(R)evolution in the knowledge and management of Sickle Cell Disease

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Overview

Background

Disease-modifying therapies

Curative therapies

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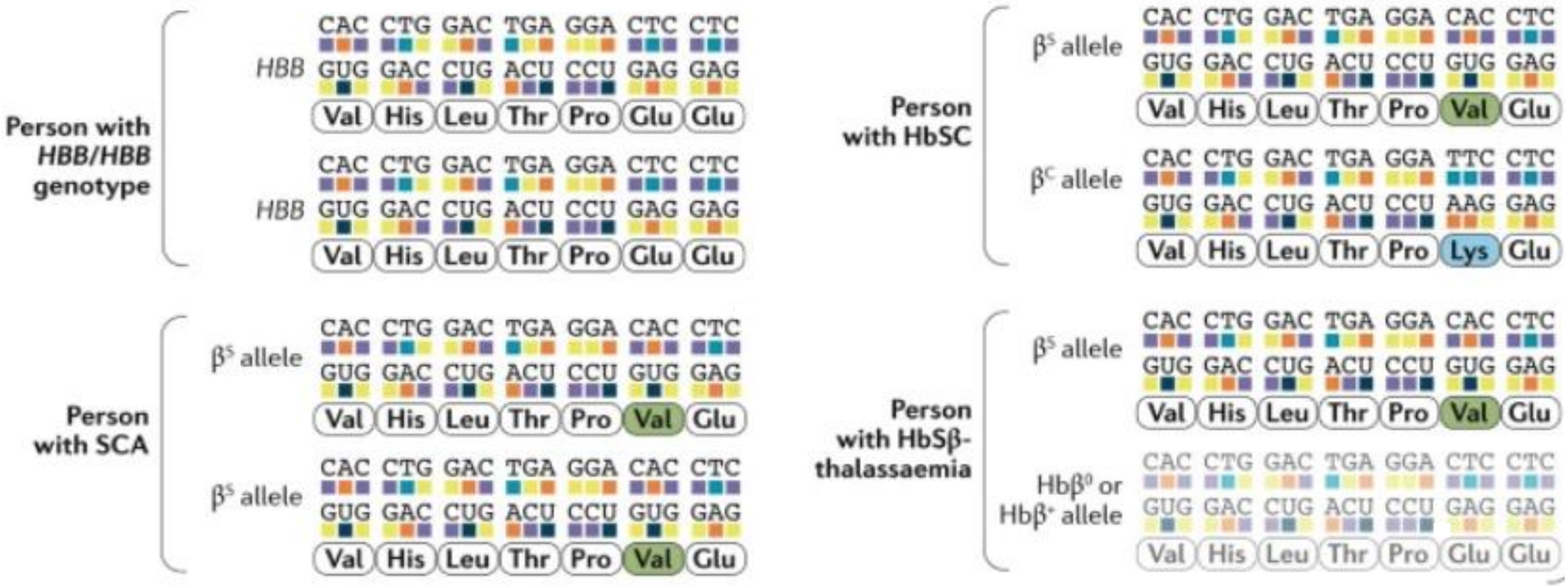
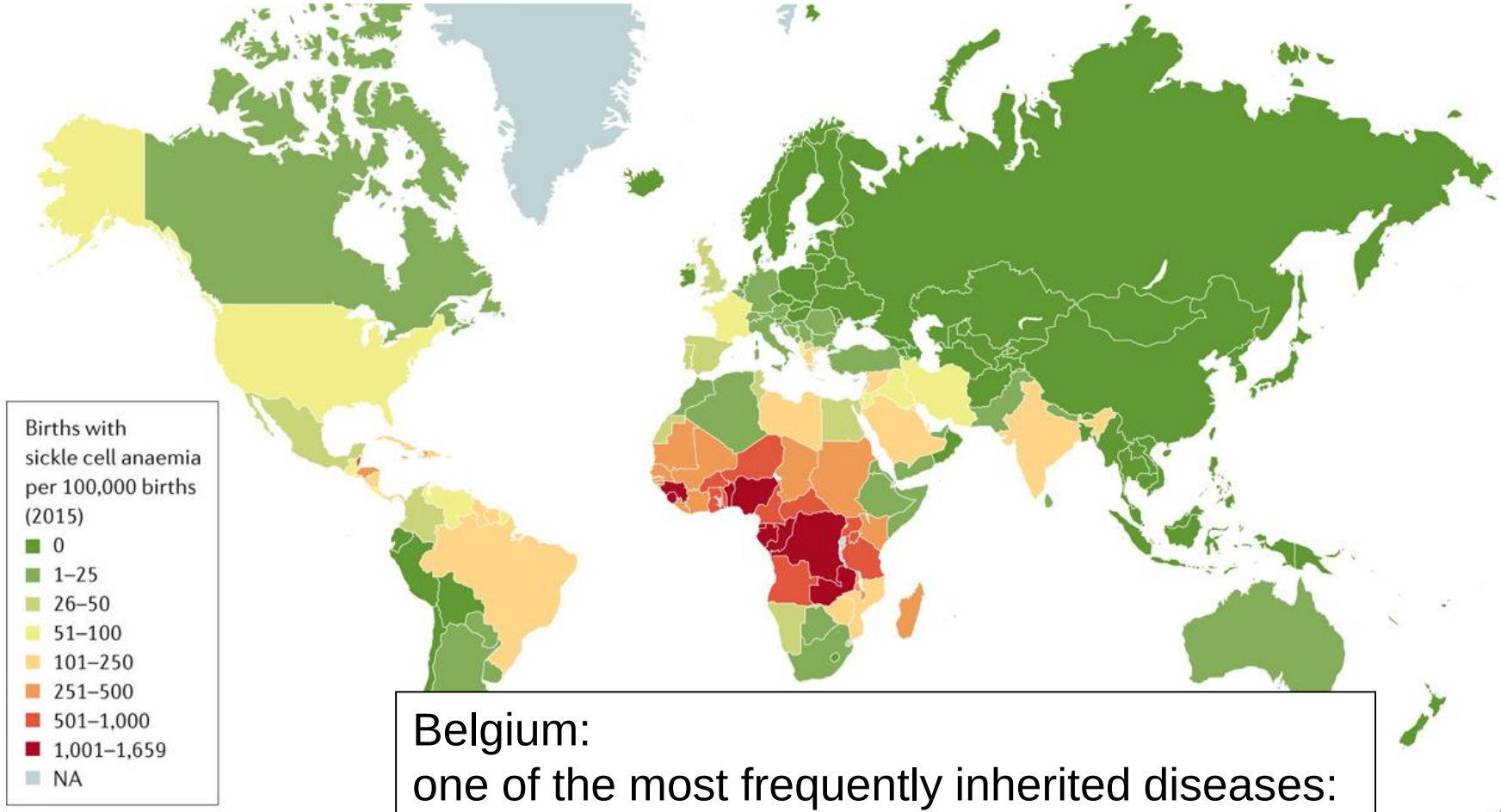
Introduction: autosomal recessive disorder



Kato et al., Nature Reviews 2018

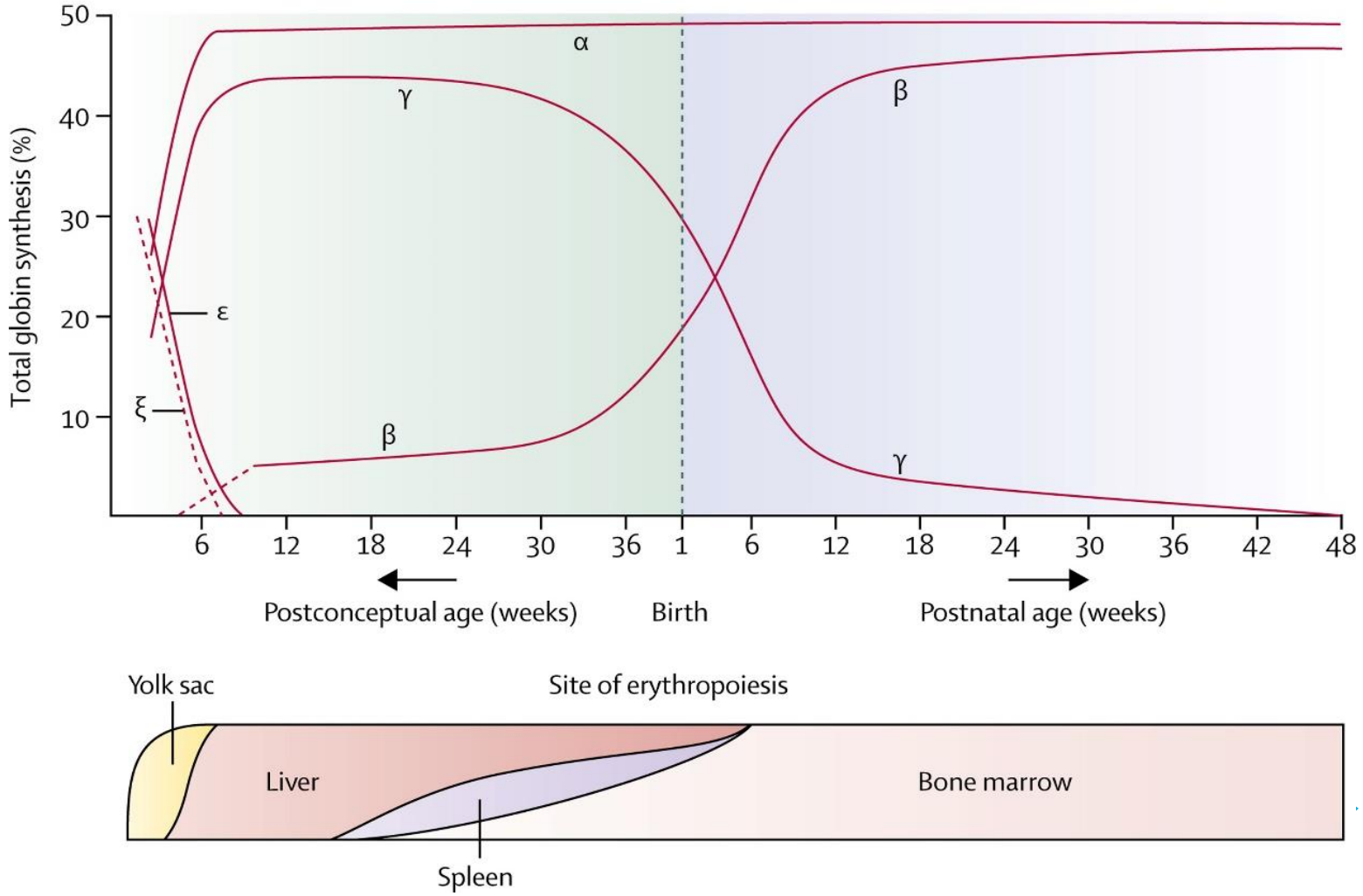
Most prevalent hemoglobinopathy worldwide



Belgium:
one of the most frequently inherited diseases:
1/2,329 newborns Ketelslegers et al., BJH 2015

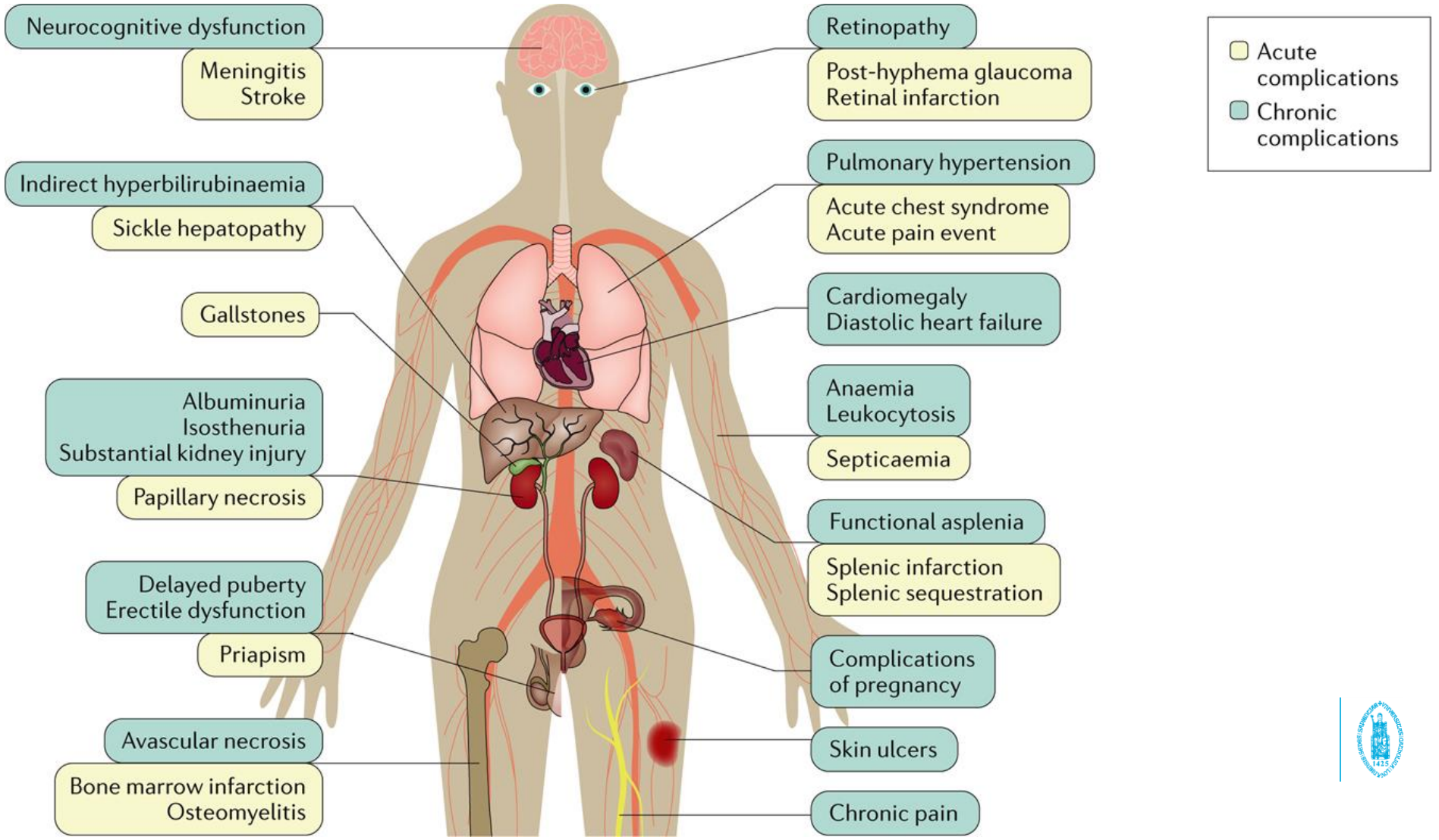
Kato et al., Nature Reviews 2018

Symptoms occur from the age of 6 months



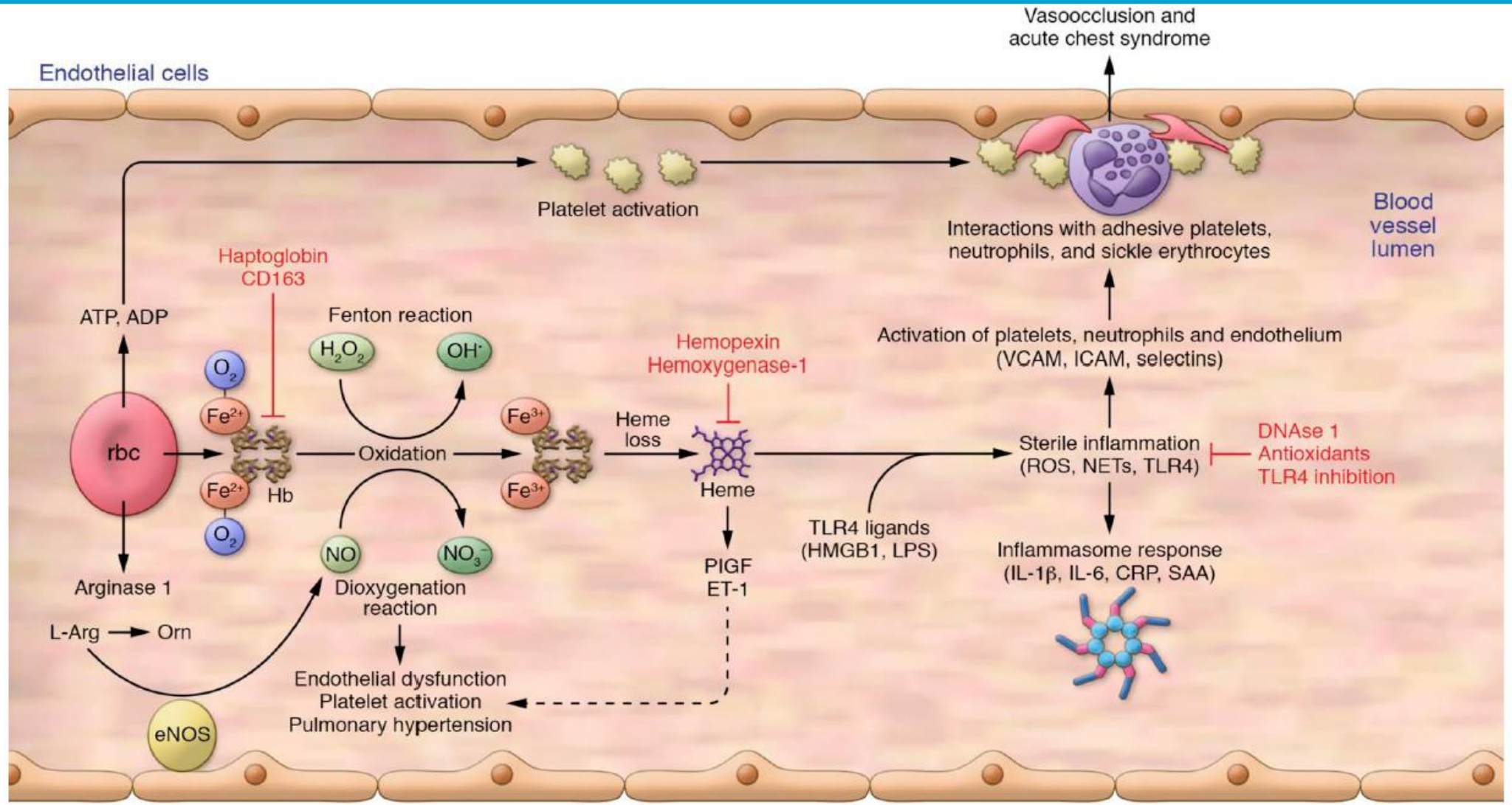
Taher et al., Lancet 2017

Fatal in childhood > chronic in adulthood



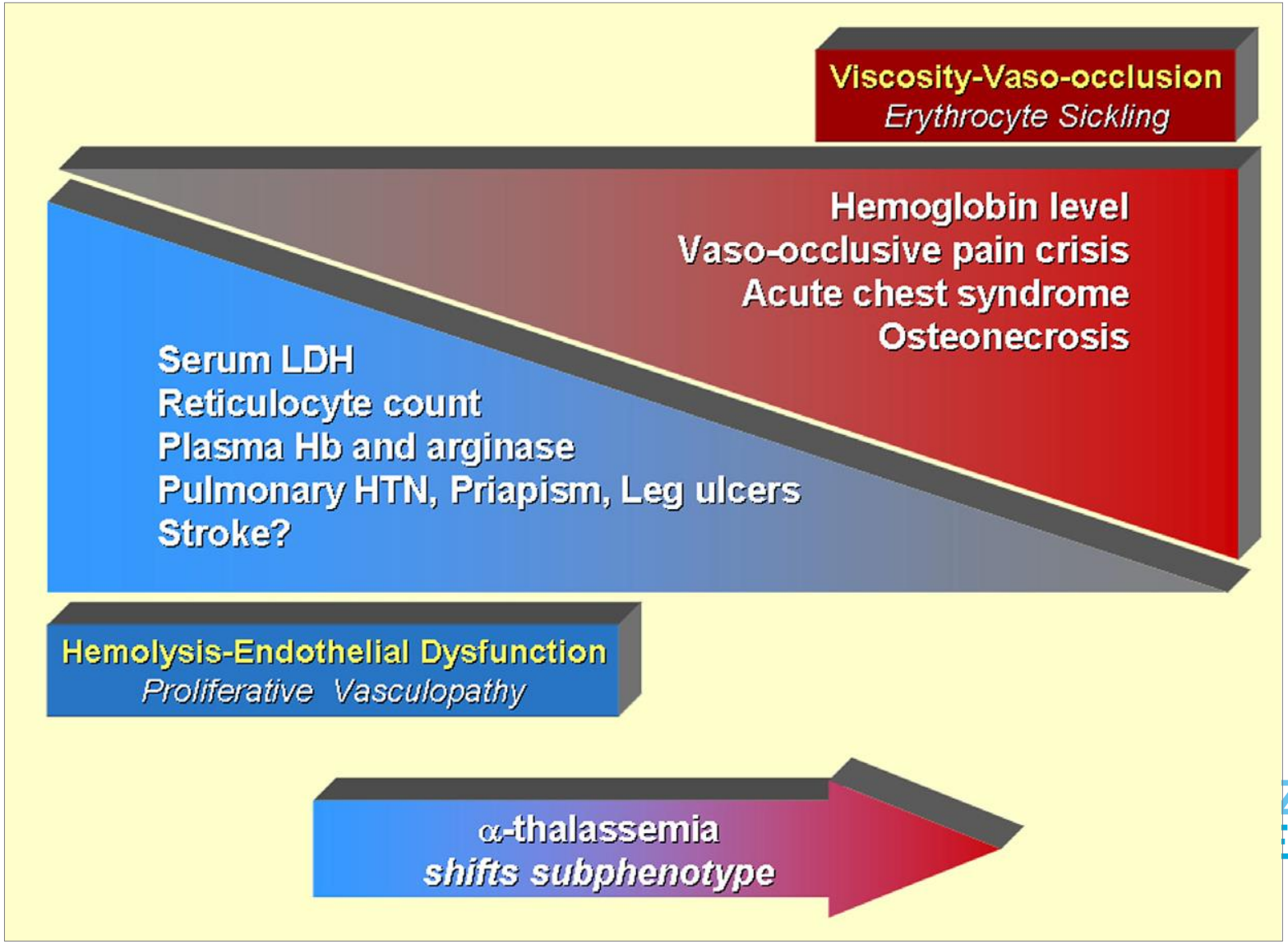
Kato et al., Nature Reviews 2018

Pathophysiology is multifactorial and complex



Osunkwo et al., Ther Adv Hematol 2020

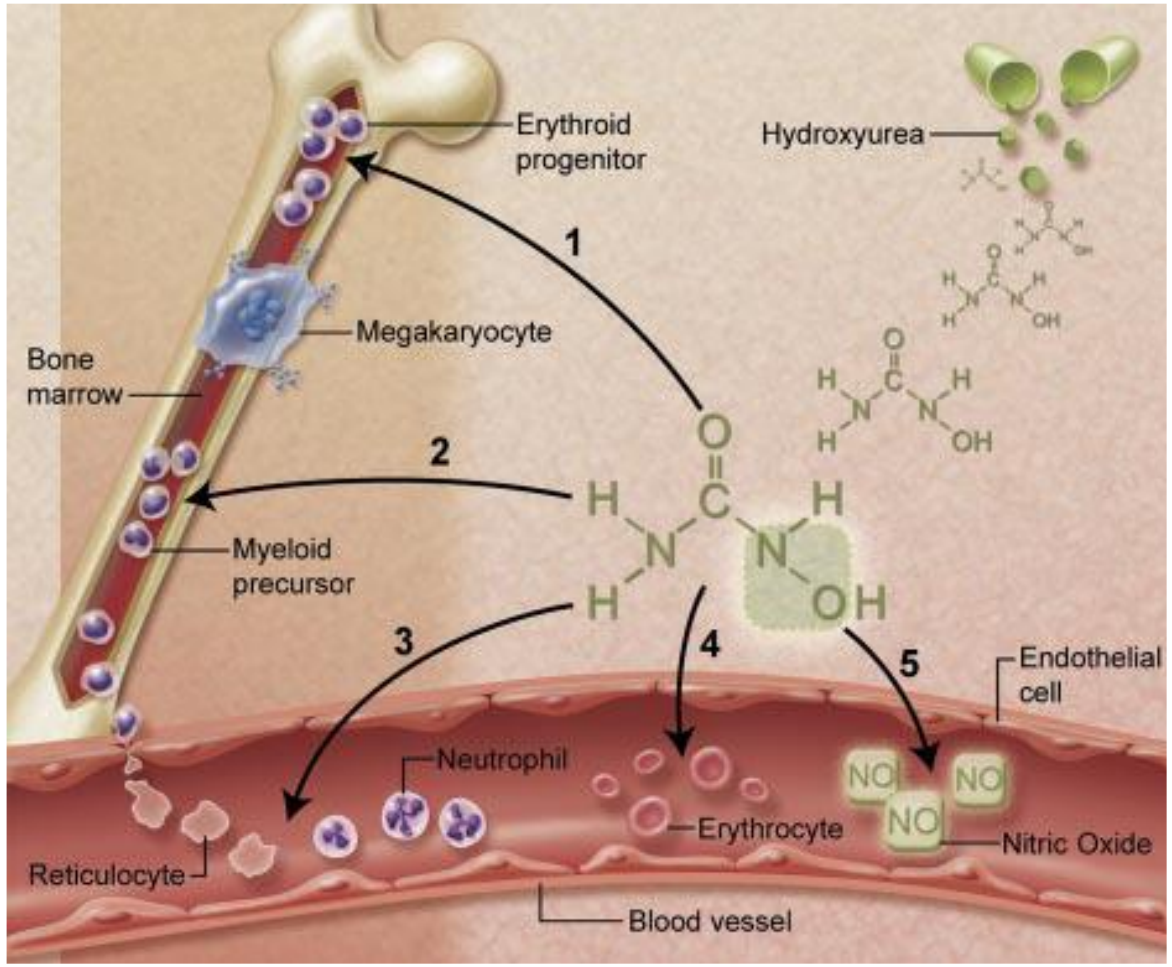
Heterogeneous spectrum of phenotypes

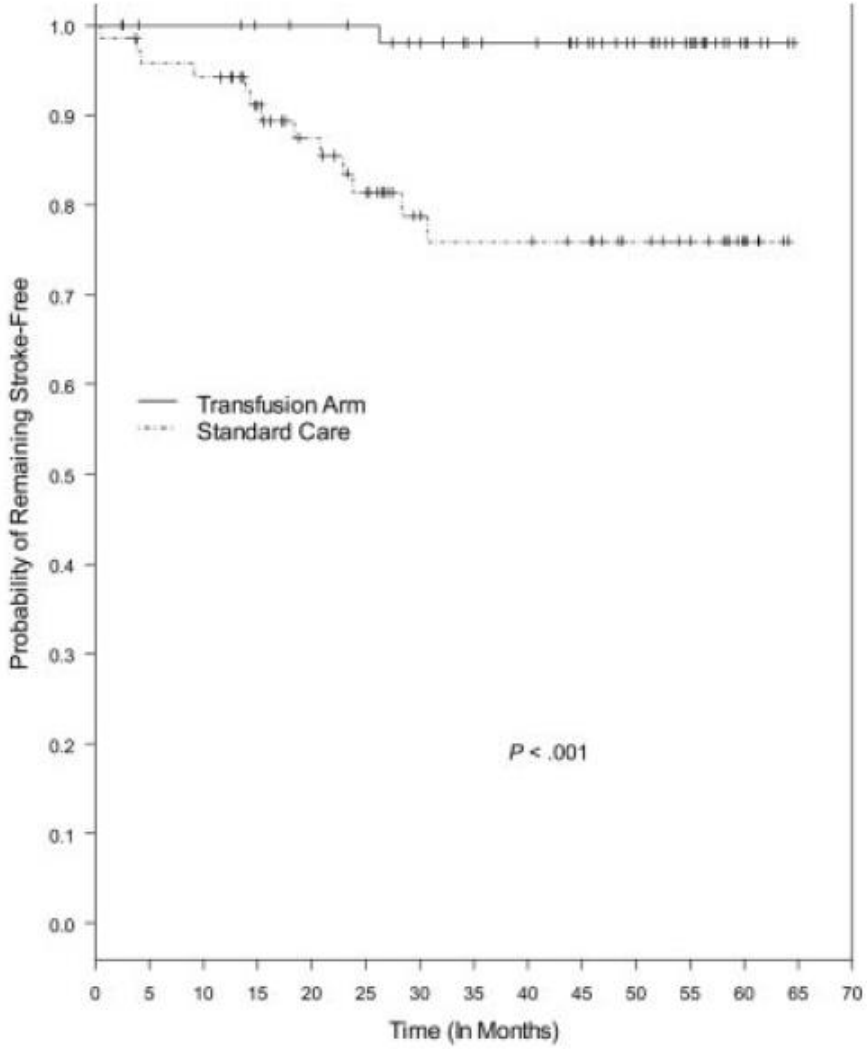


Kato et al., Nature Reviews 2018

Disease-modifying therapies

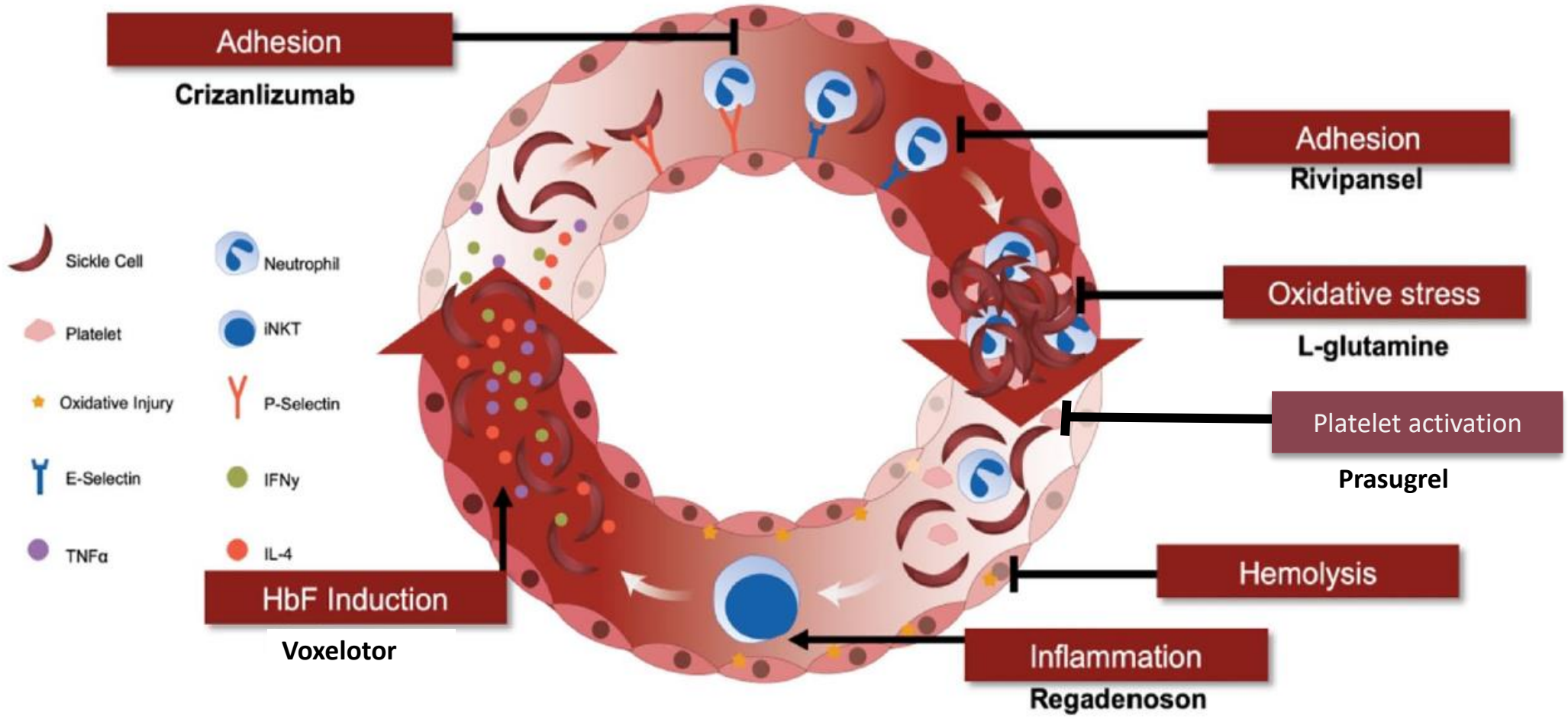
Current standard-of-care: hydroxyurea or chronic (exchange) transfusions





Ware et al., Blood 2010
Lee et al., Blood 2006

New disease-modifying therapies on the way



Osunkwo et al., Ther Adv Hematol 2020

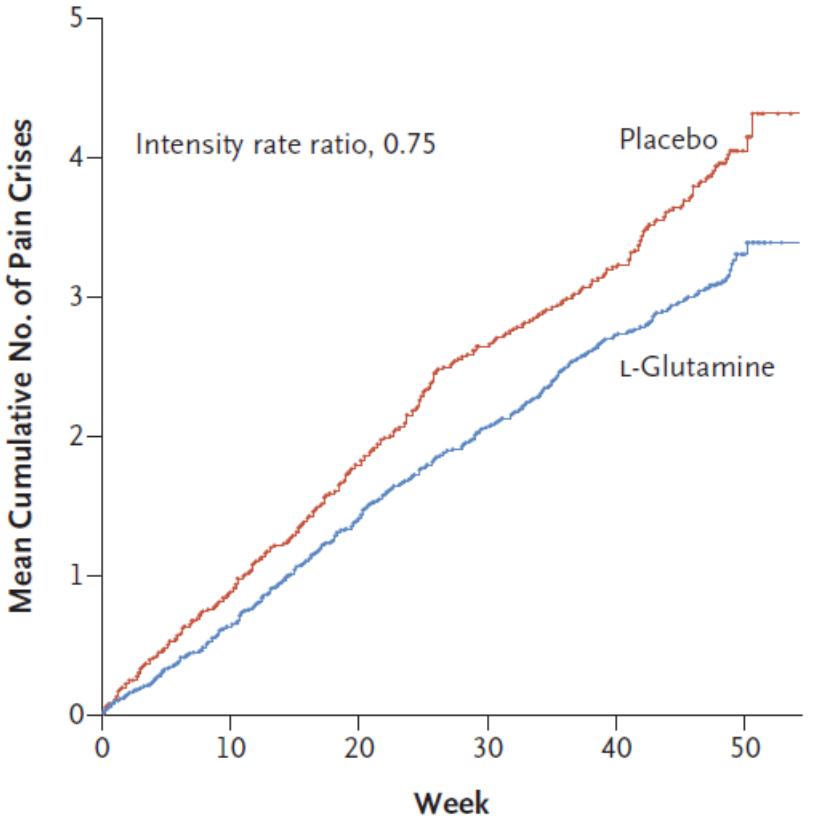
L-glutamine: antioxidant

multicenter, randomized, placebo-controlled, double-blind, phase 3 trial: oral L-glutamine (0.3 mg/kg; 2x/day)

156/230 patients (5 - 58 years); HbSS / HbSβ^0thal; 2/3 on concomitant HU

fewer pain crises; fewer hospitalizations

low-grade nausea, non-cardiac chest pain, fatigue, musculoskeletal pain



Niihara et al., NEJM 2018

Voxelotor: stabilizator of oxygenated HbS state

multicenter, randomized, placebo-controlled, double-blind, phase 3 trial: oral voxelotor (1500 mg or 900 mg daily vs placebo) for 72 weeks

274 patients (12 - 65 years); all genotypes; 2/3 on concomitant HU

@ 72 weeks: increased hemoglobin; decreased bilirubin and reticulocytes

no difference in adverse events between groups; most not related

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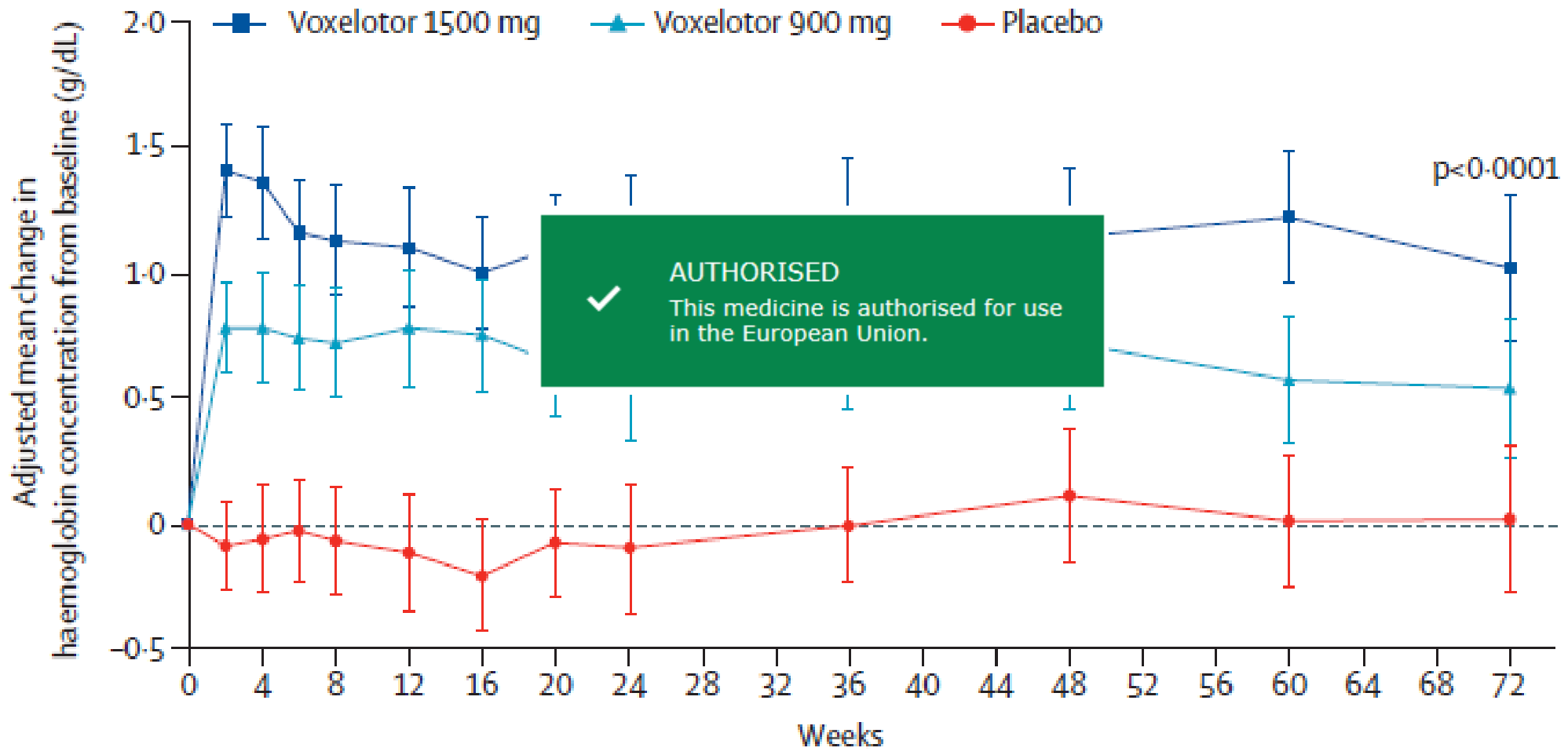
Howard et al., Lancet Haematol 2021

Voxelotor: stabilizator of oxygenated HbS state



Howard et al., Lancet Haematol 2021

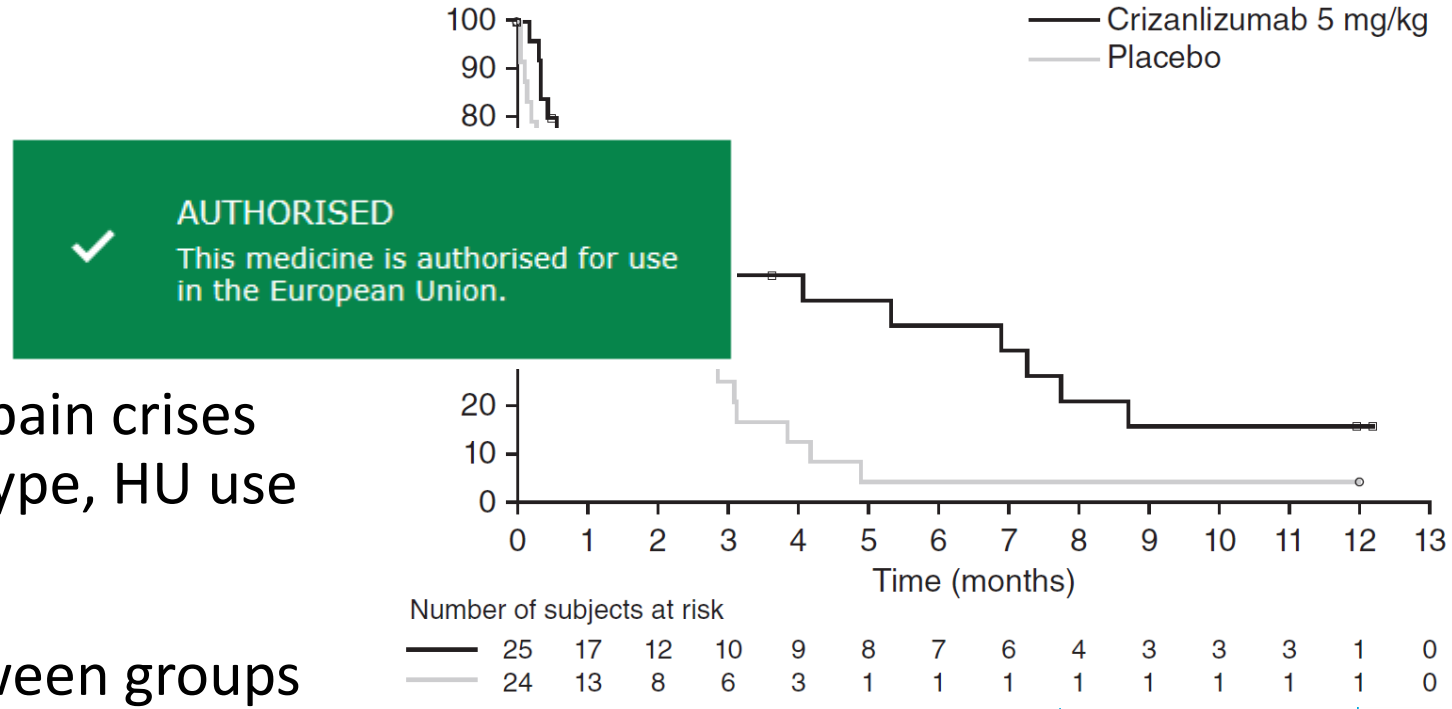
Crizanlizumab: humanized, anti-P-selectin monoclonal antibody

randomized, placebo-controlled, double-blind, phase 2 trial: IV crizanlizumab (5 mg/kg or 2.5 mg/kg monthly)

198 patients (16 - 65 years); all genc
40% on concomitant HU

more patients VOC-free and fewer pain crises irrespective of prior severity, genotype, HU use

rates of adverse events similar between groups



AUTHORISED
This medicine is authorised for use in the European Union.

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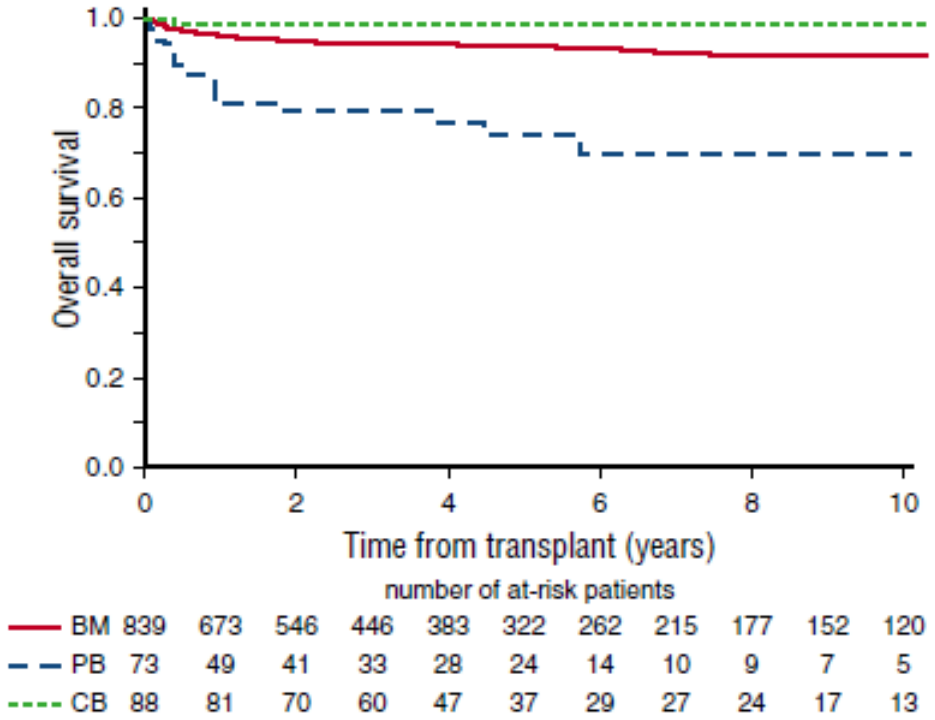
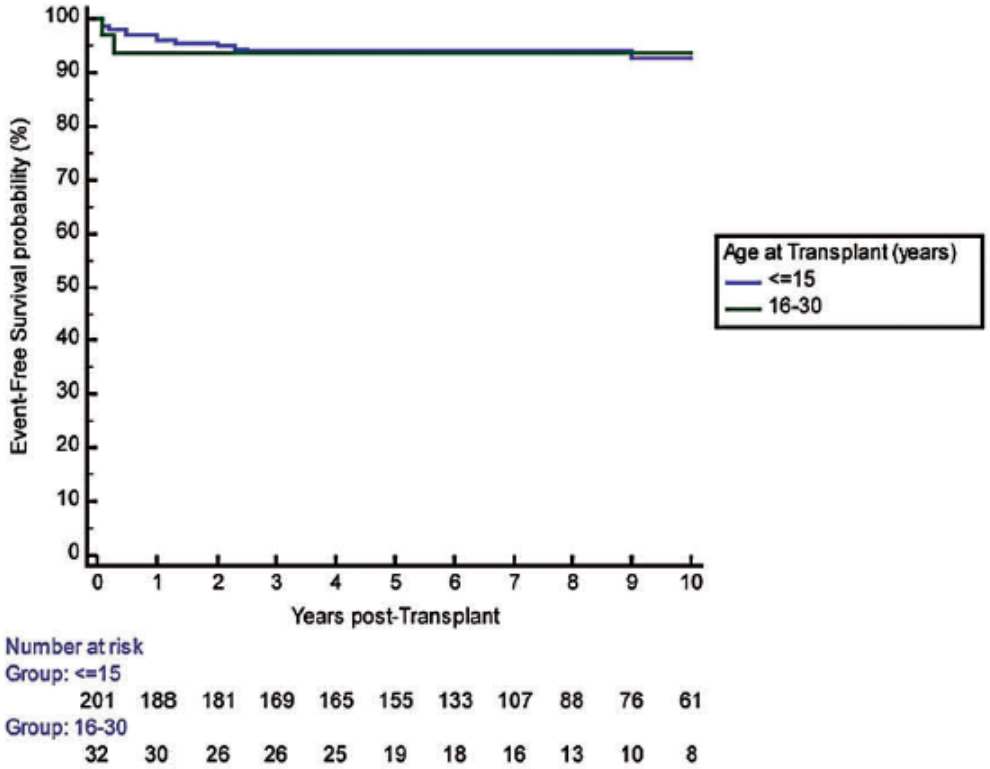
Kutlar et al., Am J Hematol 2019

Curative therapies

Transplantation: MSD





Gluckman et al., Blood 2017
Bernaudin et al., Haematologica 2019

Haplo-identical stem cell transplantation + PTCY

n=17 (14 haplo; 3 MSD)

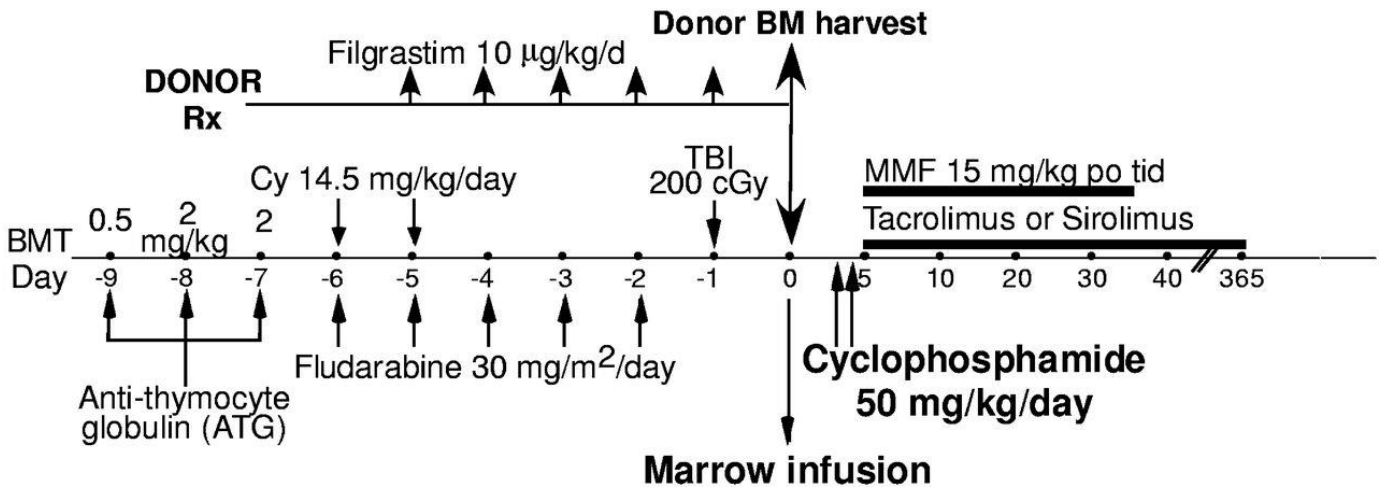
median age 30 years (15 - 46)

OS 100% (median FU 24 mths)

no GVHD

viral reactivation: n=4 (24%)

graft failure (43%) is main problem



Bolaeños-Meade et al., Blood 2012

Haplo-identical stem cell transplantation + TT + PTCY

n=15 (all HbSS)

median age 20 years (12 - 26)

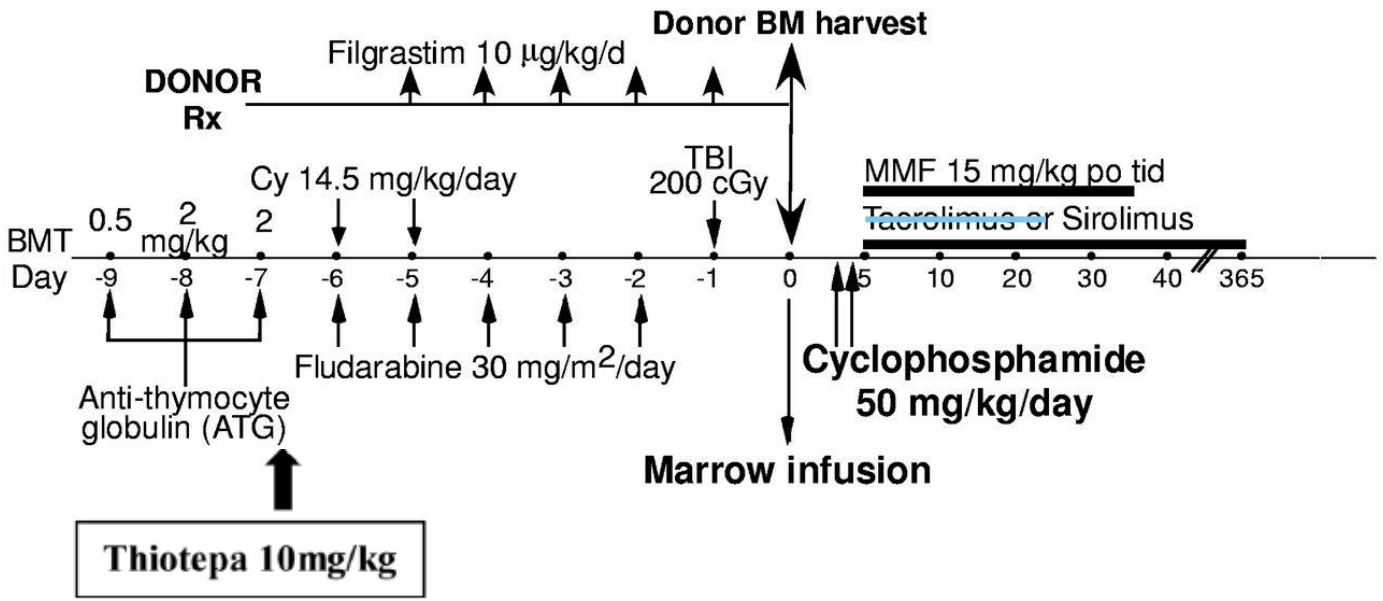
OS 100% (median FU 13 mths)

aGVHD II-IV: n=3 (20%)

cGVHD moderate: n=1 (7%)

viral reactivation: n=9 (60%)

graft failure: 7% (n=1 @ D+31)



de la Fuente et al., Biol Blood Marrow Transplant 2019

Haplo-identical stem cell transplantation + αβ/CD19 T-cell depletion

38 pts transplanted for advanced stage SCD-related complications

- bone marrow from an MSD : n=13
- peripheral blood stem cells from a haploidentical donor: n=25

conditioning regimen: thiotepa (2x5mg/kg), fludarabine (4x40mg/m^2),

treosulfan (3x14g/m^2) and ATG (3x15mg/kg)

GvHD prophylaxis: CSA or Tacrolimus and MMF

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Foell et al., Hematol Oncol Stem Cell Ther 2020

Haplo-identical stem cell transplantation + αβ/CD19 T-cell depletion

	T-haplo (n=25)	**MSD (n=13)**
median age (range)	13 yrs (3-31)	11 yrs (5-36)
median FU	22 months	19 months
OS n (%)	**22/25 (88%)**	**13/13 (100%)**
aGVHD I-II	7/25 (28%)	3/13 (23%)
aGVHD III-IV	0%	0%
cGVHD mild-to-moderate	n=4 (16%)	n=2 (15%)
viral reactivation	**n=13 (52%)**	**n=6 (46%)**
mortality	n=3 (12%) CMV pneumonitis (n=1) MAS (n=1) **graft failure D+200 (n=1)**	0%

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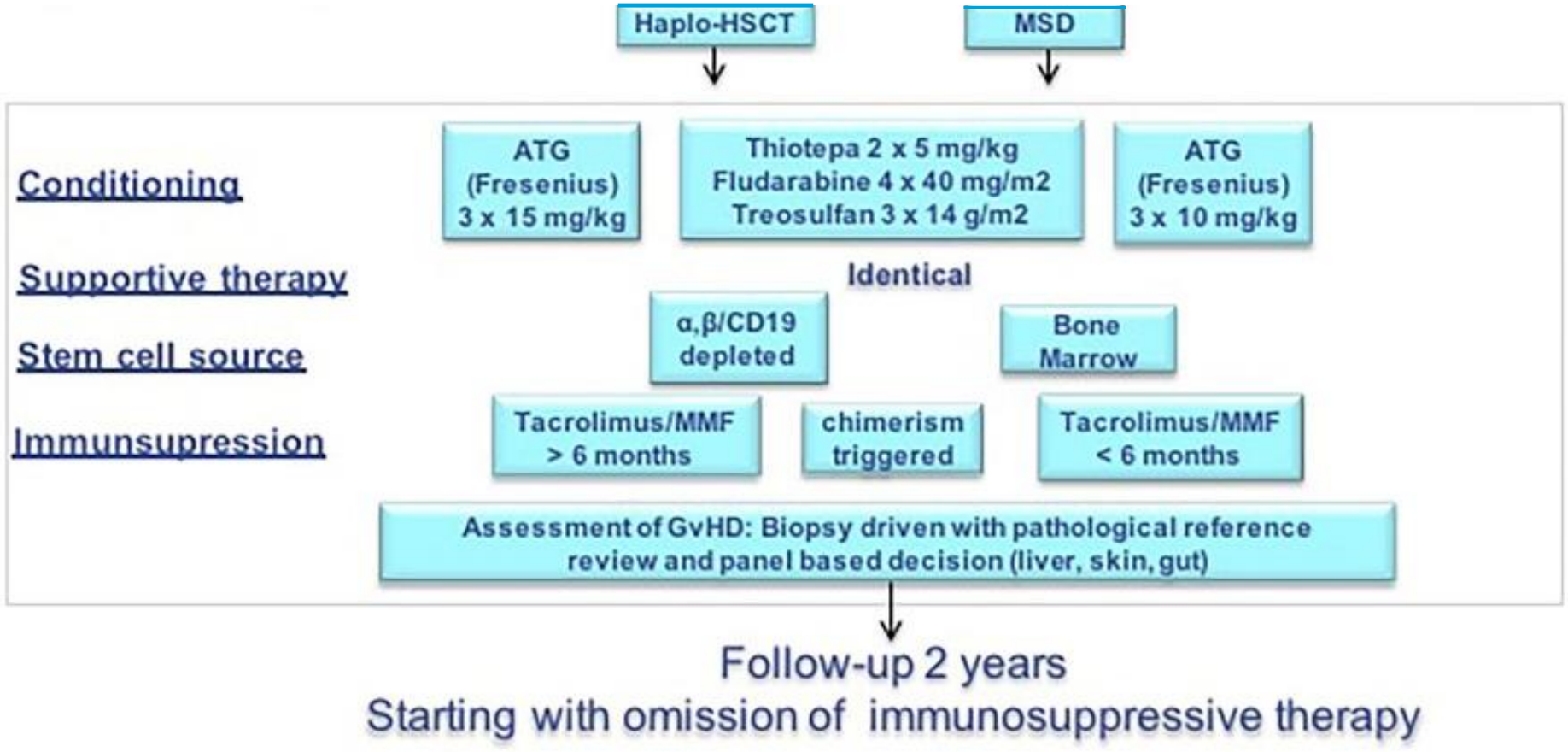
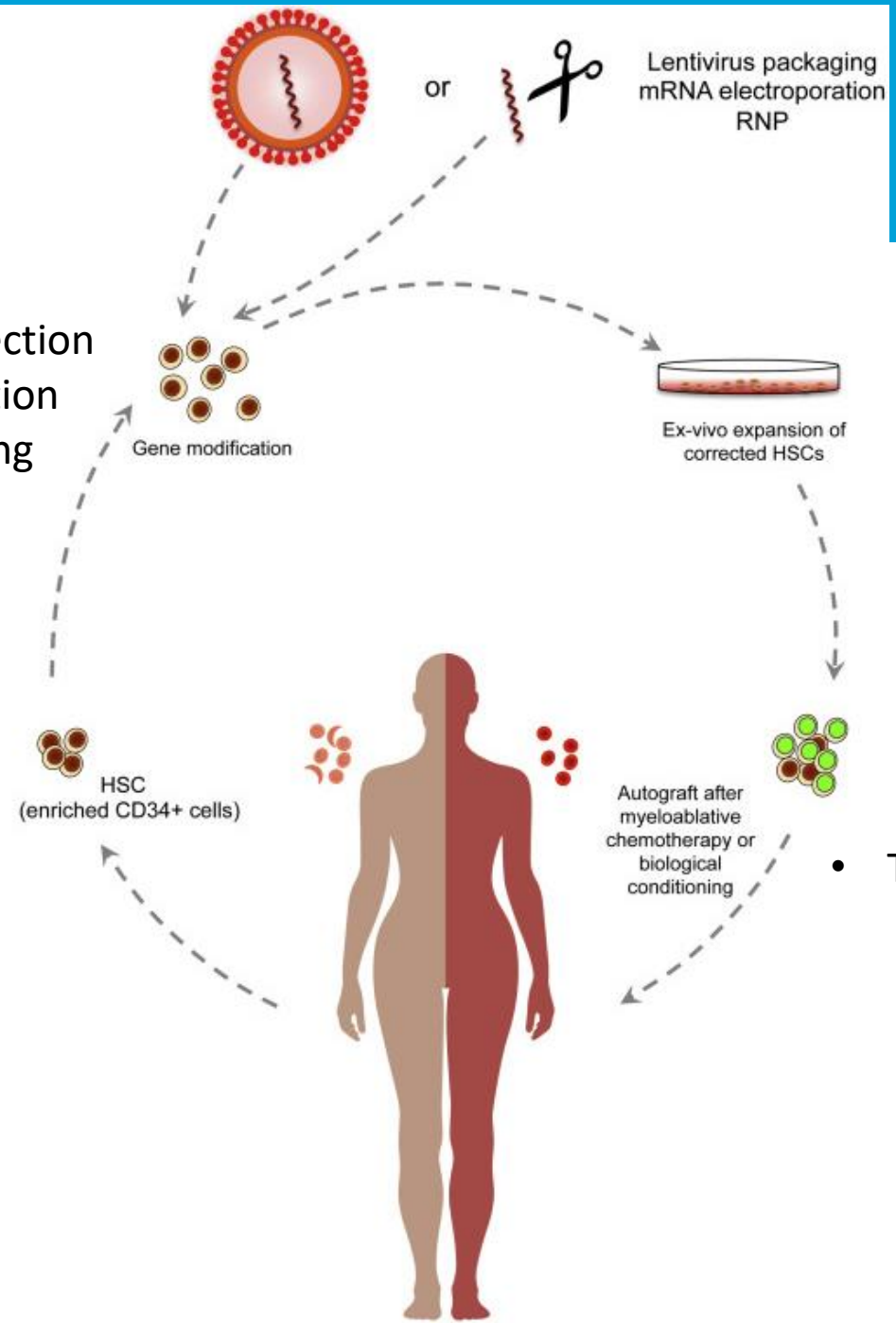
Foell et al., Hematol Oncol Stem Cell Ther 2020

Haplo-identical stem cell transplantation + αβ/CD19 T-cell depletion



Gene therapy

gene correction
gene addition
gene editing

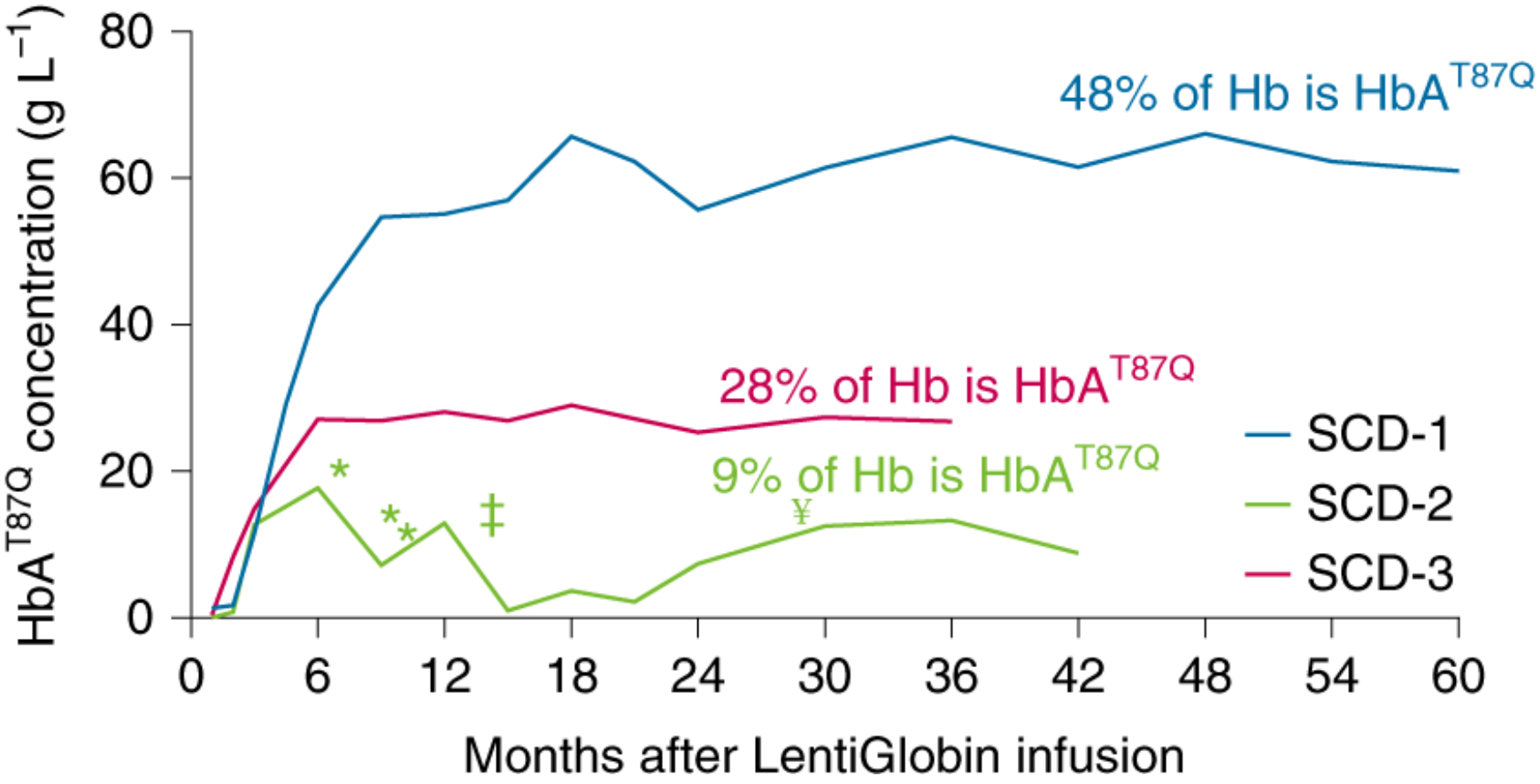


- harvest suboptimal
- plerixafor

- Toxic conditioning regimen

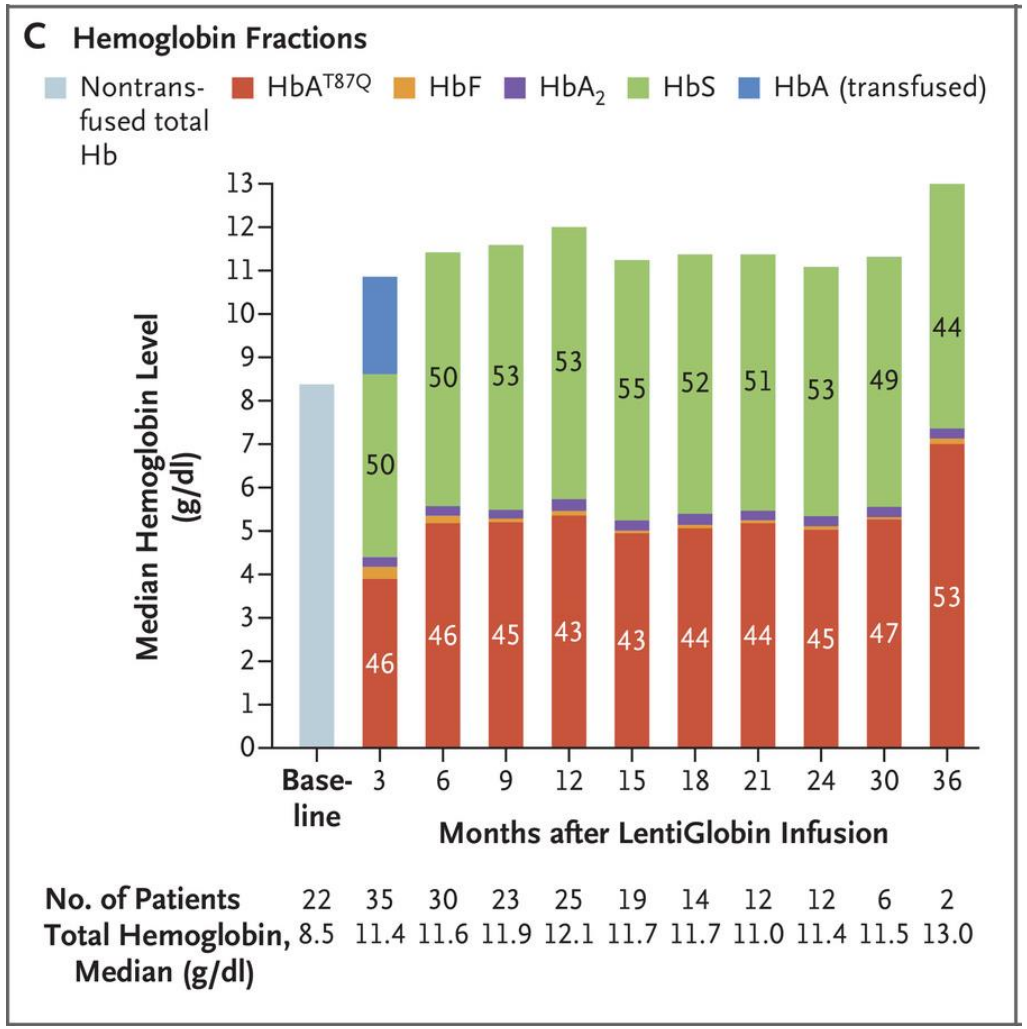
Lidonnici et al. Blood Cells, Molecules and Diseases 2018

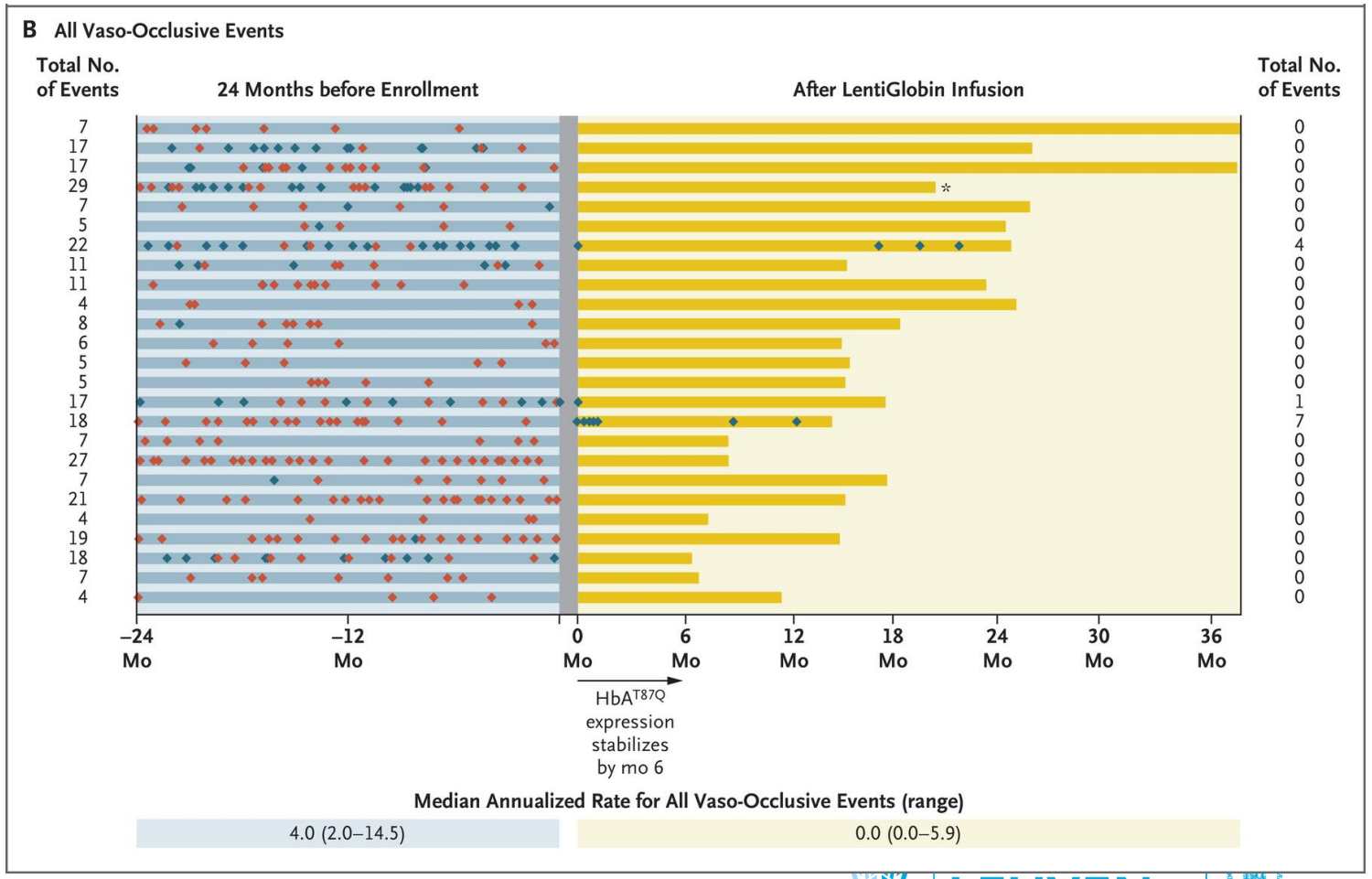
Gene addition: lentivirus with anti-sickling β-globin variant, T87Q



Ribeil et al. N Eng J Med 2017
Magrin et al. Nature Medicine 2022

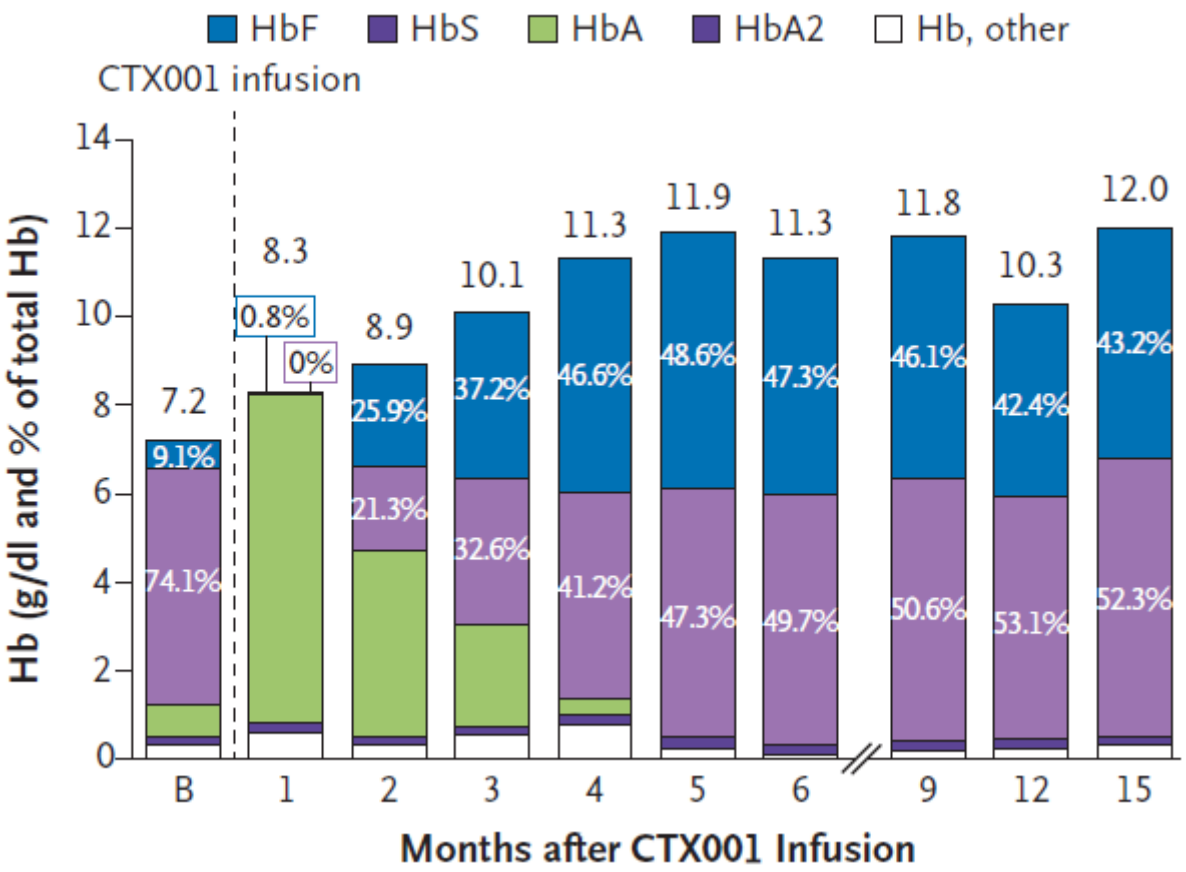
Gene addition: lentivirus with anti-sickling β-globin variant, T87Q

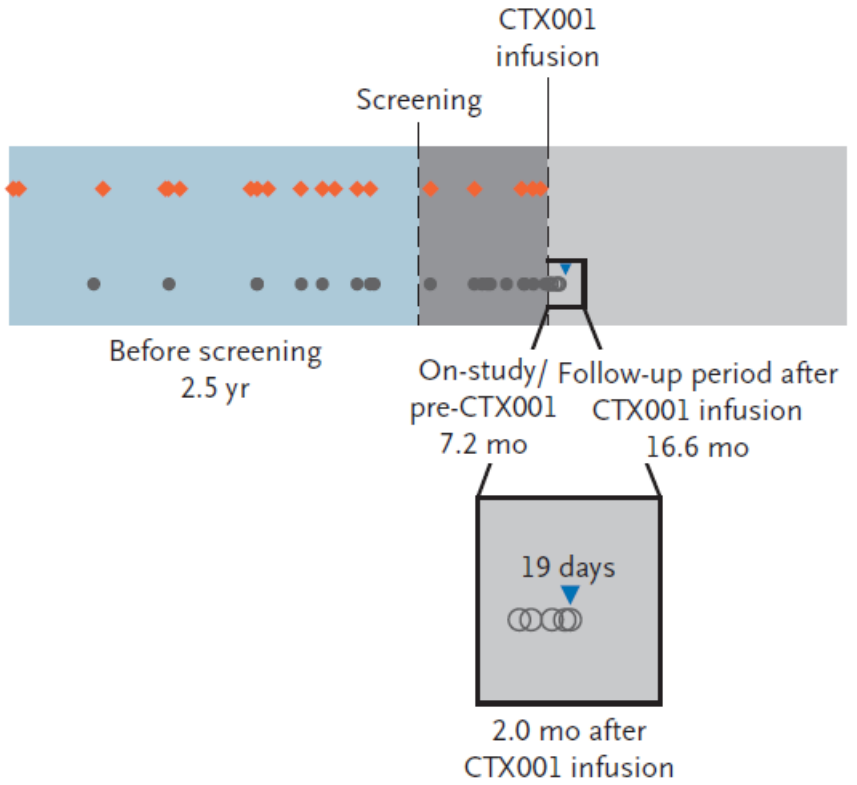




Kanter et al. N Eng J Med 2022

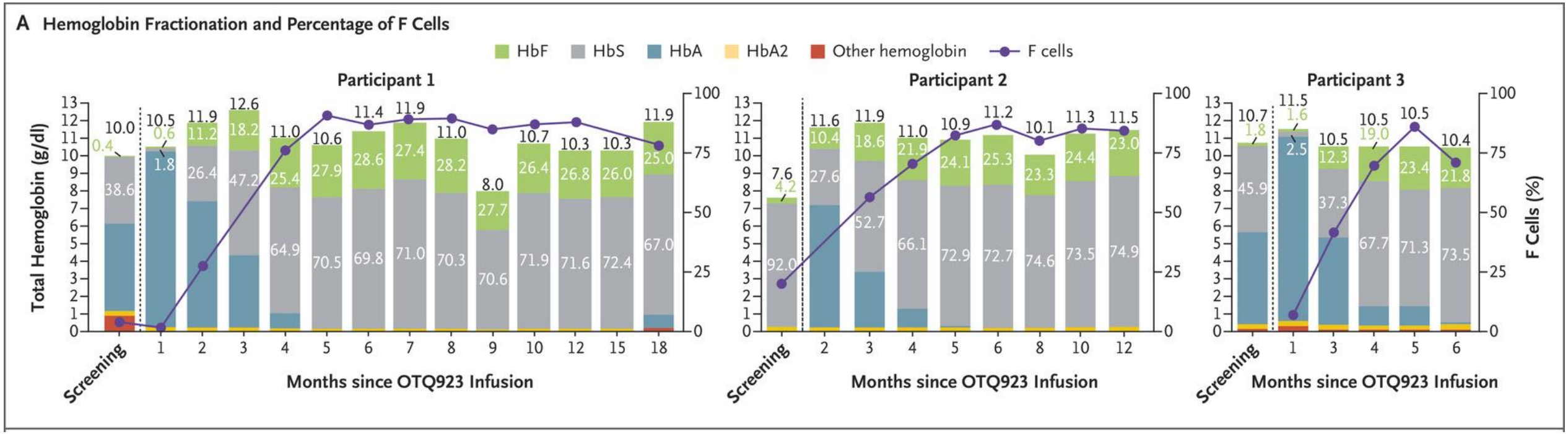
Gene editing: CRISPR-Cas9 at erythroid-specific enhancer region of BCL11A





Frangoul et al., N Eng J Med 2021

Gene editing: CRISPR-Cas9 at HBG1 and/or HBG2



Sharma et al., N Eng J Med 2023

Take home messages

- Pathophysiology of sickle cell disease includes much more than hemolysis and vaso-occlusion alone
- New disease-modifying therapies are being studied, none are (yet) available in Belgium
- Changes in the field of HSCT and advances in the success of gene therapy hold promise for a cure

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Sağol
شكرا
Ευχαριστώ
谢谢
Hvala
Tack
Tak
Danke
감사합니다
Asante
謝謝
Merci
Thank you
Gracias
תודה
Dankon
Grazie
Obrigado
Спасибо
धन्यवाद
Kiitos
متشكرم
Dank u
Хвала
ขอบคุณ
Terima kasih
Благодаря
Köszönöm
Mulţumesc
有り難う