Updates on sickle cell disease

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NCI Designated Comprehensive Cancer Center

UCDAVIS COMPREHENSIVE CANCER CENTER

Outline

- Overview of mechanism of injury in sickle cell disease (SCD)
- SCD-modifying drugs
  - Hydroxyurea
  - L-glutamine
  - Crizanlizumab
  - Voxelator
- Curative options

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Pathophysiology and mechanism of injury in SCD

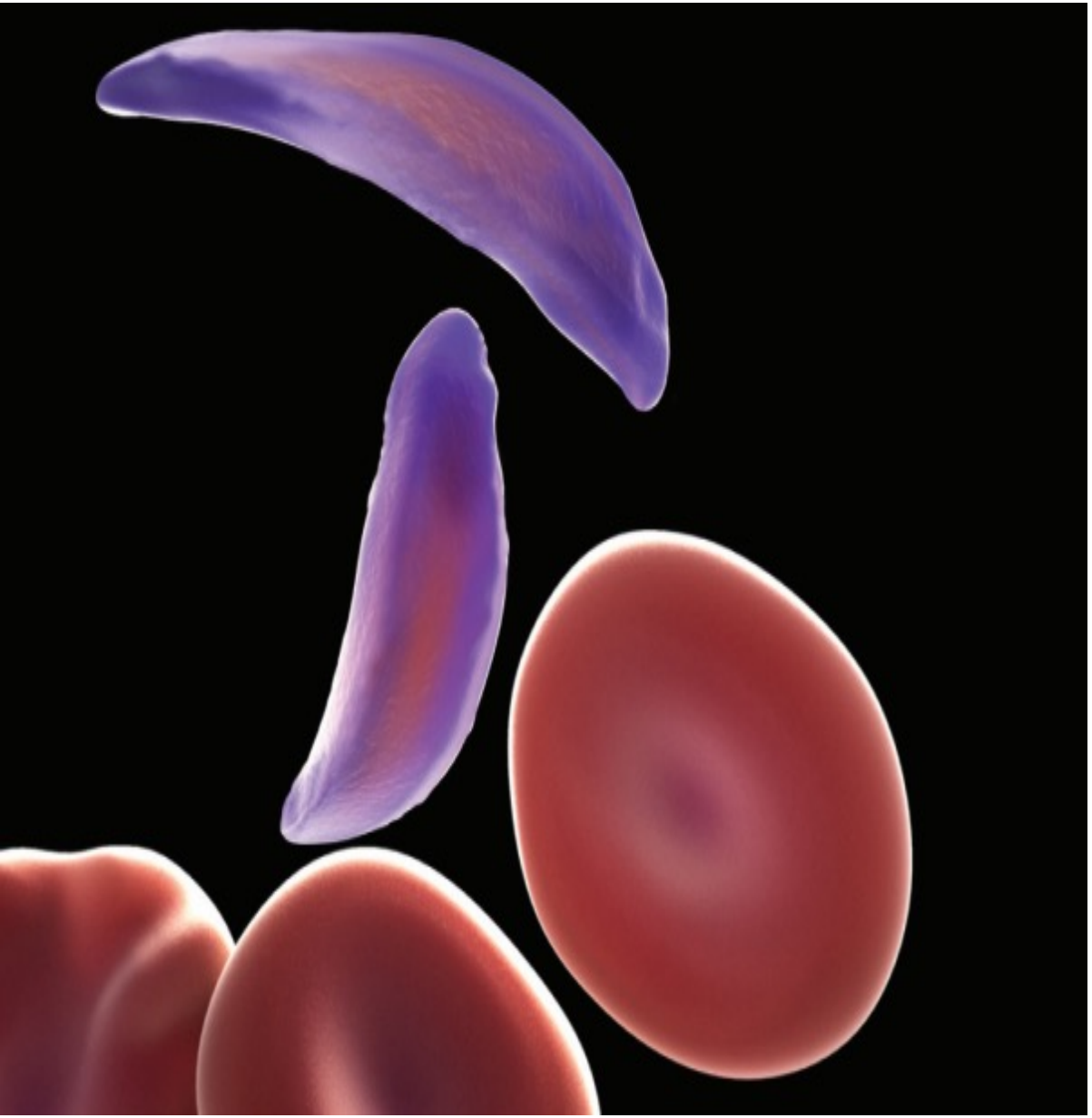


Image courtesy of National Institutes of Health

- Single nucleotide variant on β hemoglobin gene
- Deoxygenation → Hb S polymerization
- *Heterocellular-endothelial aggregates → VOCs
- Ischemia-reperfusion injury→ inflammation
- Hemolysis → cell free Hb, oxygen free radicals and sterile inflammation
- Nitric oxide (NO) scavenging → dysregulation of vasomotor tone
- Recurrent hypoperfusion → end-organ damage

*Sickled erythrocytes, activated neutrophils, platelets

Sickling syndromes

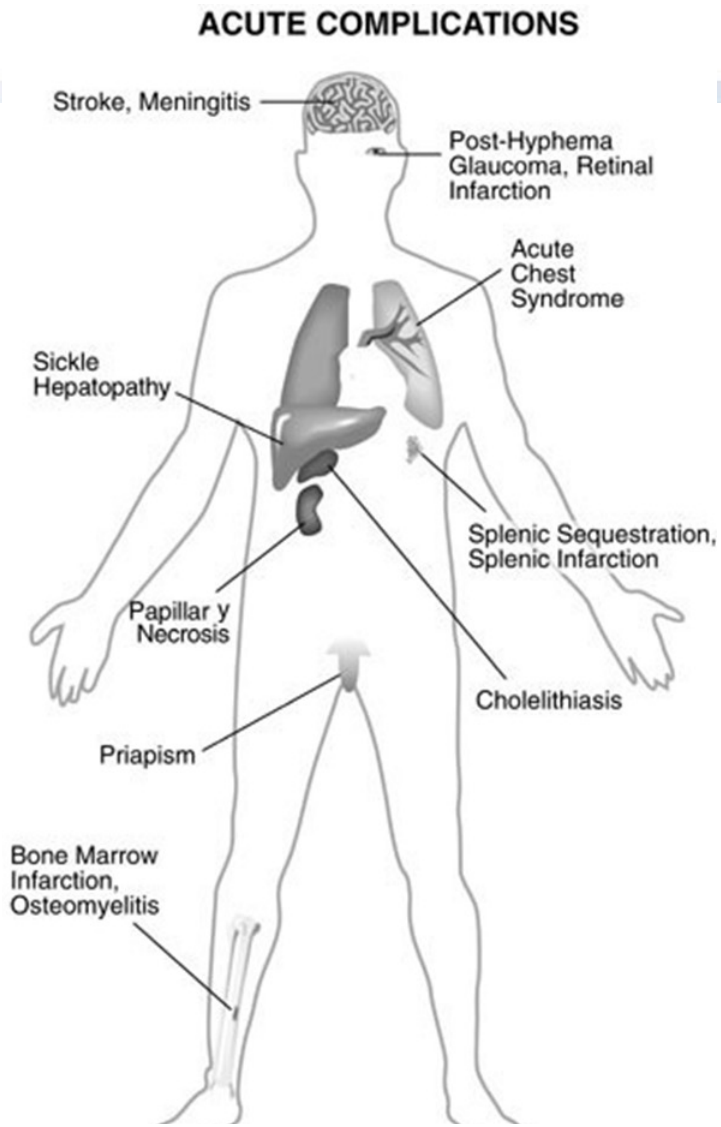
Table 1. Genotypes of Sickling Syndromes and Their Relative Severities

Genotype	Severity	Characteristics
HbSS	Severe	Most common form
HbSβ⁰	Severe	Clinically indistinguishable from HbSS[6]
HbSO-Arab	Severe	Relatively rare[6]
HbSD-Punjab	Severe	Mostly in northern India[6]
HbSC-Harlem	Severe	Migrates like HbSC, but rare double β-globin mutation[7]
HbCS-Antilles	Severe	Rare double β-globin mutation[8]
HbSC	Moderate	25% of SCD[9]
HbSβ+, Mediterranean	Moderate	5%–16% HbA[6]
HbAS-Oman	Moderate	Dominant rare double β-globin mutation[10]
HbSβ+, African	Mild	16%–30% HbA[6]
HbSE	Mild	HbE found mostly in Southeast Asia[11]
HbS-HPFH	Very mild	Large deletions in β-globin gene complex; > 30% HbF[6]

HbA = hemoglobin A; HbE = hemoglobin E; HbF = fetal hemoglobin; HbS-HPFH = HbS and gene deletion HPFH; HbSC = heterozygous hemoglobin SC; HbSS = homozygous hemoglobin SS; HbSβ⁰ = hemoglobin S-β thalassemia⁰; HbSβ+ = hemoglobin S-β thalassemia+; SCD = sickle cell disease.

Vivien A. Sheehan. Hematology-Oncology 12:1, 2-15

Clinical complications of sickle cell disease

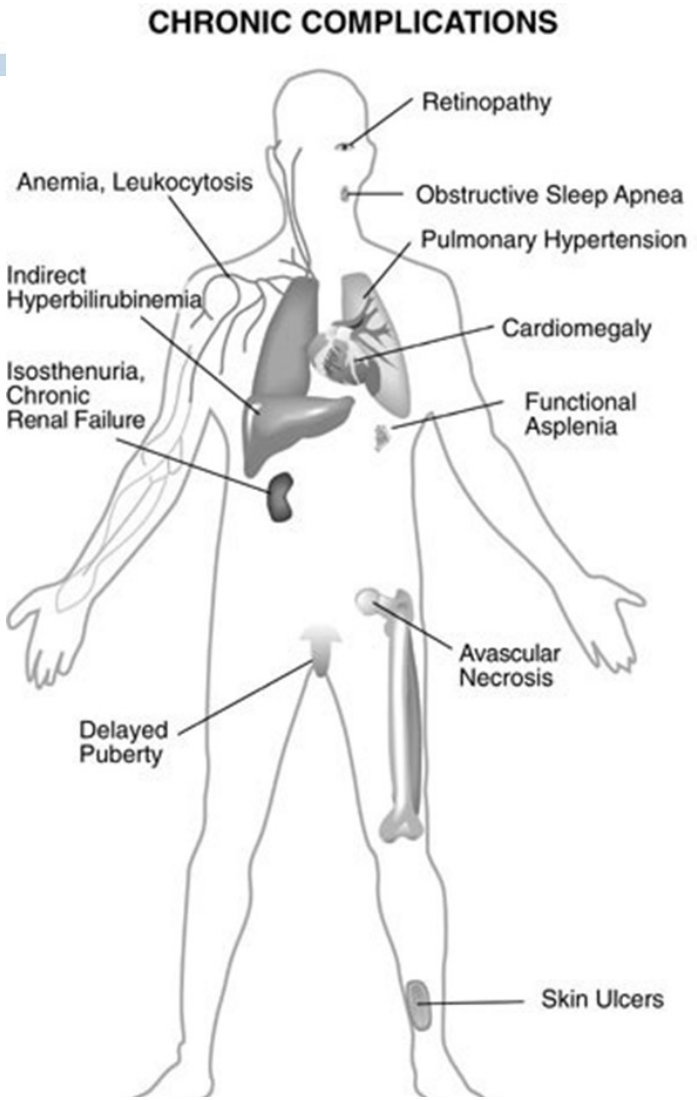


Acute complications

- Vasoocclusion (pain)
- Acute chest syndrome
- Acute stroke
- Priapism
- Hepatobiliary complications
- Splenic sequestration
- Acute renal failure

Chronic complications

- Pulmonary hypertension
- Ophthalmologic complications
- Avascular necrosis
- Leg ulcers
- Recurrent or stuttering priapism



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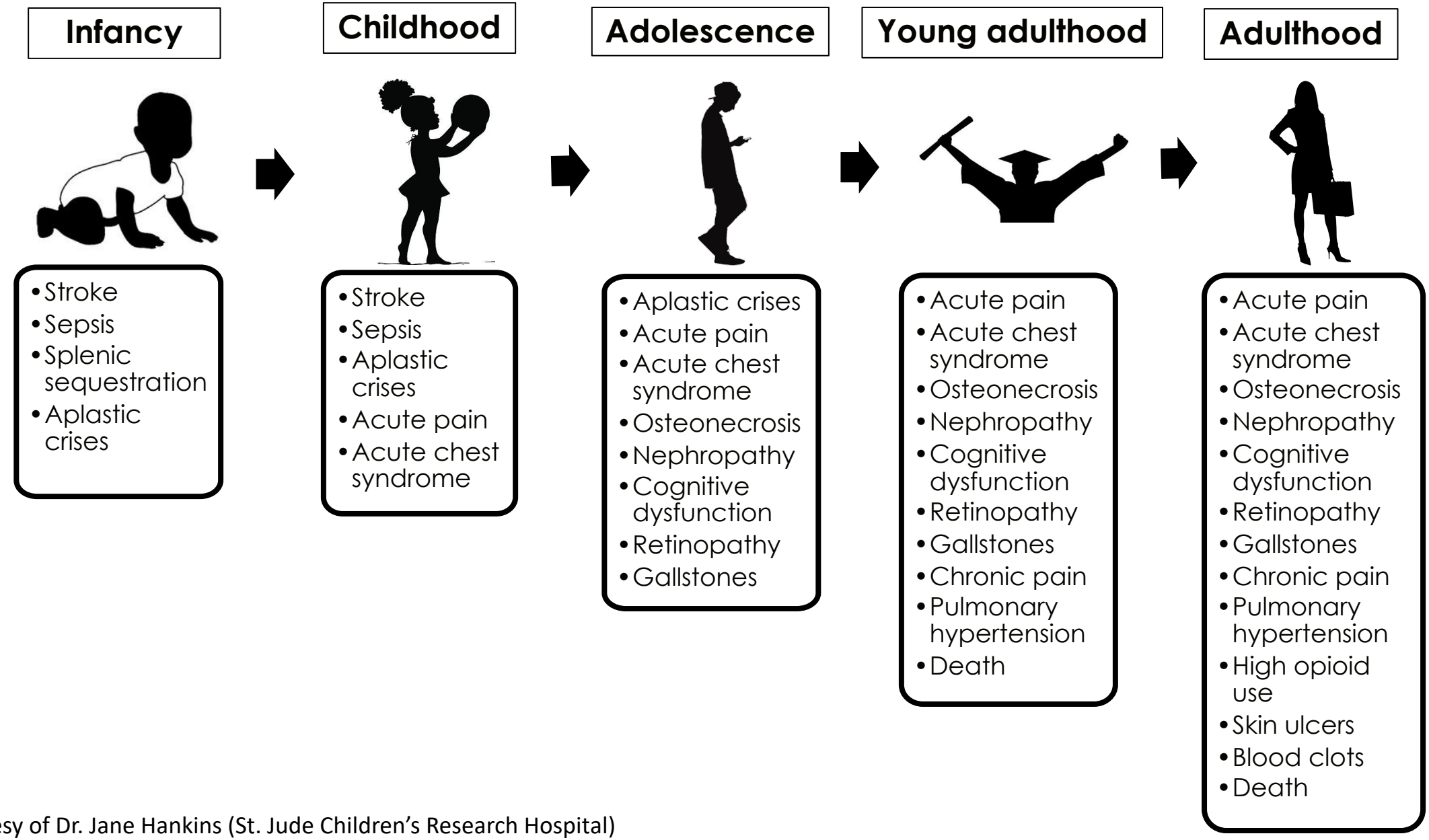
Complications of sickle cell disease accumulate with age



Slide courtesy of Dr. Jane Hankins (St. Jude Children's Research Hospital)

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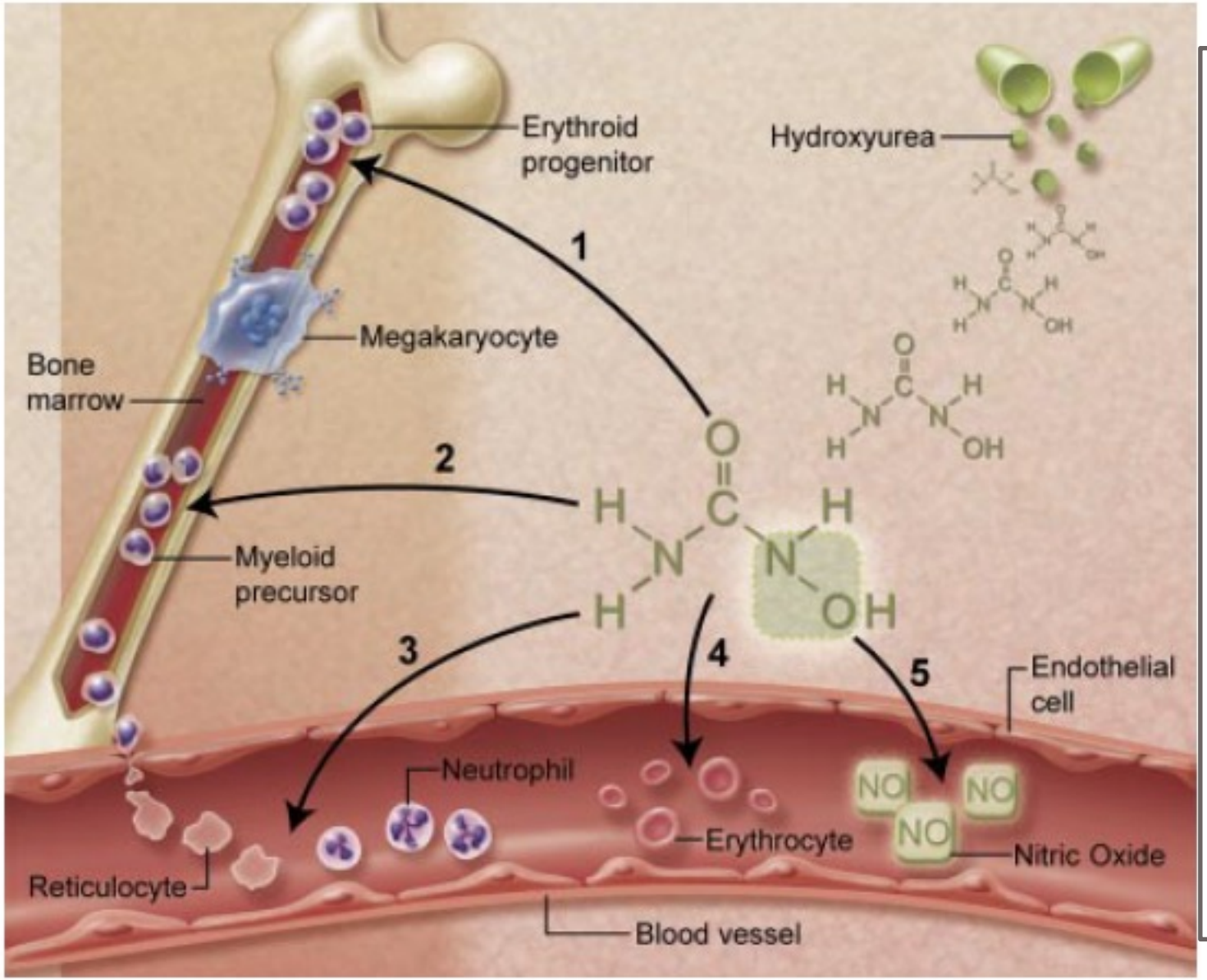
Hydroxyurea (HU) - mechanisms of action in SCD



- Activate soluble guanylyl cyclase → induce Hb F production
- Inhibit ribonucleotide reductase → decrease neutrophils and retics
- ↓ endothelial adhesion → improve rheology of neutrophils and reticulocyte
- ↑ erythrocyte hydration → decrease hemolysis, reduce intracellular sickling
- Release NO → local vasodilation, improve vascular tone

Russell E. Ware. *Blood* 2010 115:5300-5311

Optimizing hydroxyurea use in sickle cell anemia

How I Escalate Hydroxyurea to Maximum Tolerated Dose (MTD)

Goal: A stable daily dose of oral hydroxyurea that is well-tolerated and provides mild myelosuppression

Target: Absolute Neutrophil Count (ANC) of 1.5 – 3.0 x 10^9/L and Absolute Reticulocyte Count (ARC) of 100 – 200 x 10^9/L

Procedure: (adapted from the 2014 NHLBI evidence-based Guidelines)[12]

1. Perform baseline laboratory studies including a complete blood count with WBC differential, peripheral blood smear, reticulocyte count, hemoglobin electrophoresis, as well as assessment of renal function (BUN, creatinine) and hepatic function (ALT, bilirubin).
2. Initiate hydroxyurea at 15-20 mg/kg/day; the lower end of this range is suitable for teens and adults, while almost all young patients tolerate 20 mg/kg/day.
3. Use the same daily dose whenever possible for simplicity and adherence, but additional dosing schemes (e.g., one capsule per day alternating with two capsules per day) can be used safely and effectively. A liquid formulation can be prepared extemporaneously and provided for young patients.
4. Provide dosing instructions that include recommendations about regular medication timing, frequency, adherence, and potential side-effects.
5. Obtain monthly blood counts (CBC with differential, reticulocytes) to assess toxicity and promote adherence. The absolute neutrophil count (ANC) and absolute reticulocyte count (ARC) are the most important measures of marrow suppression to guide dosing and toxicity. If toxic, hold the dose until recovery (typically a week) and restart at the same or lower dose.
6. Assess for early treatment effects by an increased MCV and RDW, along with lower ANC and ARC. Review of the peripheral blood smear should identify non-reticulocyte macrocytosis.
7. After two months of treatment, assess for laboratory toxicities and determine if the blood counts are in the target range for mild myelosuppression. If not yet in the target range, increase the daily dose to 20-25 mg/kg/day.
8. Repeat monthly counts and bimonthly escalation by 5 mg/kg/day until a stable daily dose leads to the desired mild myelosuppression. At that point, the dose can be considered the maximum tolerated dose (MTD) and those blood counts serve as a reference point for future assessments.
9. Do not exceed an average daily dose of 30-35 mg/kg/day. Once MTD has been established, visits can be spaced out to every 2-3 months as needed, but adherence must be encouraged at every visit. Every 3-6 months, measure HbF for efficacy and assess for renal and hepatic toxicity.
10. Certain scenarios warrant special consideration and modification of dose escalation, such as pre-existing renal disease, baseline low blood counts due to hypersplenism, and select concomitant medications, among others.

Russell E. Ware. Hematology Am Soc Hematol Educ Program, 2015

Clinical indications for HU initiation in SCD

- Children age ≥ 2 years with moderate to severe sickle cell anemia
  - Ok to start in children by age 9 months to prevent SCD complications
- Adults with sickle cell anemia and
  - ≥ 3 pain crises per year
  - pain that interferes with ADLs or QOL
  - history of severe or recurrent acute chest syndrome
- Adults with SCD *variants complicated by pain impacting ADLs/QoL
- Adults with sickle cell-related CKD on exogenous erythropoietin

Yawn et al. *JAMA.* 2014;312(10):1033-1048
Vivien A. Sheehan. Hematology-Oncology 12:1, 2-15

*HbSC and Hb $S\beta^+$ thalassemia

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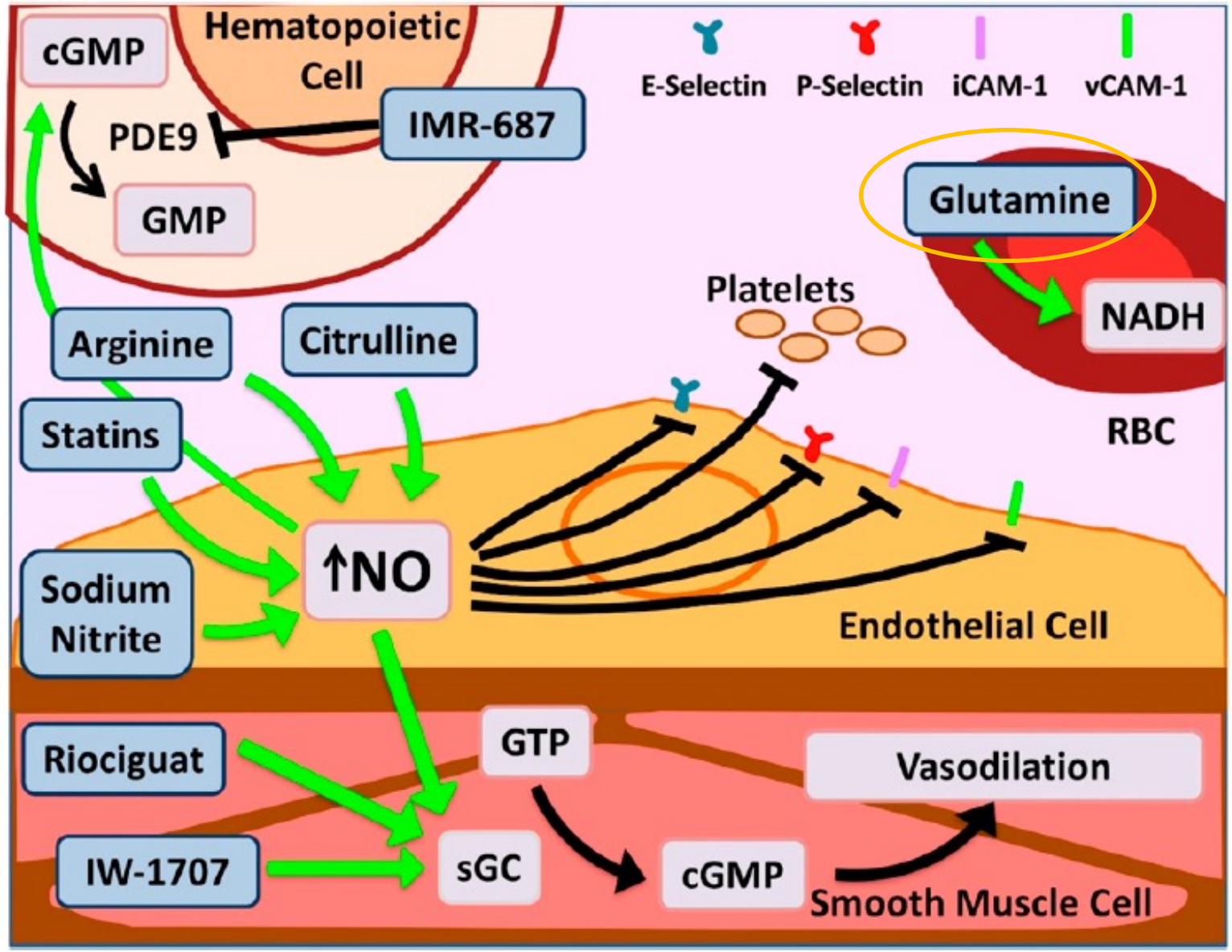
Novel agents → inflammation and NO bioavailability in SCD



Moerdler and Manwani. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):493-506.

The NEW ENGLAND JOURNAL of MEDICINE

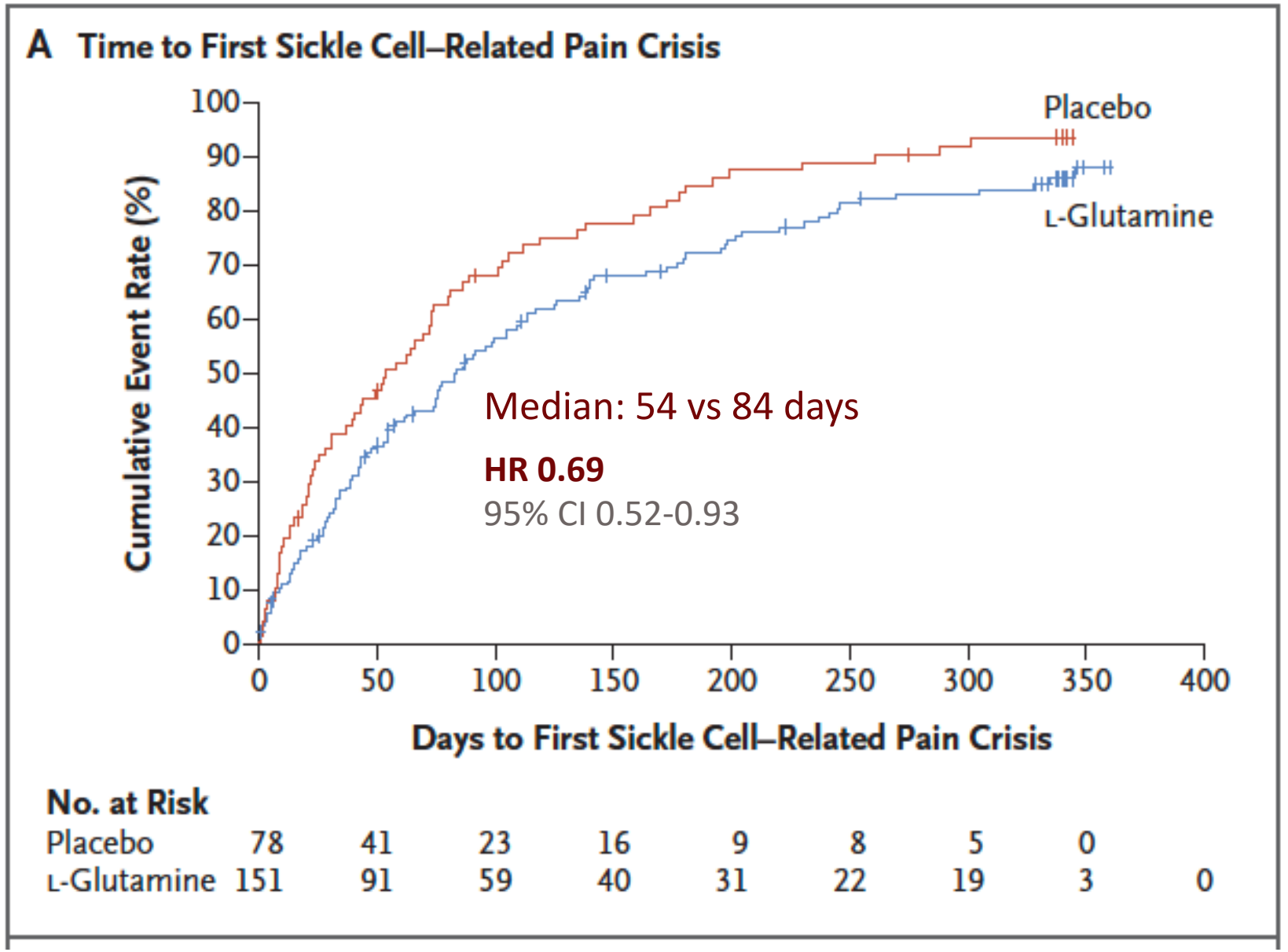
ORIGINAL ARTICLE

A Phase 3 Trial of L-Glutamine in Sickle Cell Disease

Yutaka Niihara, M.D., M.P.H., Scott T. Miller, M.D., Julie Kanter, M.D., Sophie Lanzkron, M.D., M.H.S., Wally R. Smith, M.D., Lewis L. Hsu, M.D., Ph.D., Victor R. Gordeuk, M.D., Kusum Viswanathan, M.D., Sharada Sarnaik, M.D., Ifeyinwa Osunkwo, M.D., Edouard Guillaume, M.D., Swayam Sadanandan, M.D., Lance Sieger, M.D., Joseph L. Lasky, M.D., Eduard H. Panosyan, M.D., Osbourne A. Blake, M.D., Tamara N. New, M.D., Rita Bellevue, M.D., Lan T. Tran, M.P.H., Rafael L. Razon, M.D., Charles W. Stark, Pharm.D., Lynne D. Neumayr, M.D., and Elliott P. Vichinsky, M.D., for the Investigators of the Phase 3 Trial of L-Glutamine in Sickle Cell Disease*

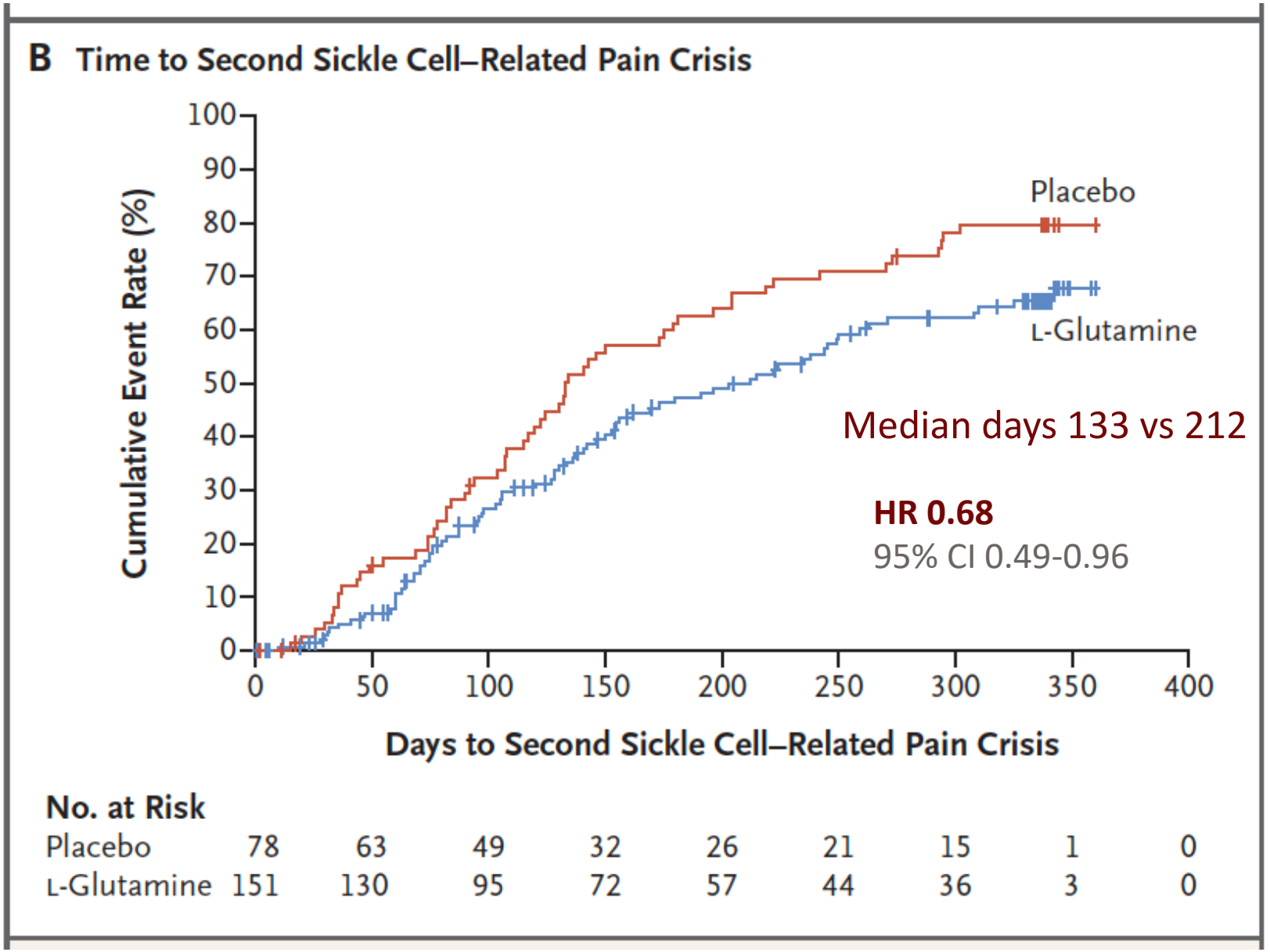
Niihara et al. N Engl J Med 2018 Jul 19;379(3):226-235.

Time to 1st SCD pain episode delayed by 30 days



Niihara et al. N Engl J Med 379;3 July 19, 2018

Time to 2nd SCD pain episode delayed by 79 days



Niihara et al. N Engl J Med 379;3 July 19, 2018

Table 2. End-Point and Additional Analyses.

Through Week 48	L-Glutamine (N=152)	Placebo (N=78)	P Value
Primary end point			
No. of pain crises			0.005*
Mean	3.2±2.24	3.9±2.54	
Median (range)	3 (0–15)	4 (0–15)	
Secondary end points			
No. of hospitalizations for sickle cell–related pain			0.005*
Mean	2.3±1.99	3.0±2.33	
Median (range)	2 (0–14)	3 (0–13)	
No. of emergency department visits for sickle cell–related pain			0.09*
Mean	1.1±1.49	1.5±2.29	
Median (range)	1 (0–12)	1 (0–15)	
Additional analyses			
Cumulative no. of days in hospital			0.02†
Mean	12.1±16.6	18.1± 27.4	
Median (range)	6.5 (0–94)	11 (0–187)	
Median no. of days to first pain crisis (95% CI)	84 (62–109)	54 (31–73)	0.02‡
Median no. of days to second pain crisis (95% CI)	212 (153–250)	133 (115–179)	0.03‡
Episodes of acute chest syndrome — no. (%)			0.003*
0	139 (91.4)	60 (76.9)	
≥1	13 (8.6)	18 (23.1)	
1	10 (6.6)	13 (16.7)	
2	3 (2.0)	4 (5.1)	
3	0	1 (1.3)	

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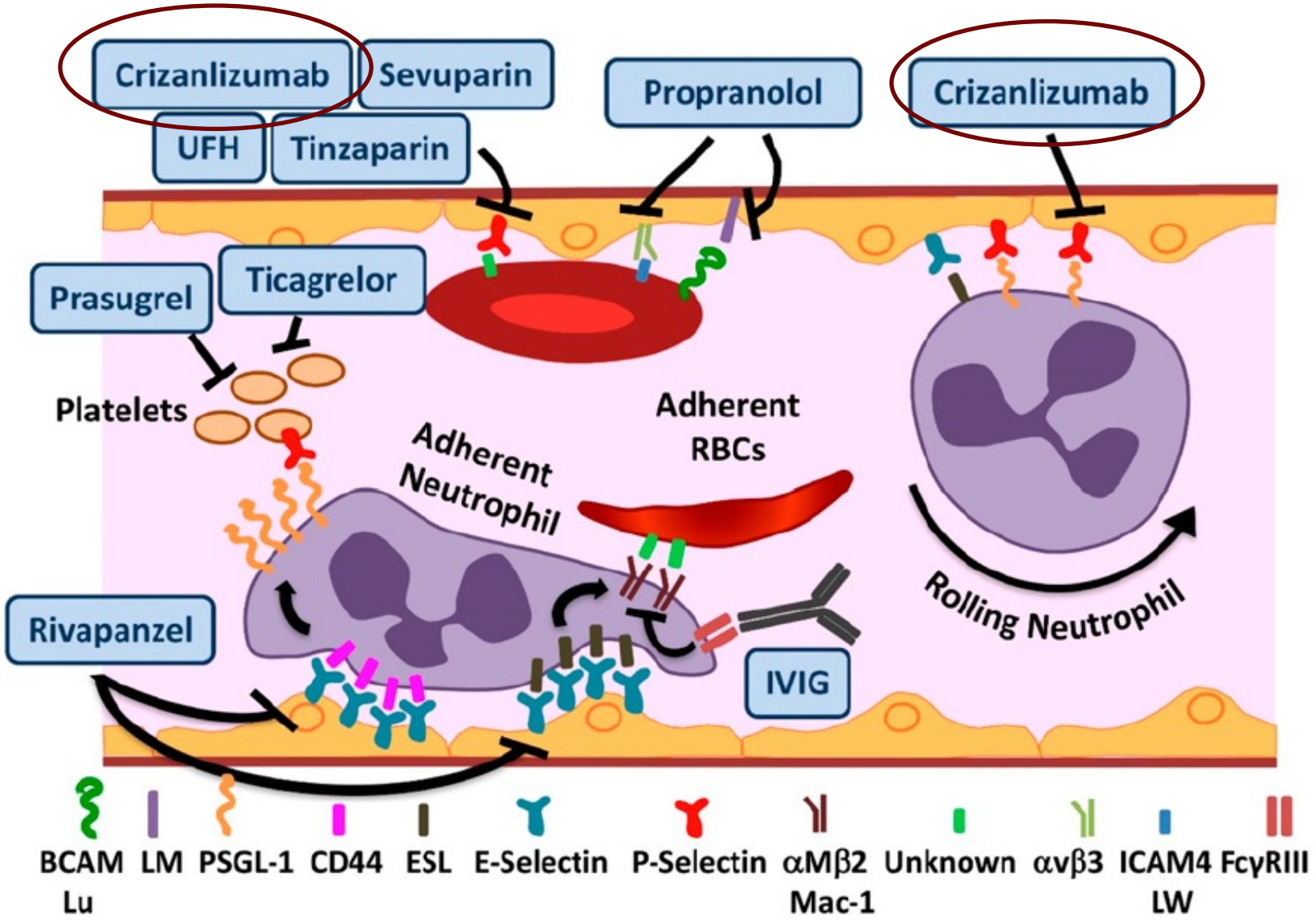
Novel agents → adhesion in SCD



Moerdler and Manwani. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):493-506.

The NEW ENGLAND JOURNAL of MEDICINE

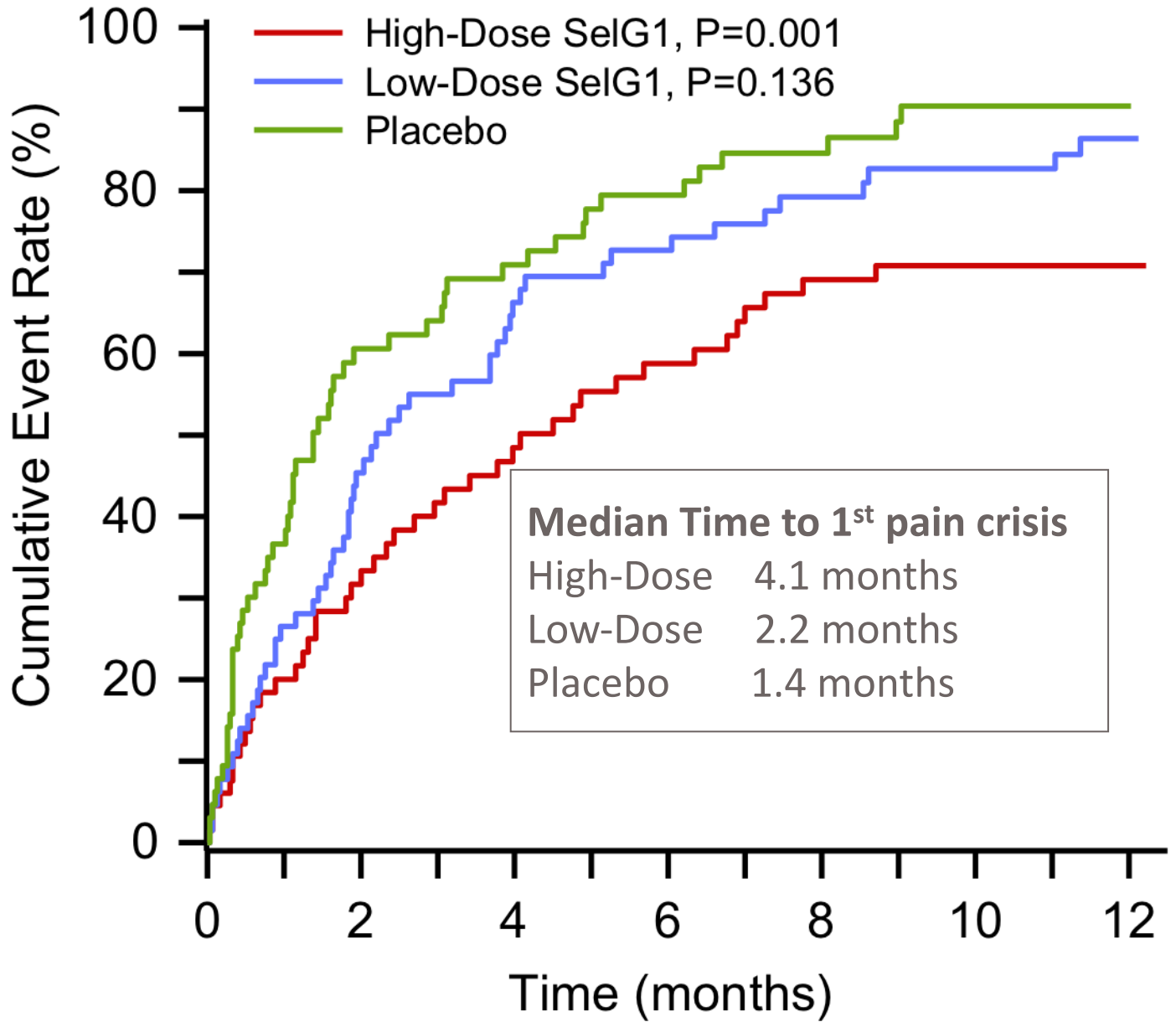
ORIGINAL ARTICLE

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

K.I. Ataga, A. Kutlar, J. Kanter, D. Liles, R. Cancado, J. Friedrisch, T.H. Guthrie, J. Knight-Madden, O.A. Alvarez, V.R. Gordeuk, S. Gualandro, M.P. Colella, W.R. Smith, S.A. Rollins, J.W. Stocker, and R.P. Rother

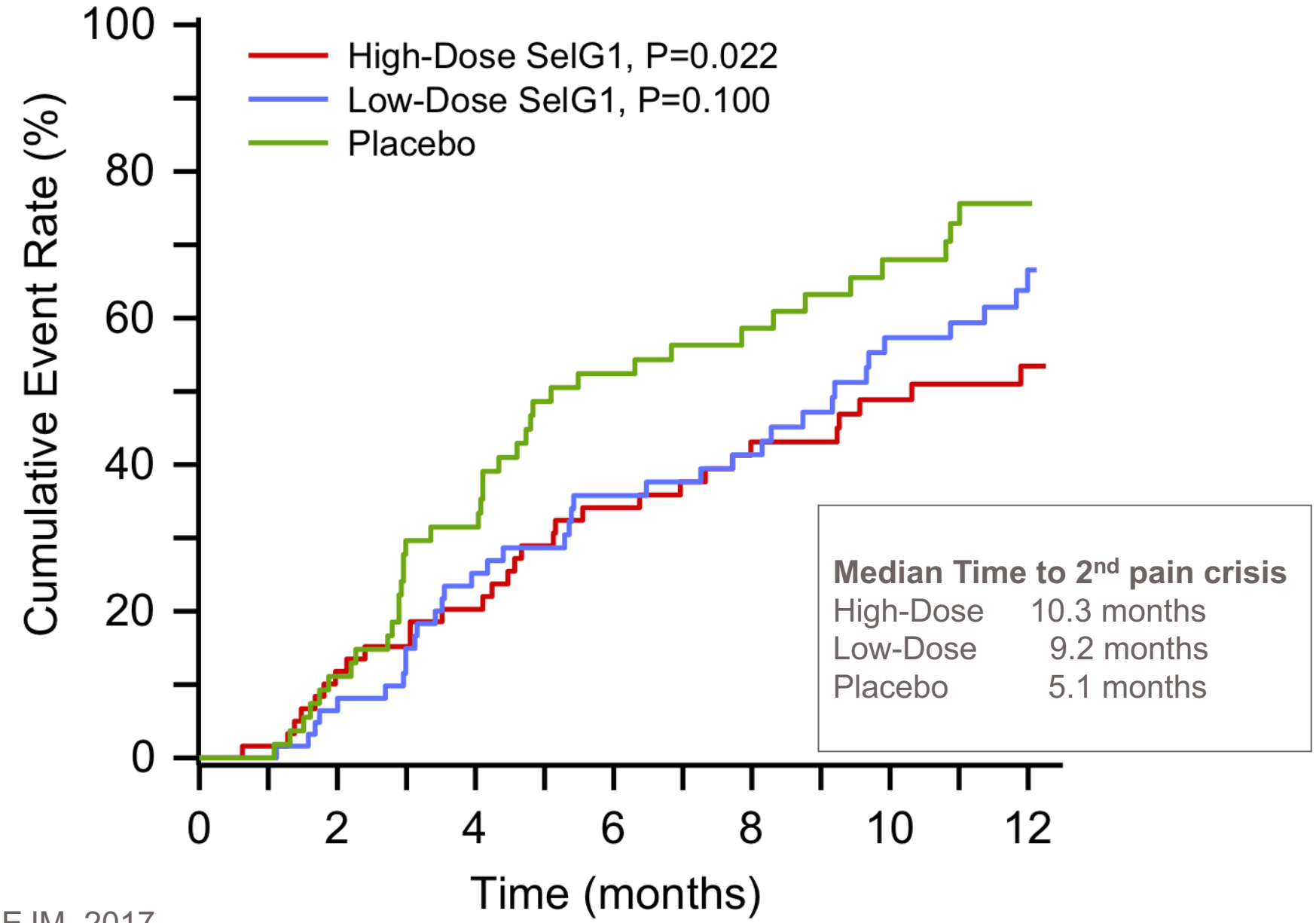
Ataga KI et al. *N Engl J Med.* 2017;376(5):429-439

Time to 1st sickle cell-related pain crisis



Ataga KI, et al. NEJM, 2017

Time to 2nd sickle cell pain crisis



Ataga KI, et al. NEJM, 2017

Table 4. Adverse Events in the Safety Population.*

Variable	High-Dose Crizanlizumab (N=66)	Low-Dose Crizanlizumab (N=64)	Placebo (N=62)
		no. of patients (%)	
Serious adverse events			
No. of patients with ≥1 serious adverse event	17 (26)	21 (33)	17 (27)
Most frequent serious adverse events†			
Pyrexia	2 (3)	0	1 (2)
Influenza	0	3 (5)	0
Pneumonia	3 (5)	2 (3)	3 (5)
Adverse events			
No. of patients with ≥1 adverse event	57 (86)	56 (88)	55 (89)
Most frequent adverse events‡			
Headache	11 (17)	14 (22)	10 (16)
Back pain	10 (15)	13 (20)	7 (11)
Nausea	12 (18)	11 (17)	7 (11)
Arthralgia	12 (18)	9 (14)	5 (8)
Pain in extremity	11 (17)	8 (12)	10 (16)
Urinary tract infection	9 (14)	7 (11)	7 (11)
Upper respiratory tract infection	7 (11)	7 (11)	6 (10)
Pyrexia	7 (11)	6 (9)	4 (6)
Diarrhea	7 (11)	5 (8)	2 (3)
Musculoskeletal pain	8 (12)	4 (6)	6 (10)
Pruritus	5 (8)	7 (11)	3 (5)
Vomiting	5 (8)	7 (11)	3 (5)
Chest pain	1 (2)	7 (11)	1 (2)

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DOI: 10.1002/ajh.26002

Severe infusion-related reaction to crizanlizumab in an adolescent with sickle cell disease

Karkoska et al. https://doi.org/10.1002/ajh.26002

Laboratory changes pre- and post- crizanlizumab infusion

Laboratory Value	Before Infusion	After Infusion	Day of Discharge
WBC ($\times 10^9$/L)	7.8	15.2	9.3
Hemoglobin (g/dL)	7.8	7.3 (min 6.7)	7.2
Nucleated red cells ($\times 10^3$/mcL)	0.96	2.26 (max 3.85)	0.36
Reticulocyte Count ($\times 10^9$/L)	304	179	82
AST (unit/L)	77	79	51
ALT (unit/L)	39	150	31
Total Bilirubin (mg/dL)	3.7	4.5	1.6
Phosphorous (mg/dL)	3.2[a]	1.3	4.3
Alkaline Phosphorous (unit/L)	111	349	213
sC5b-0 (ng/mL)	N/A	258	N/A

Karkoska et al. https://doi.org/10.1002/ajh.26002

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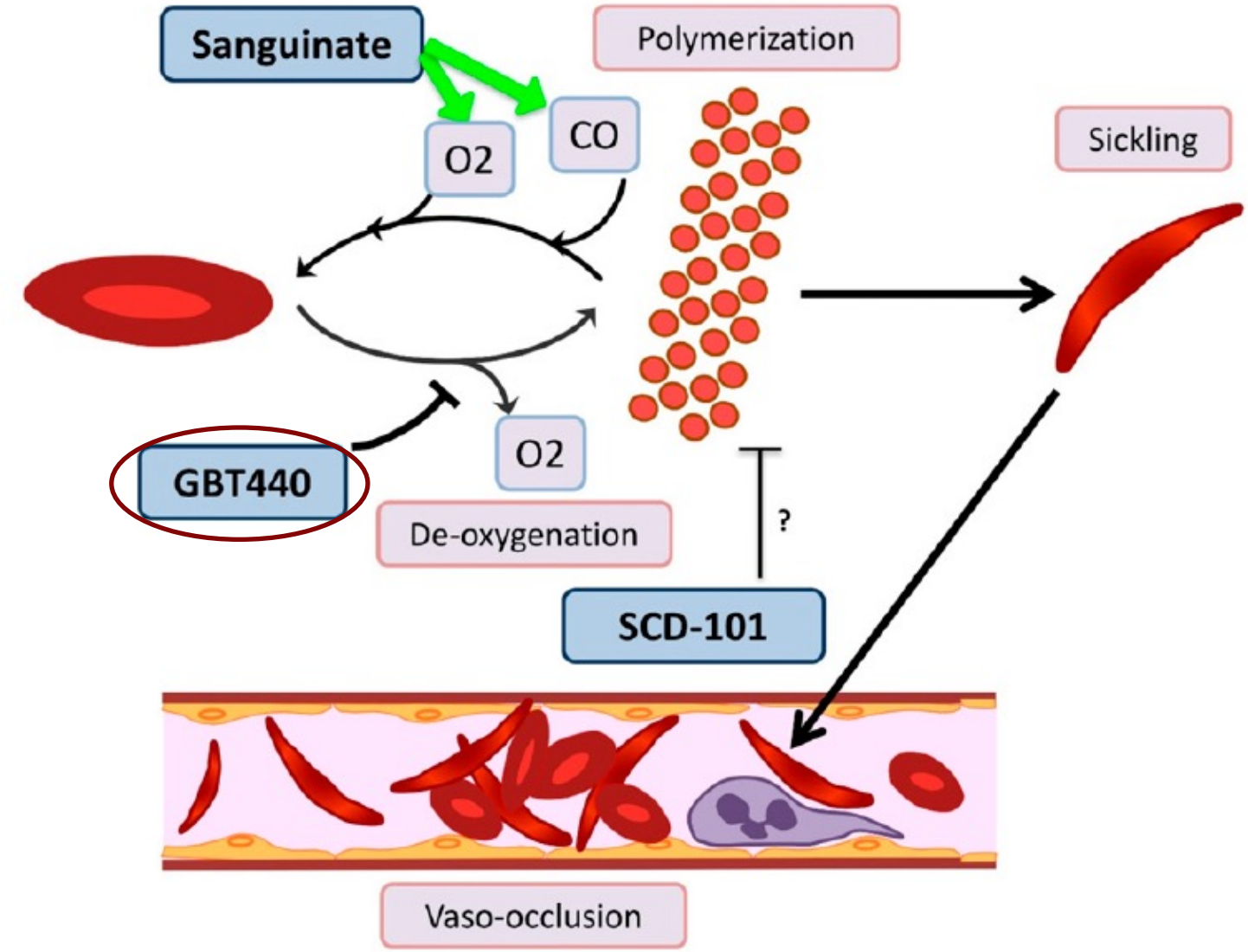
Novel agents → RBC sickling in SCD



Moerdler and Manwani. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):493-506.

The NEW ENGLAND JOURNAL of MEDICINE

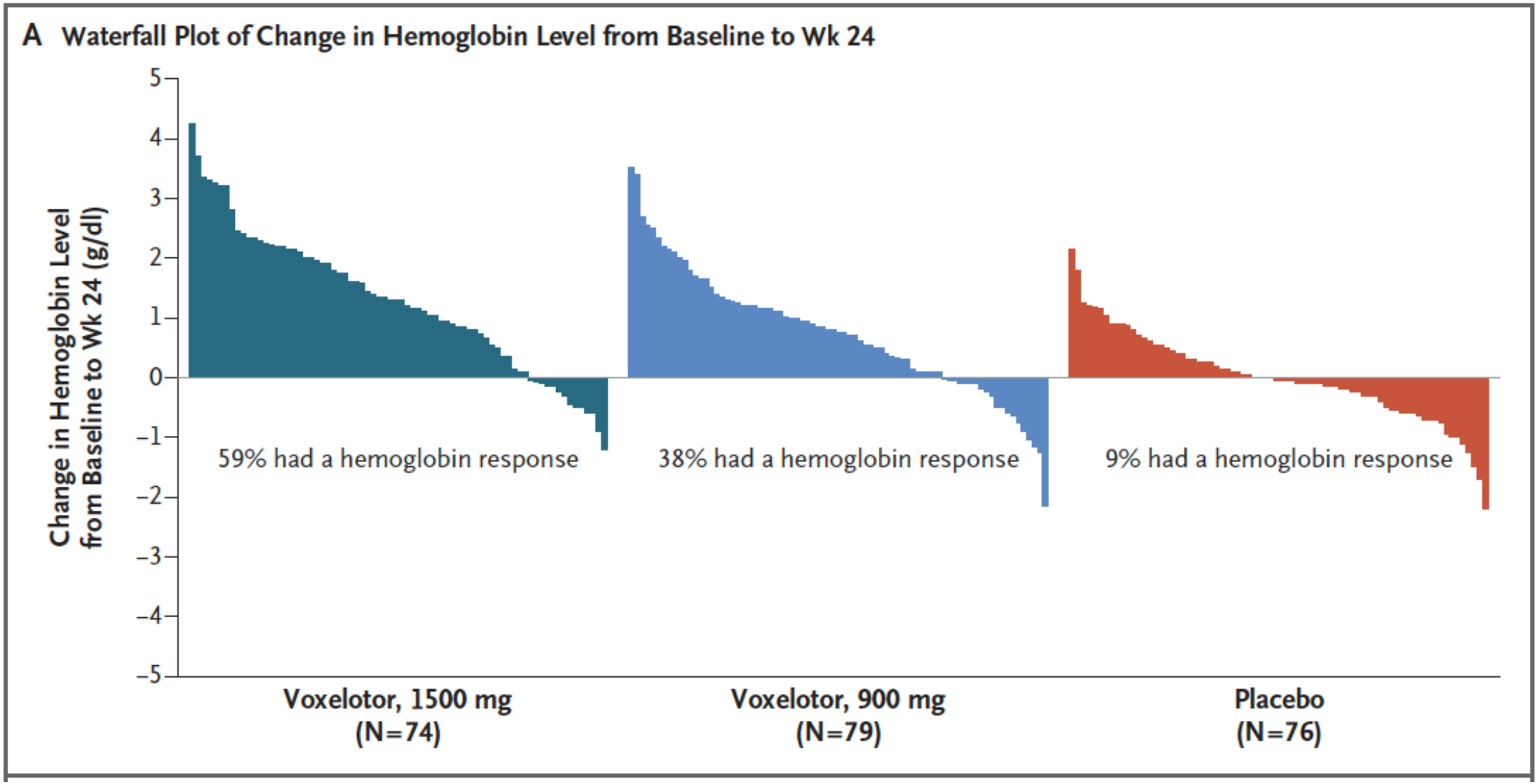
ESTABLISHED IN 1812 AUGUST 8, 2019 VOL. 381 NO. 6

A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

Elliott Vichinsky, M.D., Carolyn C. Hoppe, M.D., Kenneth I. Ataga, M.D., Russell E. Ware, M.D., Ph.D., Videlis Nduba, M.B., Ch.B., M.P.H., Amal El-Beshlawy, M.D., Hoda Hassab, M.D., Maureen M. Achebe, M.D., M.P.H., Salam Alkindi, M.B., B.Ch., R. Clark Brown, M.D., Ph.D., David L. Diuguid, M.D., Paul Telfer, M.D., Dimitris A. Tsitsikas, M.D., Ashraf Elghandour, M.D., Victor R. Gordeuk, M.D., Julie Kanter, M.D., Miguel R. Abboud, M.D., Joshua Lehrer-Graiwer, M.D., Margaret Tonda, Pharm.D., Allison Intondi, Ph.D., Barbara Tong, Ph.D., and Jo Howard, M.D., for the HOPE Trial Investigators*

Vichinsky E., et al. *N Engl J Med.* 2019;381(6):509-519.

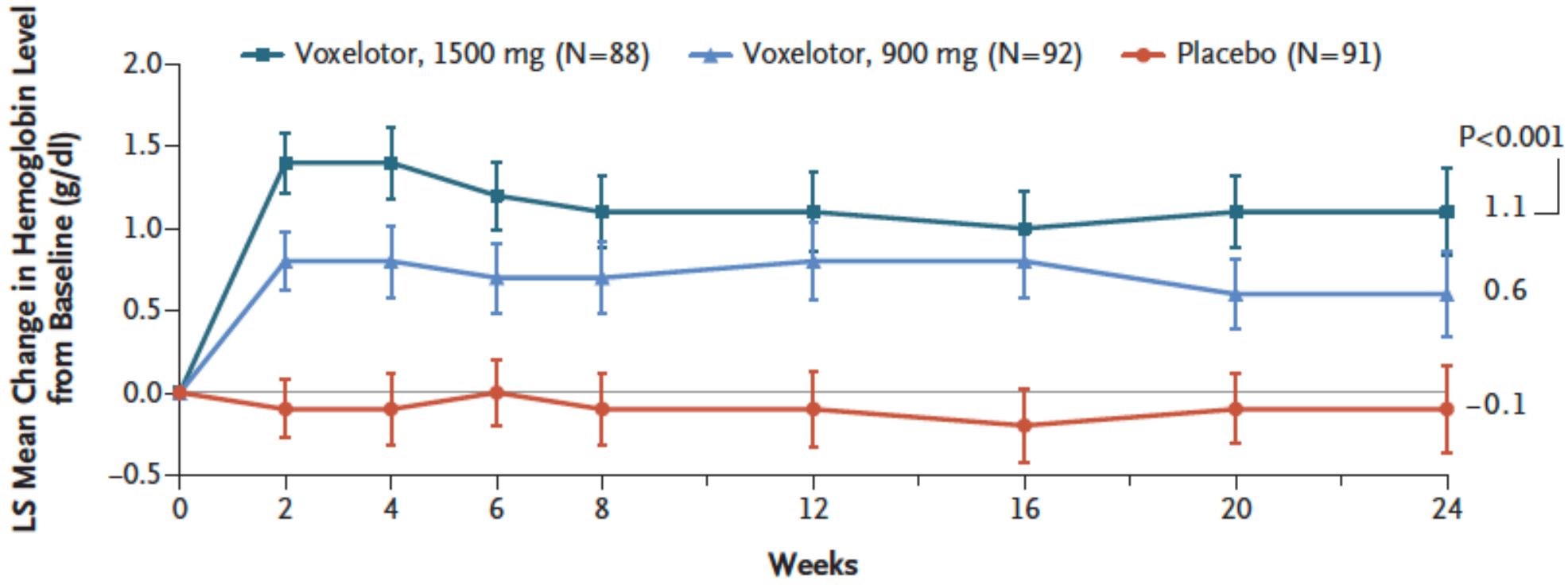
Change in Hb levels from 0-24 weeks with voxelator



Vichinsky E, et al. *N Engl J Med.* 2019;381(6):509-519

Change in Hb levels at 24 weeks with voxelator

B LS Mean Change in Hemoglobin Level from Baseline to Wk 24



No. at Risk								
Voxelotor, 1500 mg	76	78	74	74	71	76	77	72
Voxelotor, 900 mg	82	78	69	74	76	77	73	78
Placebo	82	79	81	74	81	77	78	72

Vichinsky E, Hoppe CC, Ataga KI, et al. *N Engl J Med.* 2019;381(6):509-519

Table 3. Annualized Incidence Rate of Vaso-Occlusive Crisis and the Most Common Adverse Events That Occurred or Worsened during the Treatment Period.

Variable	Voxelotor, 1500 mg (N=88)	Voxelotor, 900 mg (N=92)	Placebo (N=91)
Annualized incidence rate of vaso-occlusive crisis — no. of crises per person-yr (95% CI)*	2.77 (2.15 to 3.57)	2.76 (2.15 to 3.53)	3.19 (2.50 to 4.07)
Participants with ≥1 vaso-occlusive crisis — no. (%)	59 (67)	61 (66)	63 (69)
Total no. of vaso-occlusive crises	179	183	219
Adverse events not related to sickle cell disease — no. (%)†			
Incidence of adverse events of any grade	83 (94)	86 (93)	81 (89)
Adverse events with ≥10% incidence			
Headache	23 (26)	14 (15)	20 (22)
Diarrhea	18 (20)	16 (17)	9 (10)
Nausea	15 (17)	15 (16)	9 (10)
Arthralgia	13 (15)	11 (12)	11 (12)
Upper respiratory tract infection	12 (14)	17 (18)	10 (11)
Abdominal pain	12 (14)	13 (14)	7 (8)
Fatigue	12 (14)	12 (13)	9 (10)
Rash‡	12 (14)	10 (11)	9 (10)
Pyrexia	11 (12)	10 (11)	6 (7)
Pain in extremity	10 (11)	18 (20)	16 (18)
Back pain	10 (11)	13 (14)	10 (11)
Vomiting	10 (11)	12 (13)	11 (12)
Pain	8 (9)	10 (11)	6 (7)
Noncardiac chest pain	7 (8)	12 (13)	8 (9)
Upper abdominal pain	6 (7)	11 (12)	6 (7)

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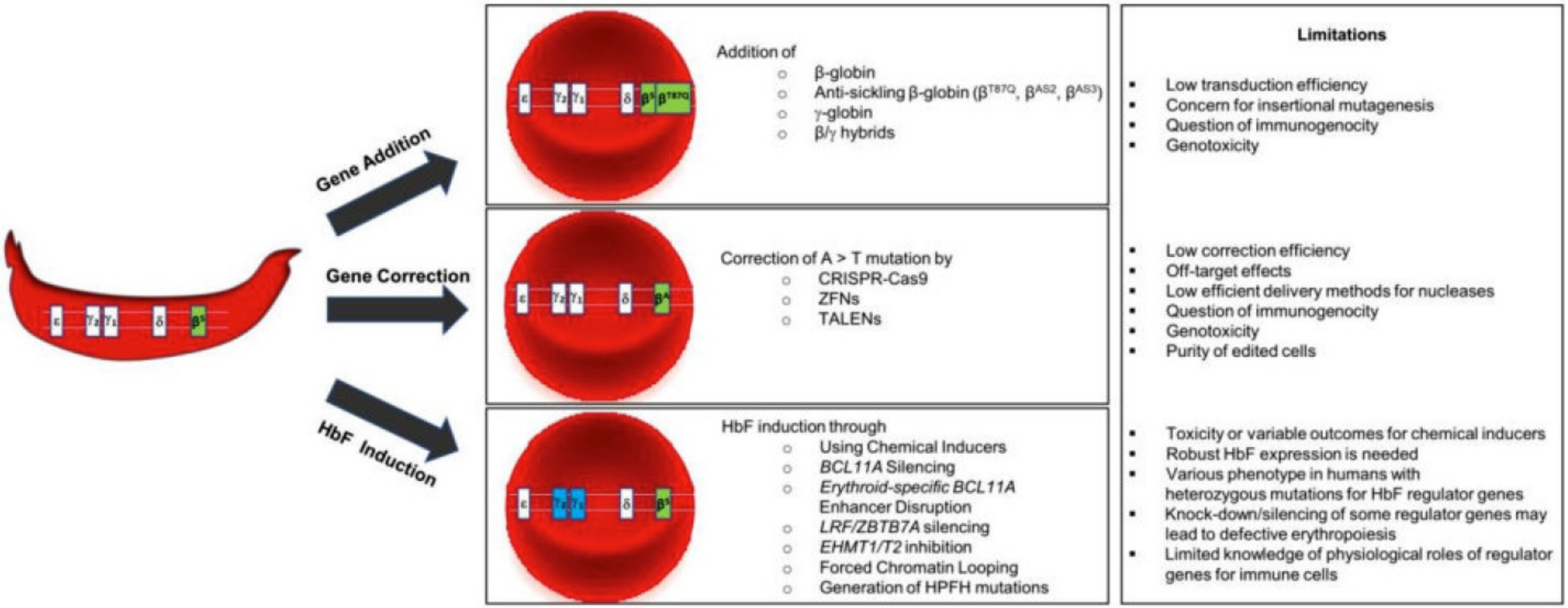
Gene therapy for SCD



Demirci, Uchida & Tisdale. Cytotherapy. 2018 July ; 20(7): 899–910
Drysdale et al. Cell Stem Cell 2021; 28:191-208

Slide courtesy of Dr. Kleber Fertrin (University of Washington, Seattle, WA)

Pros and cons of alloHCT vs. Gene therapy

- **AlloHCT – pros**
  - Data on longer follow up
  - Expanding donor pool: haplo
  - Can achieve 100% chimerism

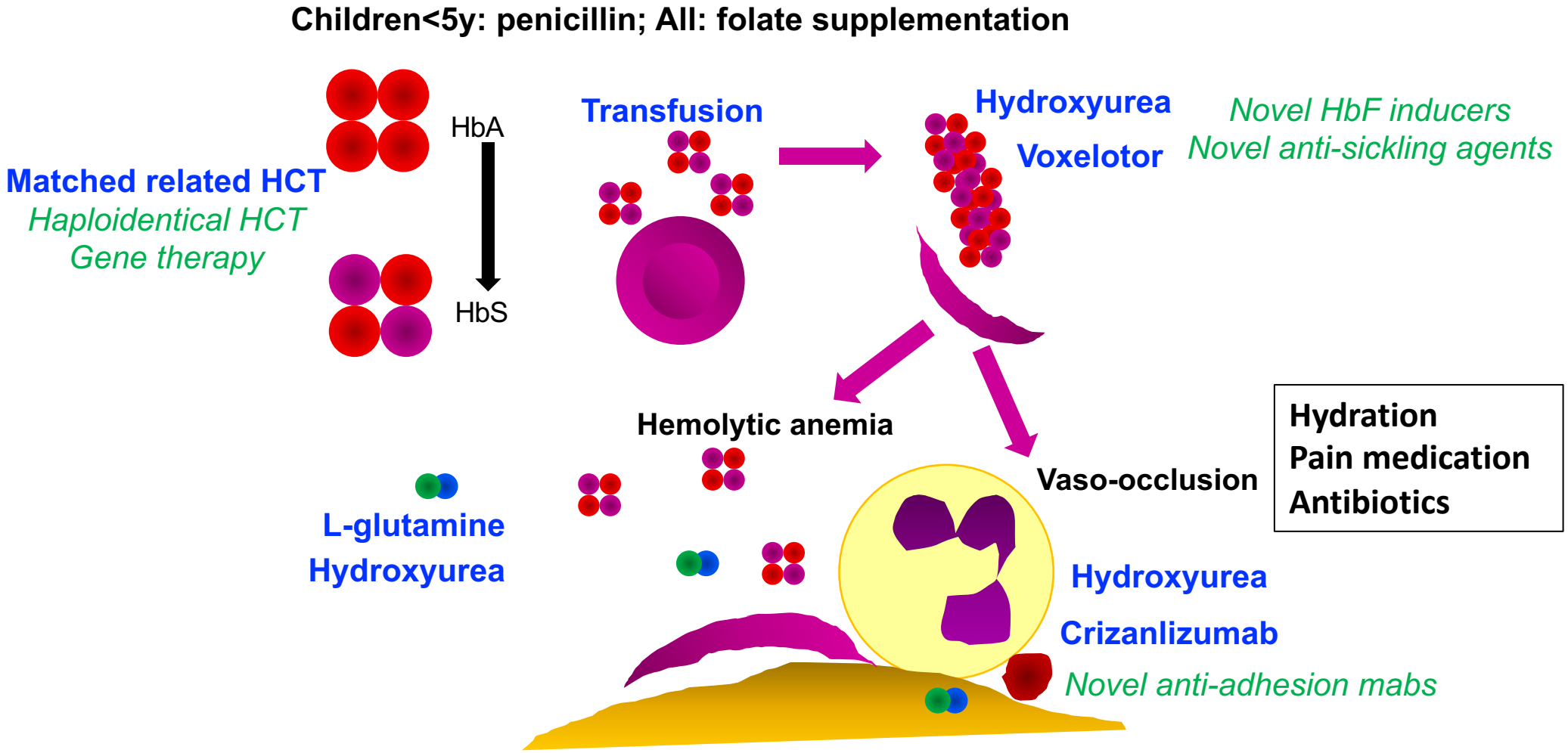
- ***AlloHCT – cons***
  - GVHD
  - Immunosuppression
  - Long-term effects of radiation?

- **Gene therapy – pros**
  - No need for donor
  - Only needs 30% Hb replacement?
  - No GVHD

- ***Gene therapy – cons***
  - Cost
  - Off-target effects, myeloid neoplasms?
  - Residual “mild” SCD?

Slide courtesy of Dr. Kleber Fertrin (University of Washington, Seattle, WA)

Summary: Therapeutic options for SCD



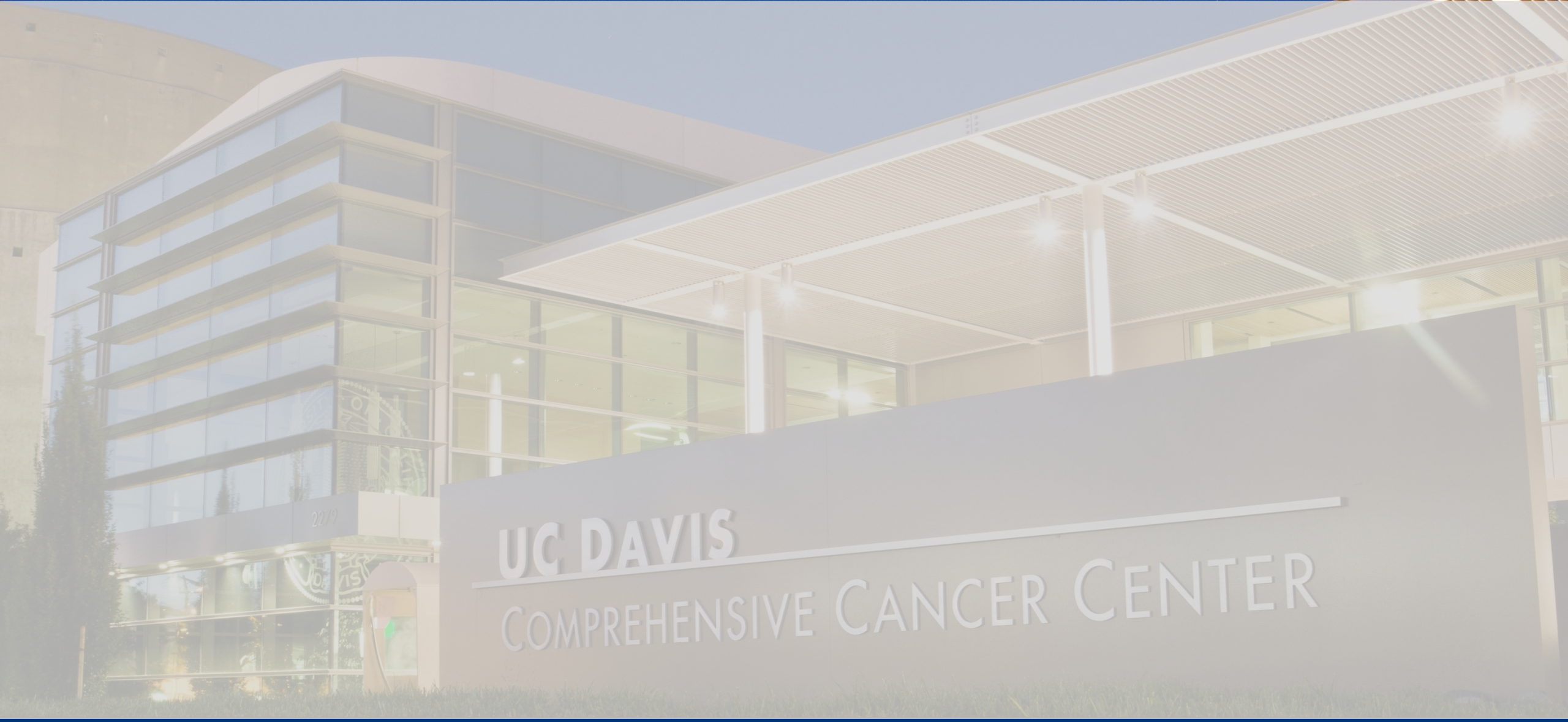
Adapted from Costa FF & Fertrin KY in: “Sickle Cell Anemia: From Basic Science to Clinical Practice”, Ch 12, Springer, 2016.

SCD Educational resources

- NHBLI Evidence-based Management of Sickle Cell Disease
  - Expert Panel Report (2014)
- ASH Benign Hematology Curriculum
  - Sickle cell disease course
- ASH Clinical Practice Guidelines on SCD*
  - Cardiopulmonary and Kidney Disease
  - Transfusion Support
  - Cerebrovascular Disease
  - Management of Acute and Chronic Pain
  - Stem Cell Transplantation
- UCSF Benioff Children's Hospital SCD Bootcamp

*ASH Pocket Guides (download from App store)

UCDAVIS COMPREHENSIVE CANCER CENTER



Thank you