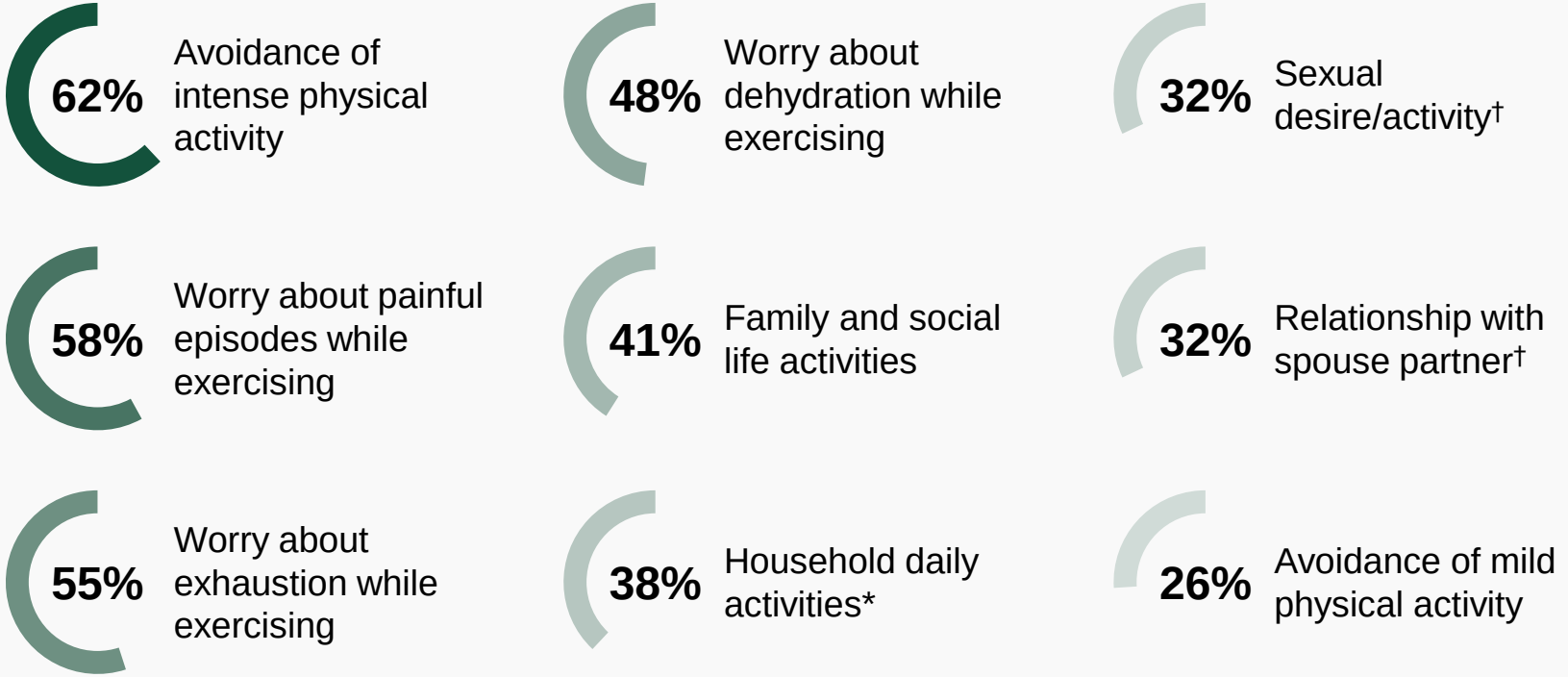
*To qualify for inclusion, individuals had at least 1 inpatient claim or 2 outpatient or emergency department claims for ICD-10 codes for SCD. Individuals were followed from their first claim encounter beginning from January 1, 2007 until December 31, 2018. Persons with records starting on or after age 65 and observations of individuals for periods with ages ≥65 years were included to eliminate periods in which they were eligible for Medicare.[1]
†Not a statistical comparison. Qualitative comparison to persons <18 years old.[1]
ACS, acute chest syndrome; ICD, International Classification of Diseases; SCD, sickle cell disease.
1. Ramsey SD, et al. *PLoS One.* 2022;17(11):e0278137.

SCD Has a Significant Impact on Patient QOL

SWAY: A multicountry, cross-sectional survey assessing the impact of SCD on the daily lives of 2145 patients between April and October 2019[1]

- SCD patients reported disruptions in both Emotional and Overall Function domains

SCD Patients Reporting Disrupted Daily Functioning



In the United States (1979 to 2017)[2,‡]

Baseline physical functioning HRQOL in SCD is comparable to or worse than chronic diseases such as:

- Cancer
- Cystic fibrosis
- Obesity

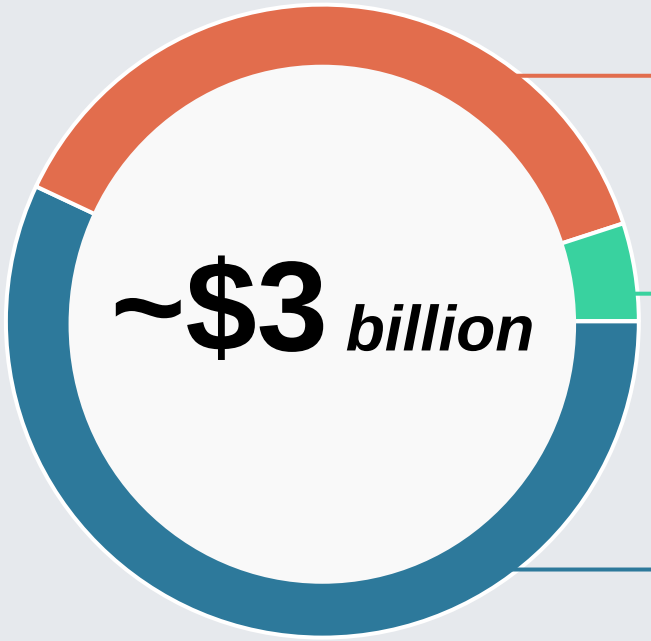
*Food preparation, housework, gardening, oral hygiene, and taking care of children.[1] †N = 1376 (patients aged ≥18 years).[1] ‡Based on generic HRQOL instruments (for example, the 36-Item Short Form Health Survey (SF-36) measuring physical, emotional and social functioning and enable the comparison of individuals with SCD with healthy individuals.[2]

HRQOL, health-related quality of life; QOL, quality of life; SCD, sickle cell disease; SWAY, Sickle Cell World Assessment Survey.

1. Osunkwo I, et al. *Am J Hematol.* 2021;96(4):404-417. 2. Kato GJ, et al. *Nat Rev Dis Primers.* 2018;4:18010.

Economic Burden in SCD Goes Beyond Patient OOP Costs

A retrospective observational study of EHR claims from 2005 through 2015 estimated the annual incremental economic burden of SCD at[1,*]:



$10,079 per patient:
Outpatient costs accounted for 38%

$1,293 per patient:
OOP expenses accounted for 5%

$15,040 per patient:
Inpatient costs accounted for 57%

A meta-analysis and systemic literature search of publications between 1997 and 2018 found adults with SCD had[2]:

- **0.3 to 3.5** annual ED visits
- **0.5 to 27.9** hospitalizations (per patient per year)
- **12% to 41%** rates of readmission

*Health care resources use, including hospitalizations, emergency room visits, outpatient visits, and the length of hospital stay, were measured within the calendar year of first occurrence date of SCD.[1]
ED, emergency department; EHR, electronic health record; OOP, out of pocket; SCD, sickle cell disease.
1. Huo J, et al. *Value in Health*. 2018;21(suppl 2):S108. 2. Lee S, et al. *Int J Gen Med*. 2020:13:361-377.

Unmet Needs in SCD and Emerging Treatments

SCD, sickle cell disease.

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SCD Diagnosis May Be Missed in Individuals Not Evaluated by Newborn Screening

Insights and Considerations on Patterns of SCD Diagnosis

Widespread adoption of newborn screening in the United States and most of Europe allows for the early detection of SCD[1-3]

Globally, lack of universal newborn screening and point-of-care diagnostic services contribute to missed diagnoses[1,4]

Immigrants to the United States may not receive SCD screening in their respective countries, and universal policies for adult screening are lacking[4,5]

Individuals born in the United States before the adoption of universal newborn screening may not be aware of their SCT status[4]

SCD, sickle cell disease; SCT, sickle cell trait.

1. McGann PT, et al. *Blood Cells Mol Dis.* 2017;67:104-113. 2. Tsevat J, et al. *J Pediatr.* 1991;118:546-554. 3. Telfer P, et al. *Haematologica.* 2007;92:905-912. 4. National Association of Academies of Science, et al. Washington (DC): National Academies Press, 2020. 5. Faro E, et al. *Am J Prev Med.* 2016;51(suppl 1):S48-S54.

No Approved Disease Modifying SCD Treatment Both Increases Hb Levels And Reduces VOEs[1]

SCD Treatments

Disease Modifying

Transfusions and pharmacotherapies[2-5]

Gene Therapy

Restoring faulty or missing gene to improve cell function via gene editing or addition[2,10]

Curative

Hematopoietic stem cell transplantation (HSCT)[2]

Treatment	Target and MOA
Transfusion[6]	• Reduction in HbS-containing RBCs
Pharmacotherapy[1,2,6-9]	• Increased HbF synthesis and release of NO • Oxidative stress reduction • P-selectin inhibition • HbS polymerization inhibition
HSCT[2,6,10]	• Restore normal erythropoiesis

Hb, hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; HSCT, hematopoietic stem cell transplant; MOA, mechanism of action; NO, nitric oxide; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

1. Brandow AM, Liem RI. *J Hematol Oncol.* 2022;15(20):1-13. 2. Tanhehco YC, et al. *Front Med (Lausanne).* 2022;9:1055540. 3. Ault A. *Lancet.* 1998;351:809. 4. Benjamin L. *Hematology Am Soc Hematol Educ Program.* 2008;466-474. 5. McClain BC, Kain ZN. *Pediatrics.* 2007;119(3):612-614. 6. NIH. Evidence-based management of sickle cell disease. Accessed October 24, 2023. https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. 7. Pace BS, et al. *Br J Haematol.* 2021;194(2):240-251. 8. Huang J, et al. *J Am Chem Soc.* 2002;124(13):3473-3480.
9. Ballas SK. *J Mediterr Hematol Infect Dis.* 2020;12(1):e2020010. 10. NIH. Sickle cell disease treatment. Accessed October 25, 2023. https://www.nhlbi.nih.gov/health/sickle-cell-disease/treatment/.

Emerging SCD Treatments Target Various Signaling Pathways

Therapeutic Strategy: PK activation[1]

- ATP increase improves RBC health and survival
- 2,3-DPG decrease reduces HbS polymerization, and thus, RBC sickling

Therapeutic Strategy: Inhibition of HbS polymerization[2-5]

- Gene modification to reverse the effects of HbS and sustain hematopoietic engraftment
  - HbS correction
  - HbF induction
  - Modified HbA addition
- Utilize therapeutic interventions to increase HbF levels to prevent HbS polymerization
- Increase Hb oxygen affinity to stabilize oxygenated HbS

Therapeutic Strategy: Target downstream pathways[1,6,7]

- Inhibition of endothelial cell activation and cellular adhesion
  - PDE9A targeting
- Reduction of chronic inflammation and oxidative stress
- Reduction of platelet activation and coagulation-related abnormalities
- Compensating for the depletion of NO signaling caused by intravascular hemolysis

2,3-DPG, 2,3-diphosphoglycerate; ATP, adenosine triphosphate; Hb, hemoglobin; HbA, normal hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; HSCT, hematopoietic stem cell transplant; NO, nitric oxide; PDE9A, phosphodiesterase 9A; PK, pyruvate kinase; RBC; red blood cell; SCD, sickle cell disease.

1. Pace BS, et al. *Br J Haematol*. 2021;194(2):240-251. 2. Tanhehco YC, et al. *Front Med (Lausanne)*. 2022;9:1055540. 3. NIH. Evidence-based management of sickle cell disease. Accessed October 24, 2023. https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. 4. Platt OS, et al. *N Engl J Med.* 1991;325(1):11-16. 5. Powars DR, et al. *Blood.* 1984;63(4):921-926. 6. Gibson JS, Rees DC. *Expert Opin Ther Targets.* 2023;27(2):133-149. 7. Hoss SE, et al. *Hemasphere.* 2022;6(9):e762.

Summary

Summary

SCD is a group of inherited disorders characterized by mutations in the β-globin gene; SCD impacts ~100,000 individuals in the United States, and >7 million globally[1-3]

In SCD, **HbS polymerization drives a cascade of pathologic processes** involving abnormal RBC function, resulting in endothelial dysfunction, vaso-occlusion, and sterile inflammation[4,5]

SCD has an **annual global mortality burden** of 376,000; individuals with SCD had a substantially impaired baseline HRQOL[3,6,7]

Missed SCD diagnoses in individuals who were born prior to universal screening or outside of the United States and its territories **remains a challenge**[8,9]

There are **currently no disease modifying treatments** that can both increase Hb levels and reduce vaso-occlusive events[10]

Hb, hemoglobin; HbS, sickle hemoglobin; RBC, red blood cell; SCD, sickle cell disease; HRQOL, health-related quality of life.

1. Sundd P, et al. *Annu Rev Pathol.* 2019;14:263-292. 2. CDC. Get screened to know your sickle cell status. Accessed September 13, 2023. https://www.cdc.gov/ncbddd/sicklecell/documents/factsheet_scicklecell_status.pdf. 3. GBD 2021 Sickle Cell Disease Collaborators. *Lancet Haematol.* 2023;10(8):e585-e599. 4. Sedrak A, Kondamudi NP. *Sickle Cell Disease*. StatPearls Publishing; 2023. Updated August 12, 2023. Accessed December 7, 2023. https://www.ncbi.nlm.nih.gov/books/NBK482384/. 5. Pace BS, et al. *Br J Haematol*. 2021;194(2):240-251. 6. Osunkwo I, et al. *Am J Hematol.* 2021;96(4):404-417. 7. Kato GJ, et al. *Nat Rev Dis Primers.* 2018;4:18010. 8. Faro EZ, et al. *Am J Prev Med.* 2016;51(suppl 1):S48-S54. 9. National Academies of Sciences, Engineering, and Medicine. *Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action*. 2020. The National Academies Press. https://doi.org/10.17226/25632. 10. Brandow AM, Liem RI. *J Hematol Oncol.* 2022;15(20):1-13.