NAEF K. BASILE
CANCER INSTITUTE

Patients and Clinical Perspectives and Management of Thalassemia

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Outline

- Molecular Understanding and Genotype-Phenotype Association
- Epidemiology and Diagnosis
- Pathogenesis and Patient characteristics
- Clinical management and treatment guidelines
- Role of Holistic Care
- Novel Therapies

Disclosures

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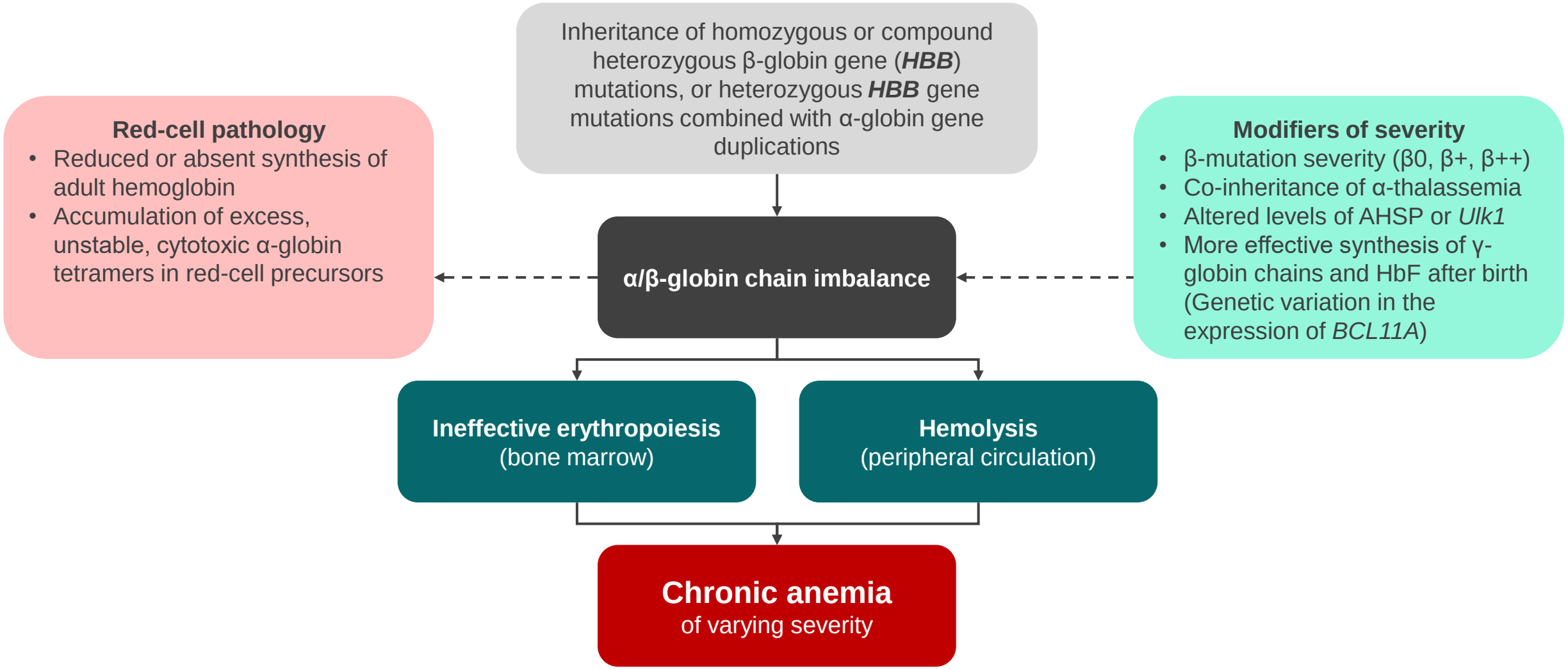
- Vifor: Consultancy, Research Funding
- Pharmacosmos: Consultancy, Research Funding
- Agios: Consultancy, Research Funding

Molecular Understanding and Genotype-Phenotype Association

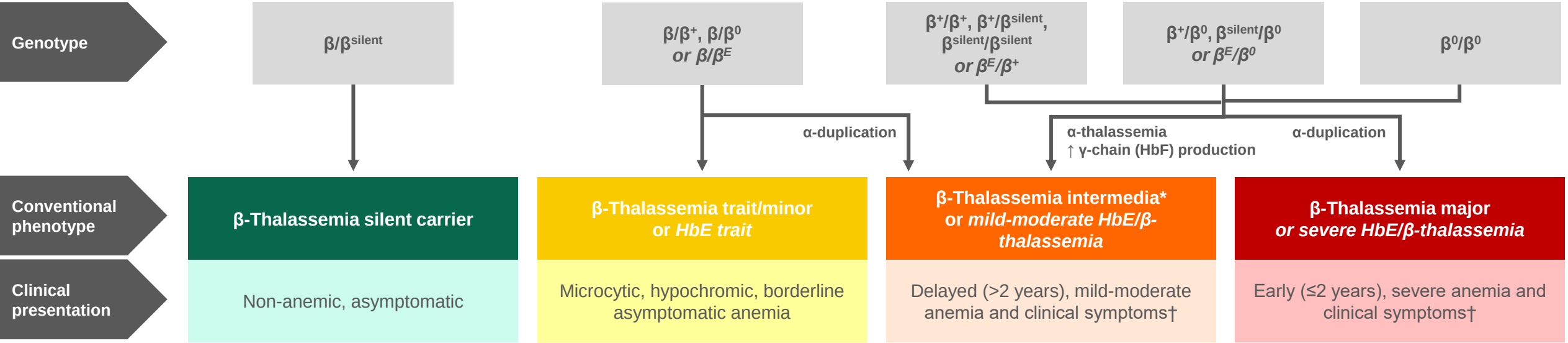
Molecular understanding of β-thalassemia



AHSP, α-hemoglobin stabilizing protein.

Taher AT, Musallam KM, Cappellini MD. *N Engl J Med* 2021;384:727-743; Musallam KM *et al. Haematologica* 2013;98:833-844; Galanello R, Origa R. *Orphanet J Rare Dis* 2010;5:11; Khandros E *et al. Blood* 2012;119:5265-5275; Premawardhena A *et al. Blood* 2005;106:3251-3255; Kihm AJ *et al. Nature* 2002;417:758-763; Kong Y *et al. J Clin Invest* 2004;114:1457-1466; Lechauve C *et al. Sci Transl Med* 2019;11:11; Menzel S *et al. Nat Genet* 2007;39:1197-1199; Sankaran VG *et al. Science* 2008;322:1839-1842; Uda M *et al. Proc Natl Acad Sci U S A* 2008;105:1620-1625; Galanello R *et al. Blood* 2009;114:3935-3937.

Conventional β-thalassemia phenotypes are defined based on clinical grounds, with genotype associations



*β-Thalassemia intermedia may also be associated with deletion forms of δβ-thalassemia and hereditary persistence of fetal hemoglobin (HbF) or dominant (inclusion- body) β-thalassemia.
†Jaundice, growth retardation, splenomegaly, and facial and bone deformities.

HbE is a is an abnormal hemoglobin that results from a single point mutation in the β-globin gene and behaves like a β+ mutation.

Taher AT, Musallam KM, Cappellini MD. *N Engl J Med* 2021;384:727-743.

Transfusion requirement is now used to distinguish two major clinical phenotypes: NTDT and TDT

- This allowed standardization of research and clinical management based on transfusion-requirement, a key driver in pathophysiology
- It also recognized that severe morbidity can be observed across both intermedia and major patients
- International management guidelines have been developed for NTDT and TDT separately

Non-transfusion-dependent thalassemia (NTDT)
- β-thalassaemia intermedia
- Mild/moderate HbE/β-thalassemia
- HbH disease (α-thalassemia intermedia)

Transfusions seldom required

Occasional transfusions required (e.g. surgery, pregnancy, infection)

Intermittent transfusions required (e.g. poor growth and development, specific morbidities)

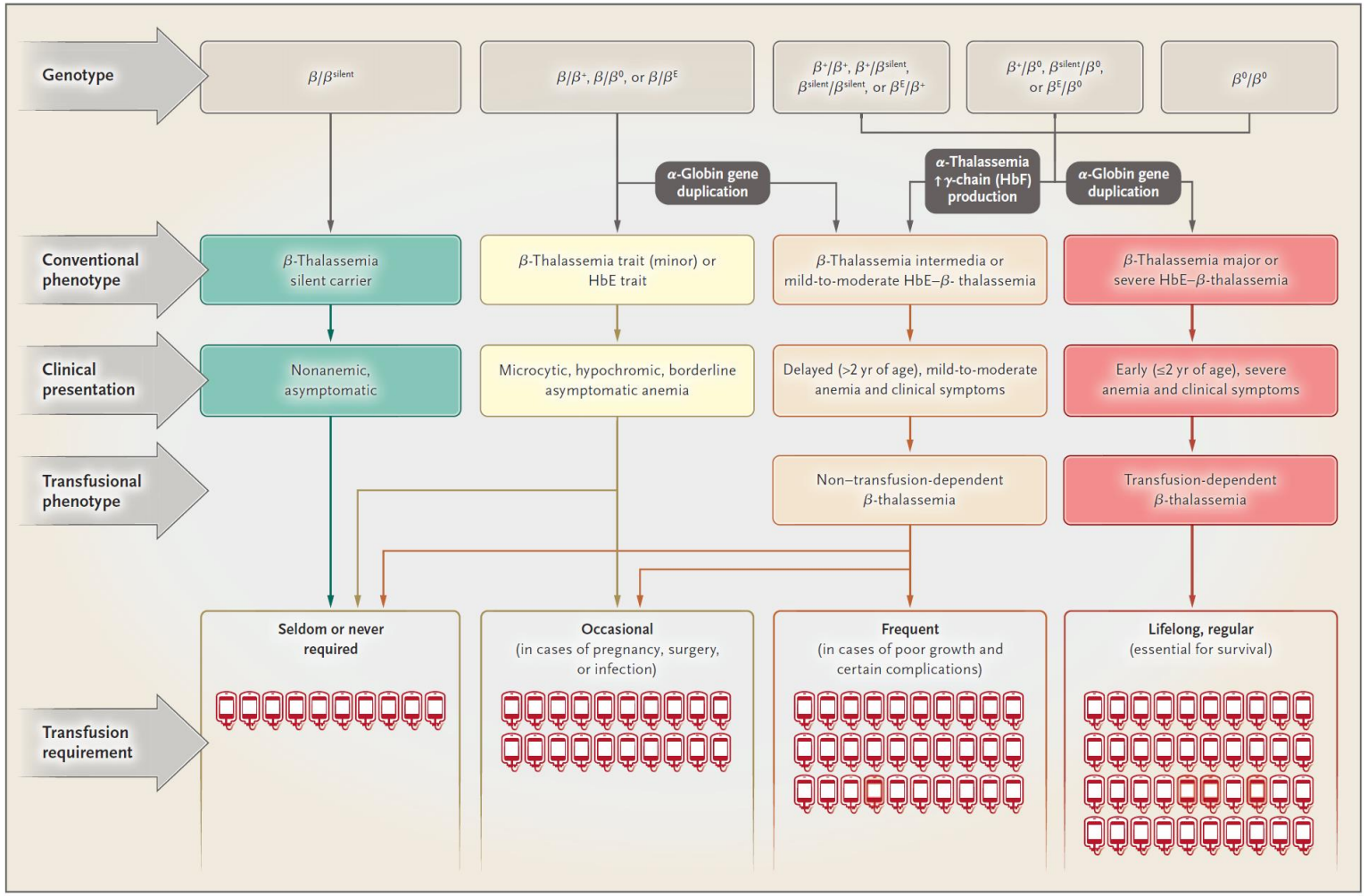
Regular, lifelong transfusions required for survival

Transfusions not required
- α-thalassemia trait
- β-thalassemia minor

Transfusion-dependent thalassemia (TDT)
- β-thalassemia major
- Severe HbE/β-thalassemia
- Hb Barts hydrops (α-thalassemia major)

Musallam KM *et al. Haematologica* 2013;98:833-844.

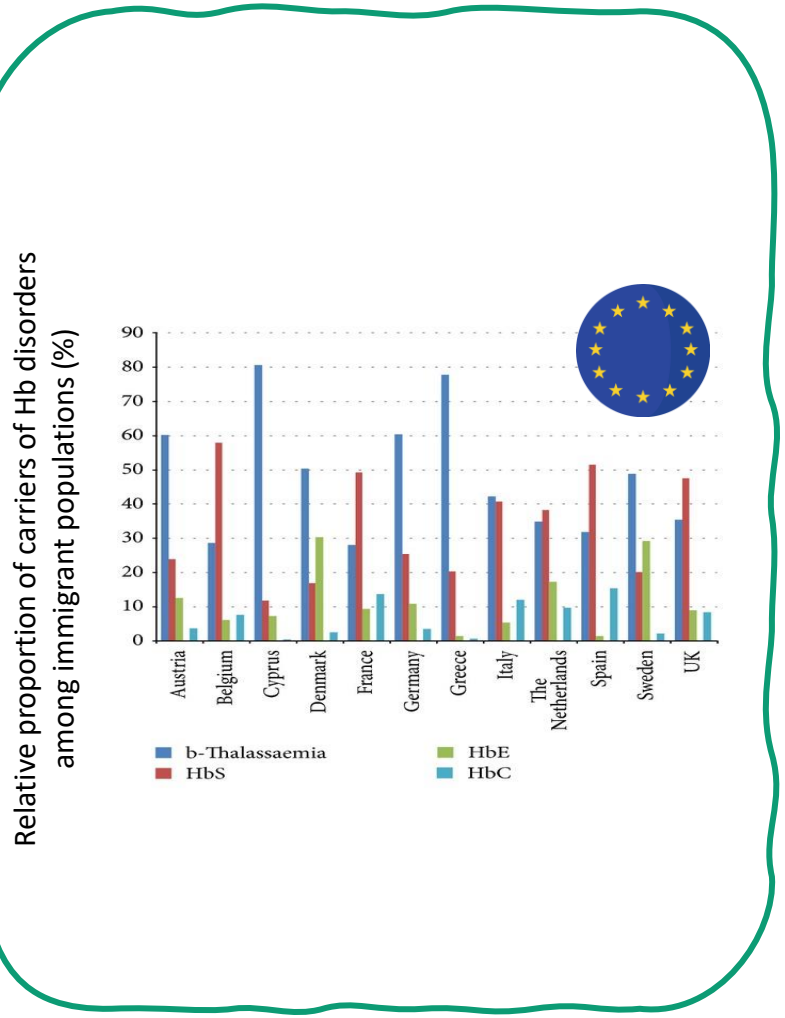
Ideally, we should keep historic and new understanding in mind when evaluating the individual patient



Taher AT, Musallam KM, Cappellini MD. *N Engl J Med* 2021;384:727-743.

Epidemiology and Diagnosis

Changing epidemiology of β-thalassemia

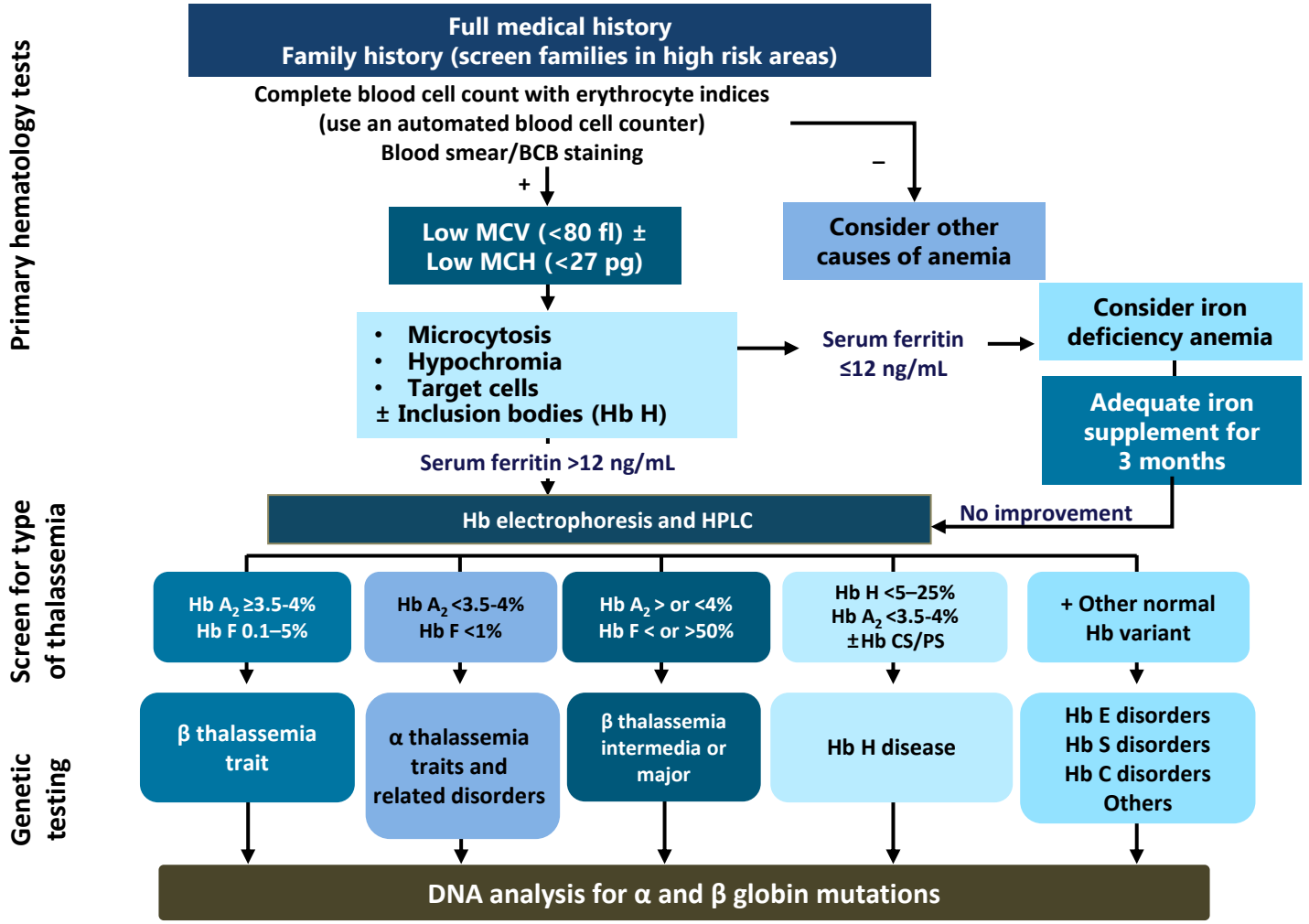


The evolutionary association between the thalassemia carrier state and resistance to ***malaria*** explains its high prevalence in the area extending from sub-Saharan Africa, the Middle East, and the Mediterranean basin to Southeast Asia[1]

Population ***migrations*** have also introduced thalassemia to Europe and the Americas, where the disease was previously relatively rare[2,3]

1. Weatherall DJ. *Blood* 2010;115:4331-4336; 2. Angastiniotis M *et al. Sci World J* 2013;2013:727905; 3. Kattamis A et a*l. Eur J Haematol* 2020;105:692-703.

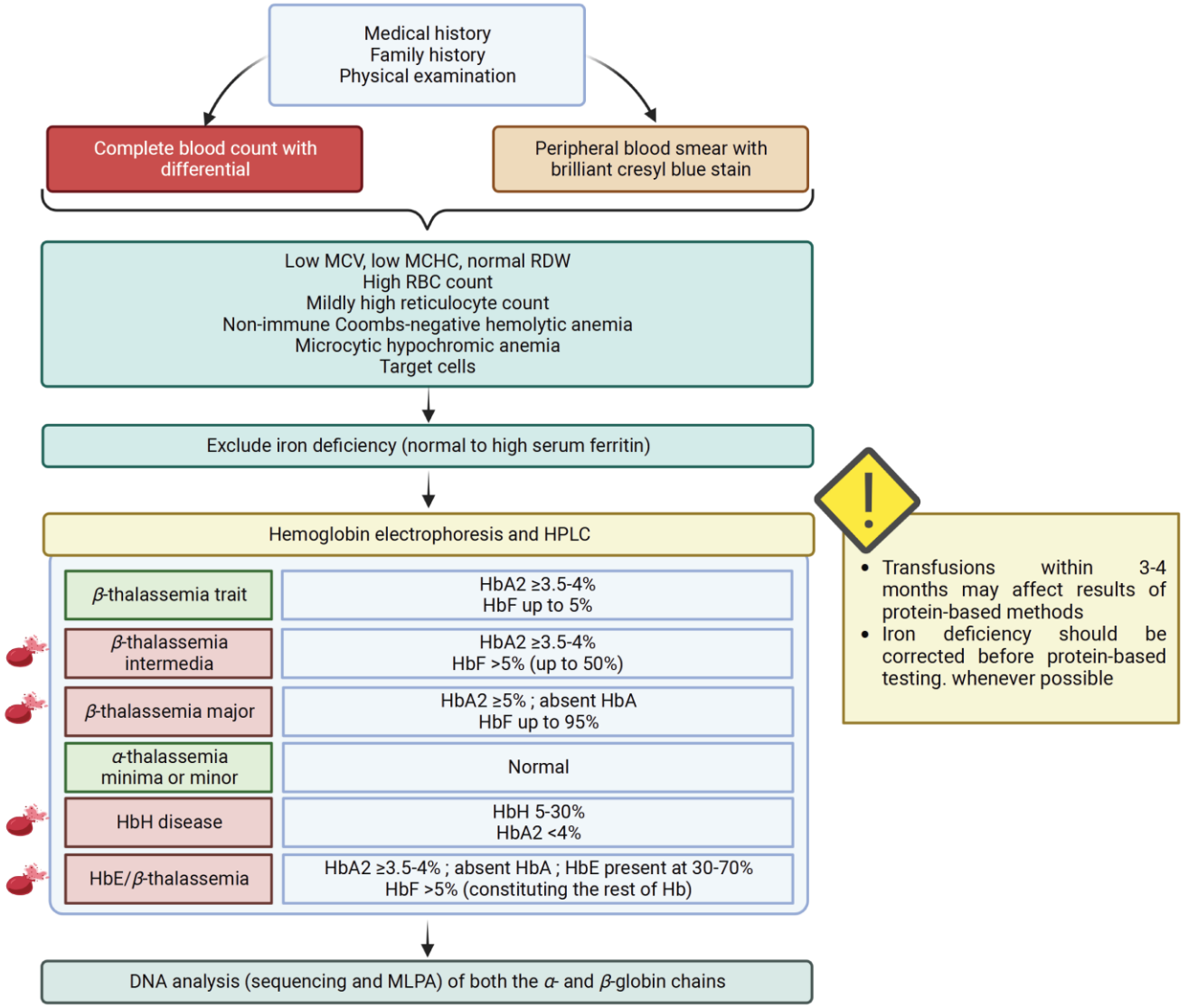
Common diagnostic pathway for thalassemia



BCB, brilliant cresyl blue; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; Hb, hemoglobin.

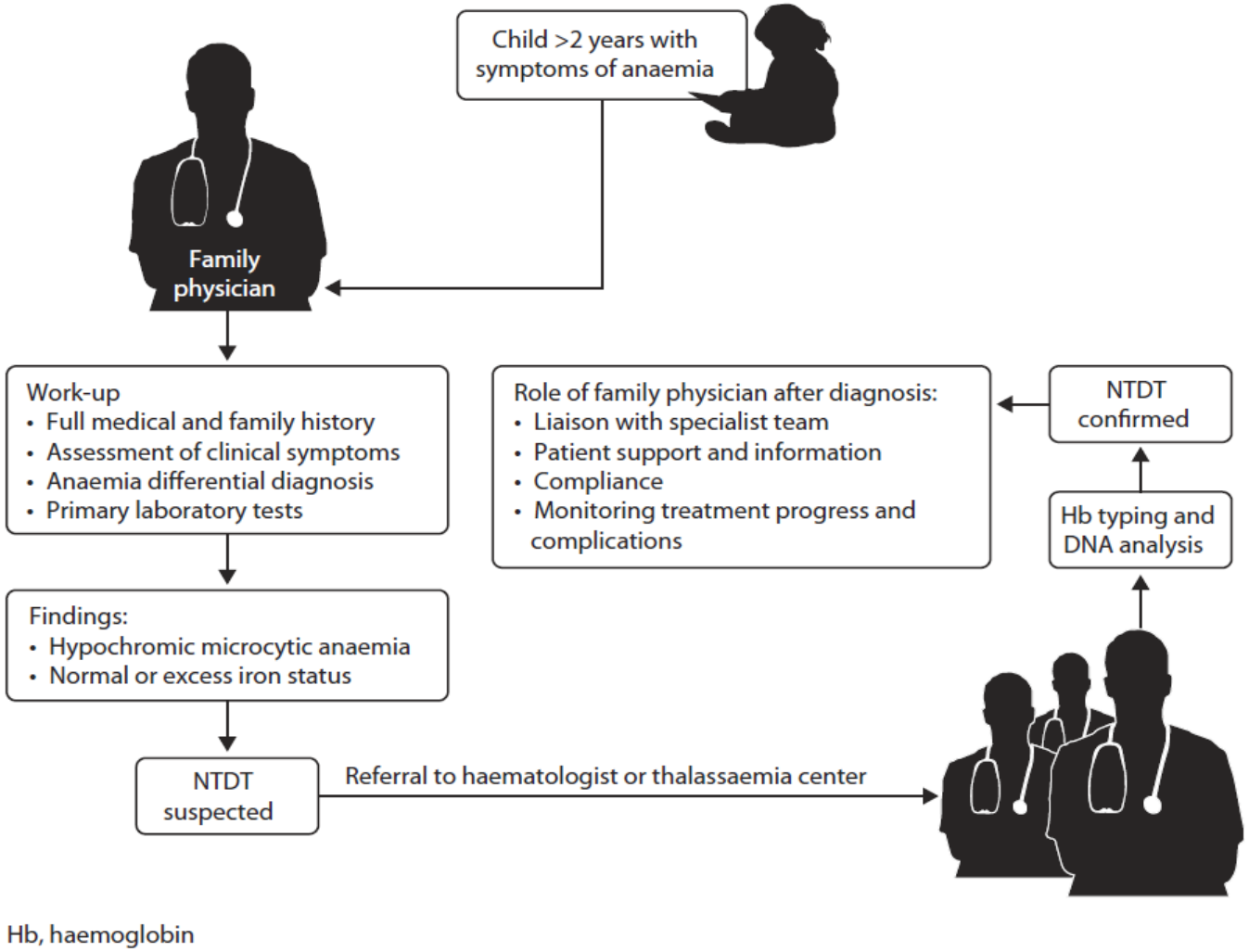
Viprakasit V *et al*. *Orphan J Rare Dis* 2014;9:131.

Diagnosis of NTDT



Saliba AN, Musallam KM *et al. Blood* 2023; Epub ahead of print.

Primary care physicians can play a key role in identification, especially for NTDT patients who may have delayed presentation

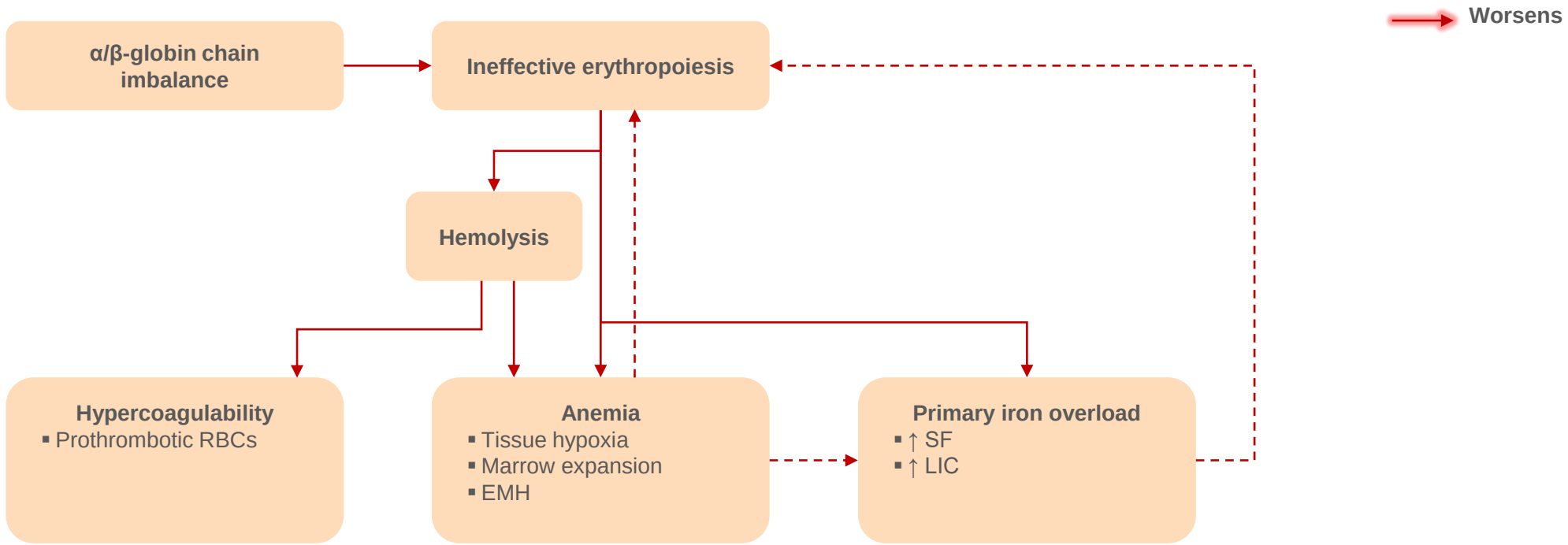


Hb, haemoglobin

Viprakasit V *et al*. *Orphan J Rare Dis* 2014;9:131.

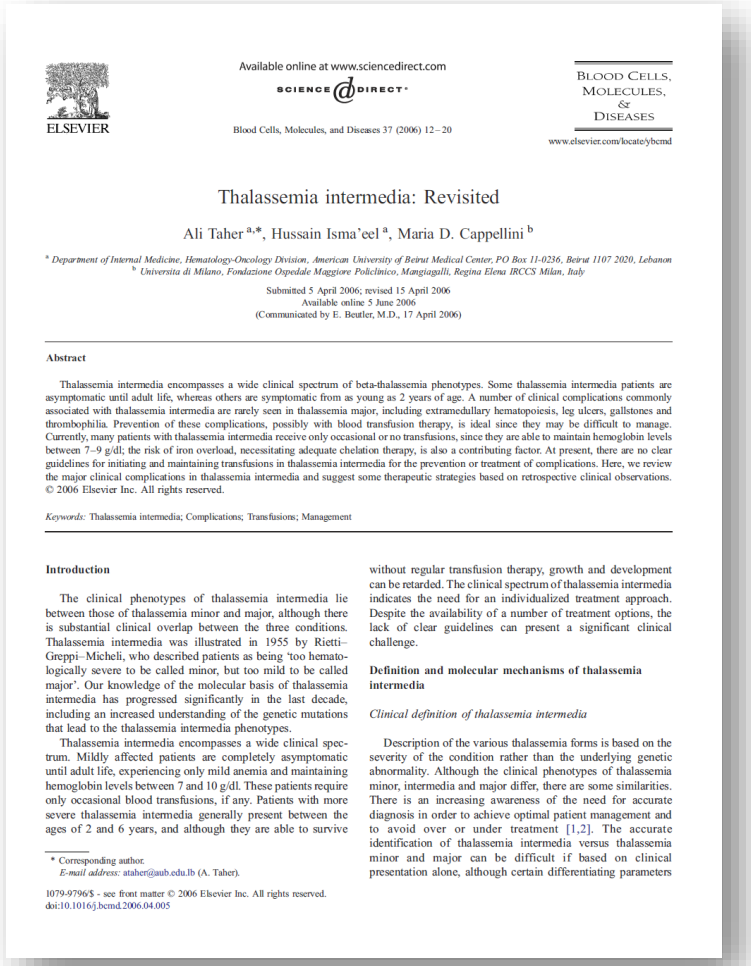
Pathogenesis in the Absence of Transfusions (NTDT)

Pathophysiology in β-thalassemia: expanding knowledge through natural history studies in patients with NTDT



Taher AT, Musallam KM, Cappellini MD. *N Engl J Med* 2021;384:727-743.

It all started with clinical observation in Lebanon and Italy



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BLOOD CELLS, MOLECULES, & DISEASES
www.elsevier.com/locate/ybcmd

Thalassemia intermedia: Revisited

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Available online 5 June 2006
(Communicated by E. Beutler, M.D., 17 April 2006)

Abstract

Thalassemia intermedia encompasses a wide clinical spectrum of beta-thalassemia phenotypes. Some thalassemia intermedia patients are asymptomatic until adult life, whereas others are symptomatic from as young as 2 years of age. A number of clinical complications commonly associated with thalassemia intermedia are rarely seen in thalassemia major, including extramedullary hematopoiesis, leg ulcers, gallstones and thrombophilia. Prevention of these complications, possibly with blood transfusion therapy, is ideal since they may be difficult to manage. Currently, many patients with thalassemia intermedia receive only occasional or no transfusions, since they are able to maintain hemoglobin levels between 7–9 g/dl; the risk of iron overload, necessitating adequate chelation therapy, is also a contributing factor. At present, there are no clear guidelines for initiating and maintaining transfusions in thalassemia intermedia for the prevention or treatment of complications. Here, we review the major clinical complications in thalassemia intermedia and suggest some therapeutic strategies based on retrospective clinical observations.

Keywords: Thalassemia intermedia; Complications; Transfusions; Management

Introduction

The clinical phenotypes of thalassemia intermedia lie between those of thalassemia minor and major, although there is substantial clinical overlap between the three conditions. Thalassemia intermedia was illustrated in 1955 by Rietti–Greppi–Micheli, who described patients as being 'too hematologically severe to be called minor, but too mild to be called major'. Our knowledge of the molecular basis of thalassemia intermedia has progressed significantly in the last decade, including an increased understanding of the genetic mutations that lead to the thalassemia intermedia phenotypes.

Thalassemia intermedia encompasses a wide clinical spectrum. Mildly affected patients are completely asymptomatic until adult life, experiencing only mild anemia and maintaining hemoglobin levels between 7 and 10 g/dl. These patients require only occasional blood transfusions, if any. Patients with more severe thalassemia intermedia generally present between the ages of 2 and 6 years, and although they are able to survive without regular transfusion therapy, growth and development can be retarded. The clinical spectrum of thalassemia intermedia indicates the need for an individualized treatment approach. Despite the availability of a number of treatment options, the lack of clear guidelines can present a significant clinical challenge.

Definition and molecular mechanisms of thalassemia intermedia

Clinical definition of thalassemia intermedia

Description of the various thalassemia forms is based on the severity of the condition rather than the underlying genetic abnormality. Although the clinical phenotypes of thalassemia minor, intermedia and major differ, there are some similarities. There is an increasing awareness of the need for accurate diagnosis in order to achieve optimal patient management and to avoid over or under treatment [1,2]. The accurate identification of thalassemia intermedia versus thalassemia minor and major can be difficult if based on clinical presentation alone, although certain differentiating parameters

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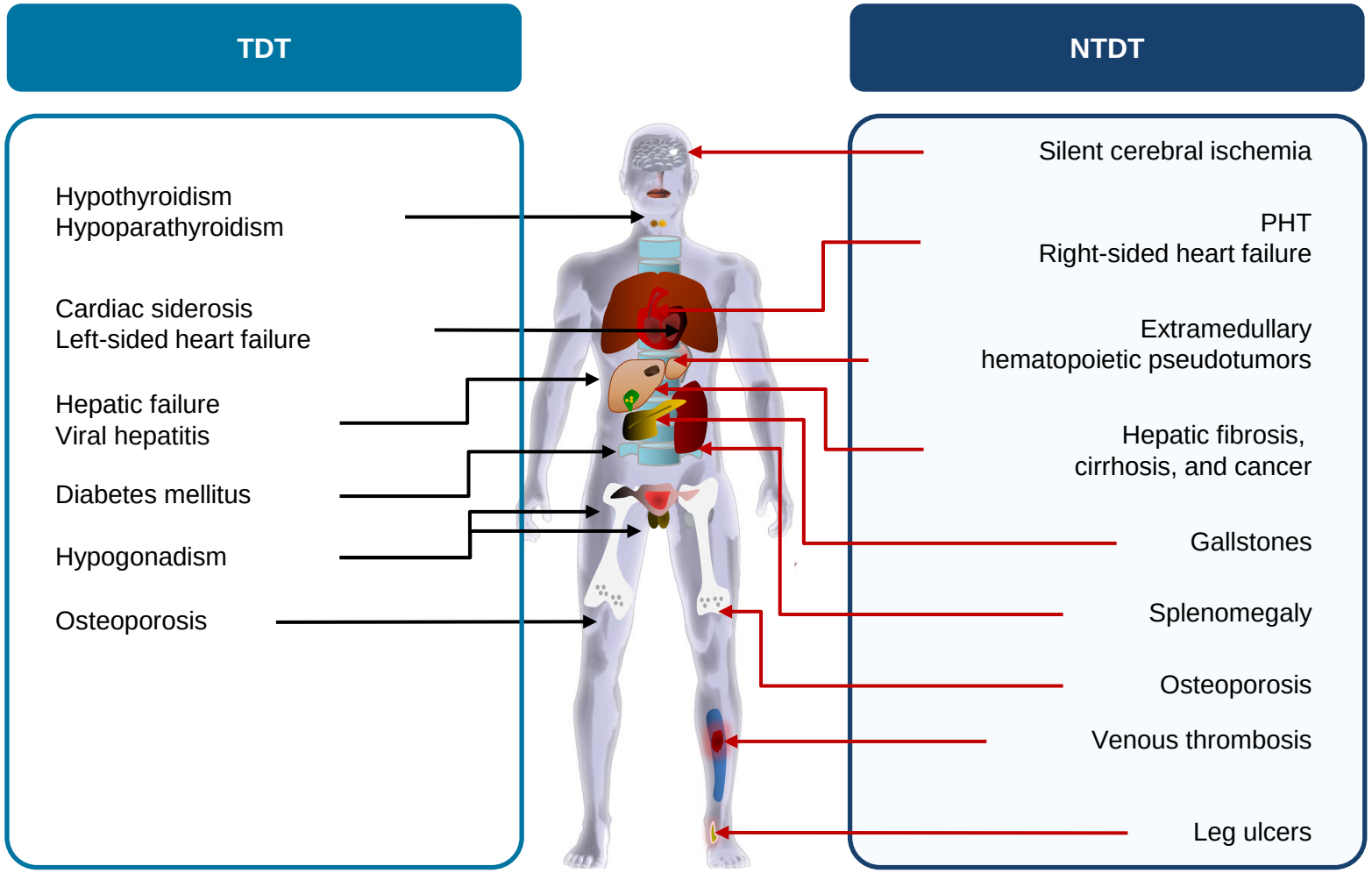


Taher AT et al. *Blood Cells Mol Dis* 2006;37:12-20; Musallam KM *et al. Haematologica* 2013;98:833-844.

The OPTIMAL CARE Study: Overview on Practices in β-Thalassemia Intermedia Management Aiming for Lowering Complication Rates Across a Region of Endemicity

Cross-sectional study of 584 patients with β-thalassemia from six comprehensive care centers in the Middle East and Italy

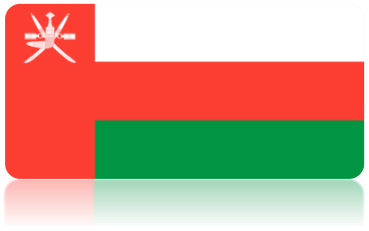
Lebanon
n = 127
A.T. Taher
K.M. Musallam

Italy
n = 153
M.D. Cappellini

Iran
n = 200
M. Karimi

Egypt
n = 51
A. El-Beshlawy

Oman
n = 12
S. Daar



United Arab Emirates
n = 41
K. Belhoul
M. Saned

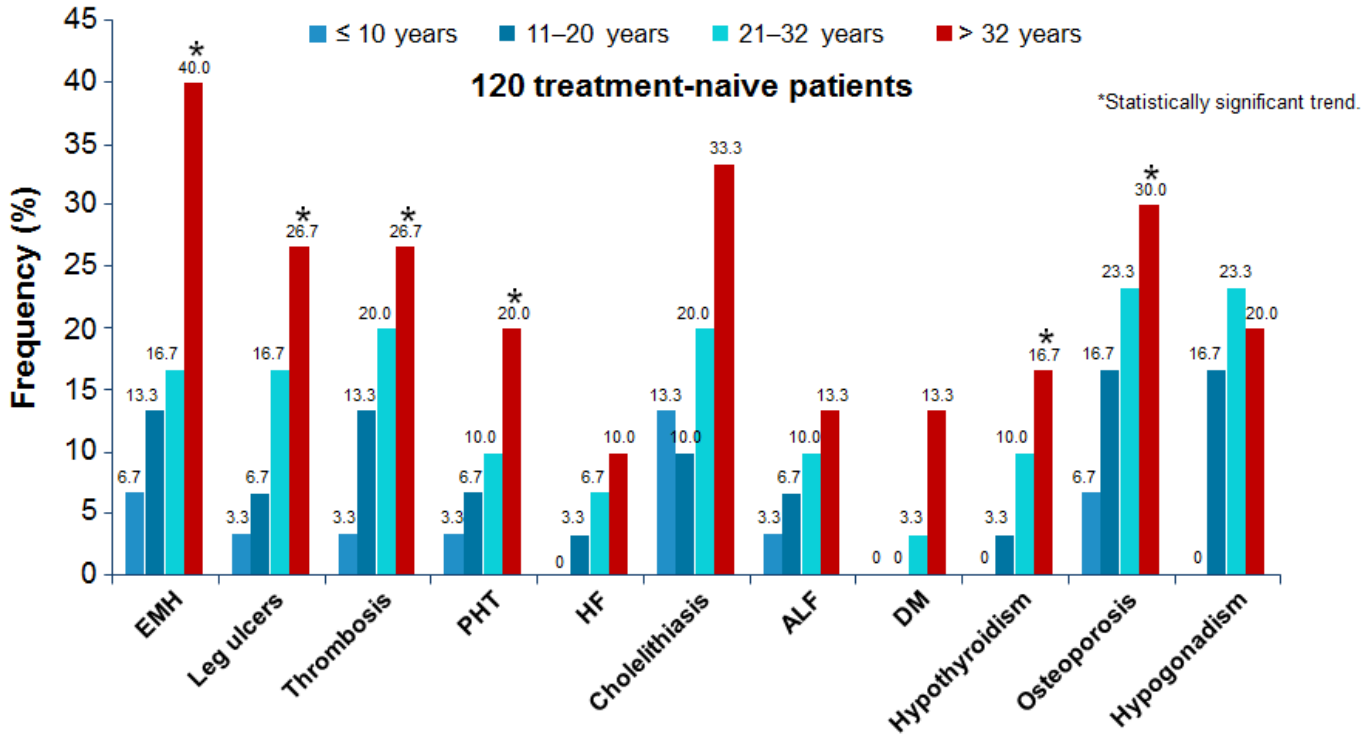
Taher AT, Musallam KM *et al. Blood* 2010;115:1886–1892.

High morbidity rates were confirmed and seemed to increase with advancing age (starting at 10 years)

Patient and Disease Characteristics[1]

Parameter	Frequency, n (%)
Age (years)	
< 18	172 (29.5)
18–35	288 (49.3)
> 35	124 (21.2)
Male:female	291 (49.8) : 293 (50.2)
Splenectomized	325 (55.7)
Serum ferritin (µg/L)	
< 1,000	376 (64.4)
1,000–2,500	179 (30.6)
> 2,500	29 (5)
Complications	
Osteoporosis	134 (22.9)
EMH	124 (21.2)
Hypogonadism	101 (17.3)
Cholelithiasis	100 (17.1)
Thrombosis	82 (14)
Pulmonary hypertension	64 (11)
Abnormal liver function	57 (9.8)
Leg ulcers	46 (7.9)
Hypothyroidism	33 (5.7)
Heart failure	25 (4.3)
Diabetes mellitus	10 (1.7)

Frequency of Complications Across the Different Age Quartiles[2]

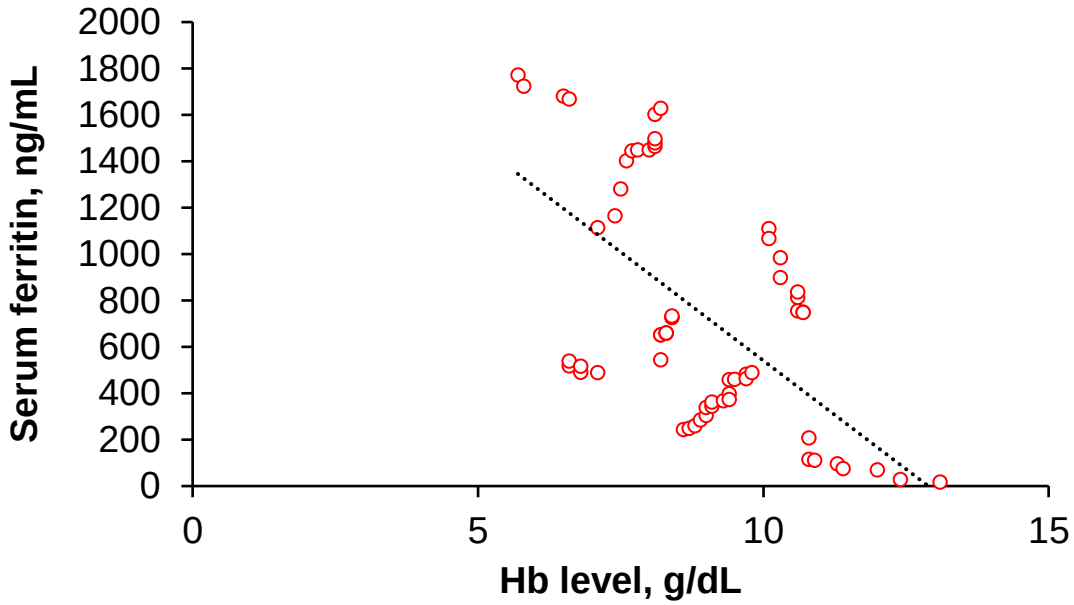


ALF, abnormal liver function; DM, diabetes mellitus; EMH, extramedullary hematopoiesis; HF, heart failure; PHT, pulmonary hypertension.

1. Taher AT, Musallam KM *et al. Blood* 2010;115:1886-1892; 2. Taher AT, Musallam KM *et al*. *Br J Haematol* 2010;150:486-489.

Chronic anemia is independently associated with clinical morbidity in NTDT

A Hb level of <7 g/dL was the level below which all patients developed a morbidity, while Hb >10 g/dL was the level after which none of the patients had a morbidity (area under the curve = 0.84, 95% CI: 0.70–0.97, p <0.001)

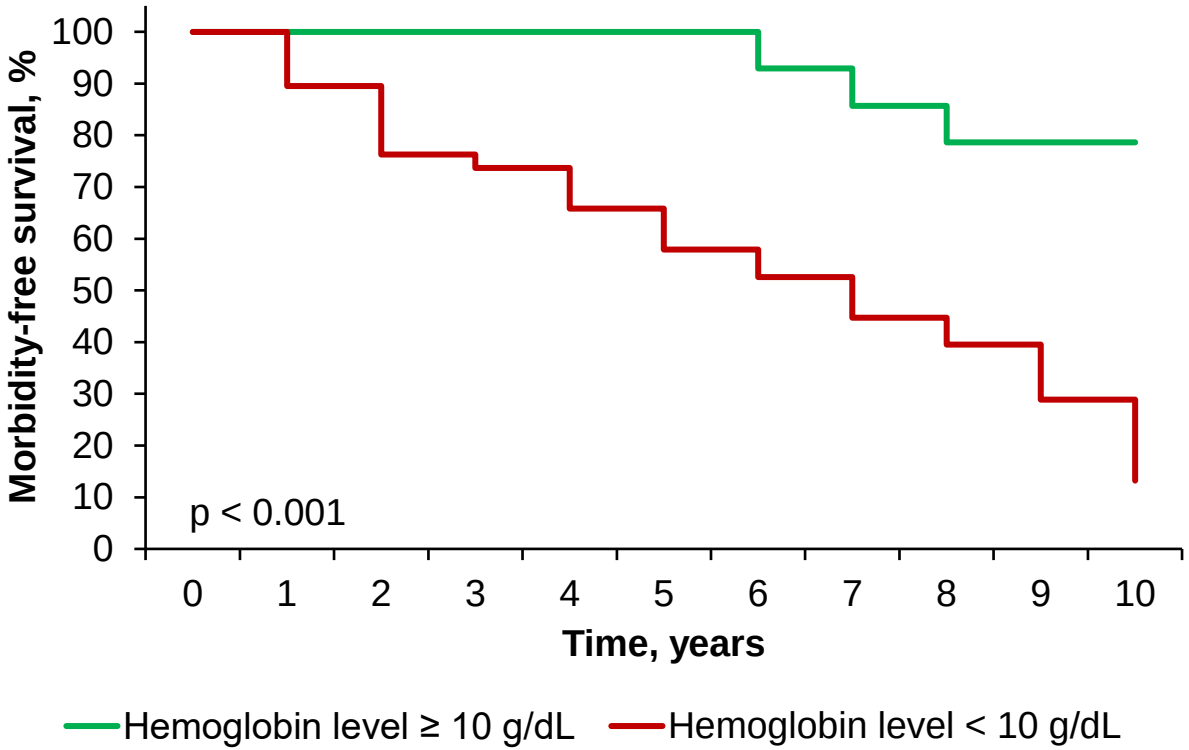


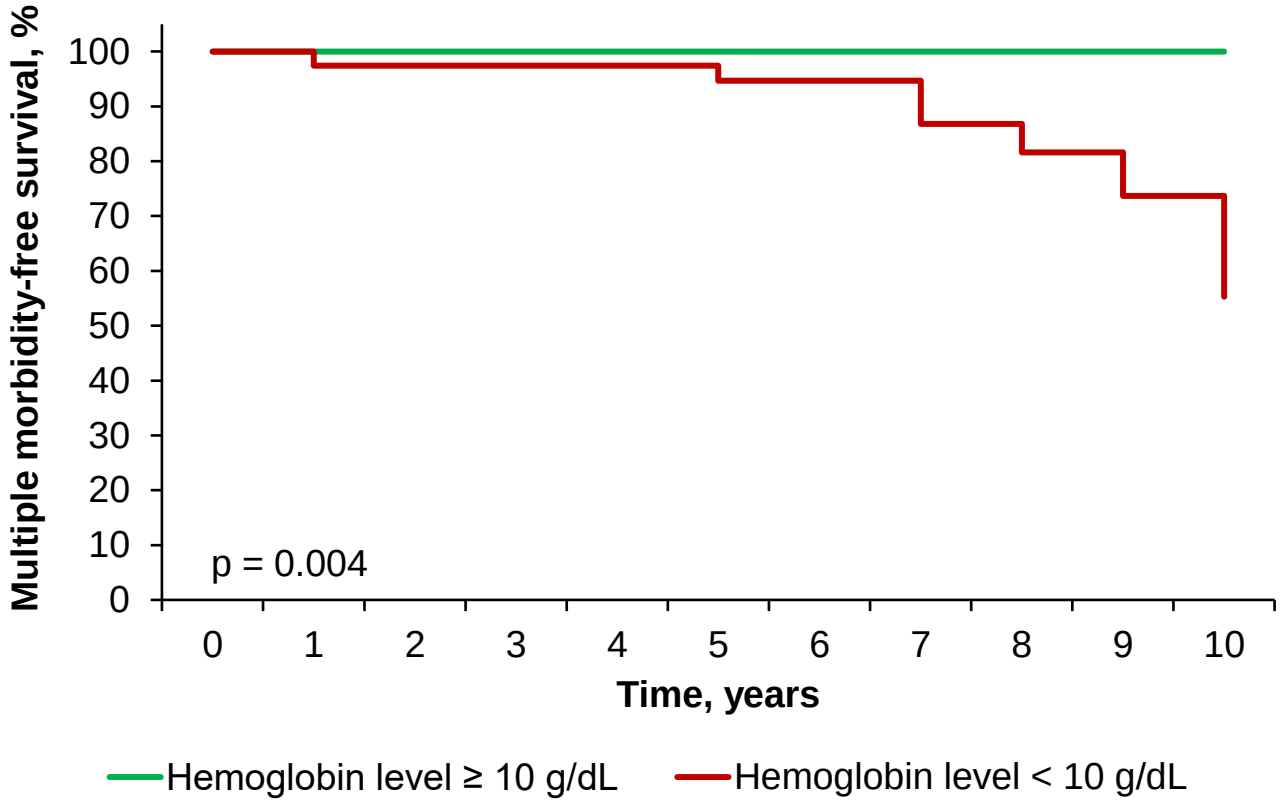
Pearson's r = −0.5951; p <0.001

63 patients

Taher AT, Musallam KM *et al. Blood Cell Mol Dis* 2015;55:108–109.

Morbidity free-survival vs hemoglobin level in NTDT

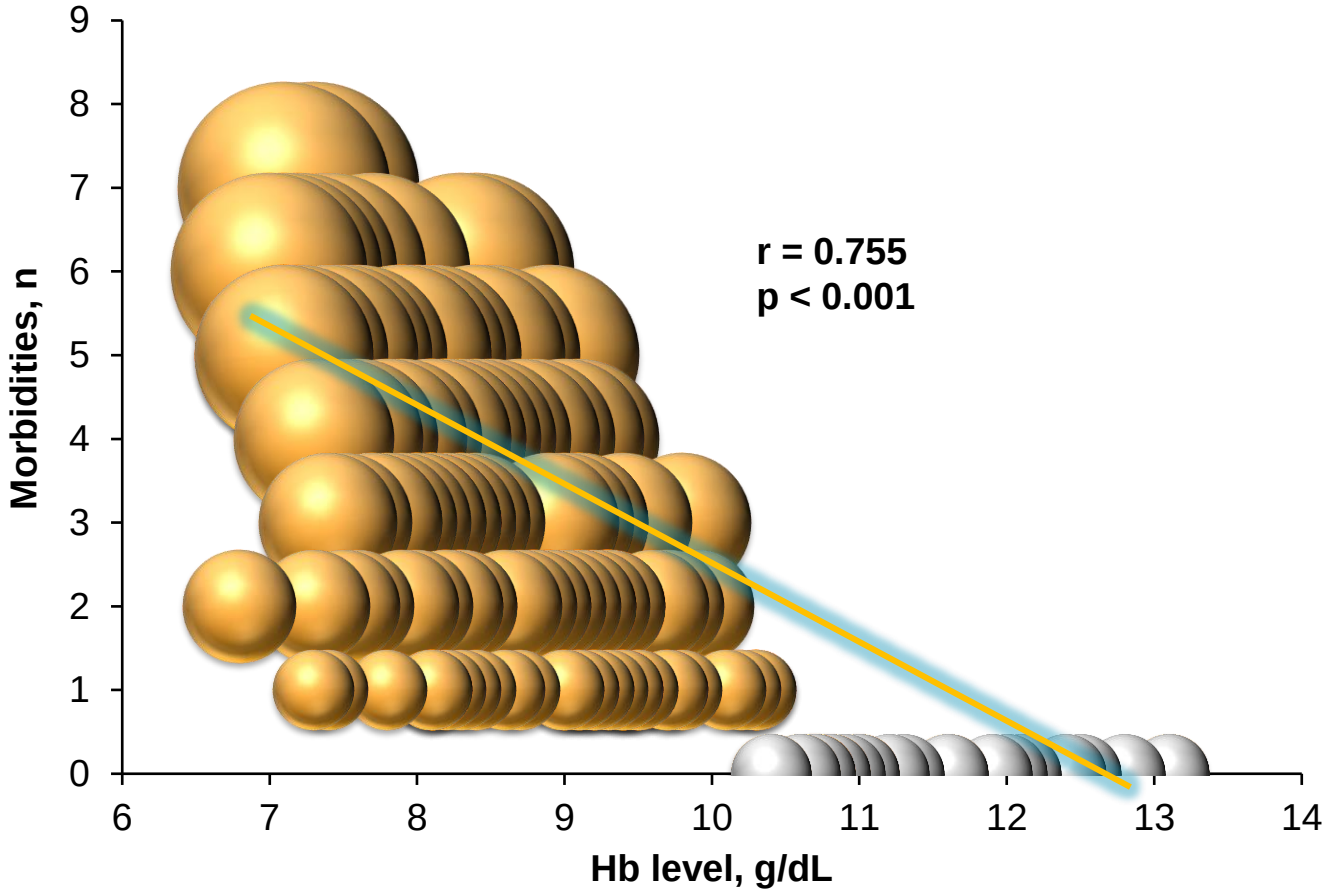


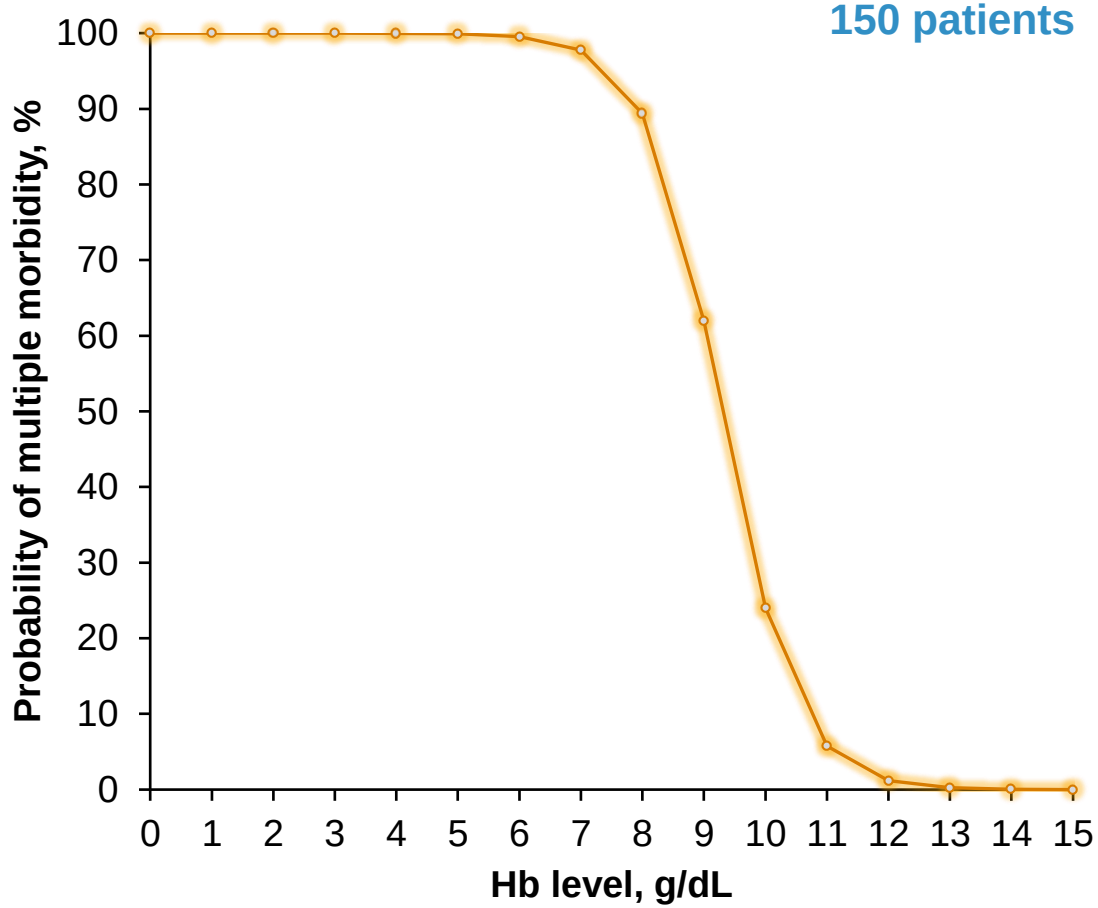


53 patients

Musallam KM *et al. Ann Hematol* 2022;101:203-204.

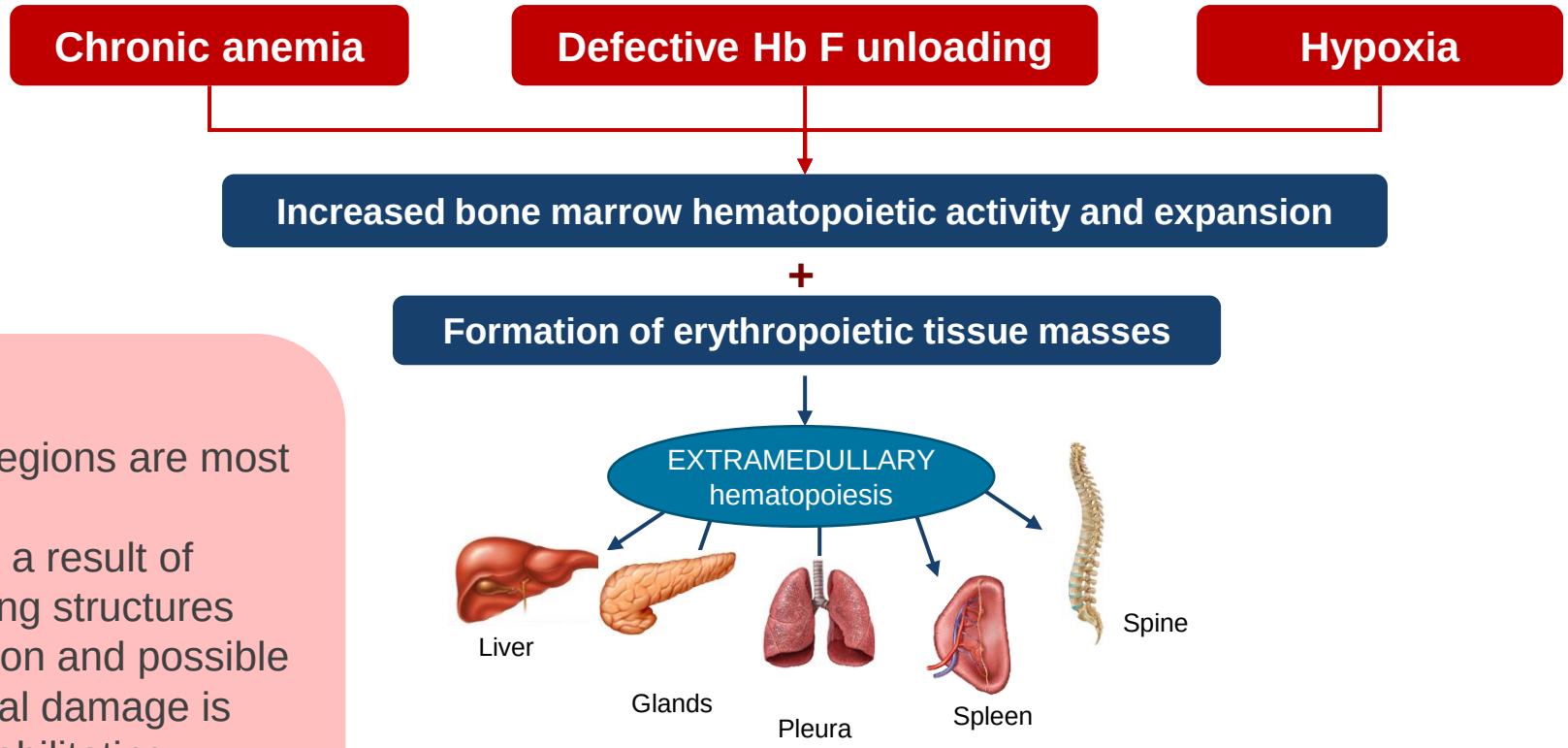
Variations of 1 g/dL in Hb level vs morbidity development in NTDT





Musallam KM *et al. Ann Hematol* 2021;100:1903-1905.

Extramedullary hematopoietic pseudotumors in NTDT as a result of ineffective erythropoiesis and anemia/hypoxia

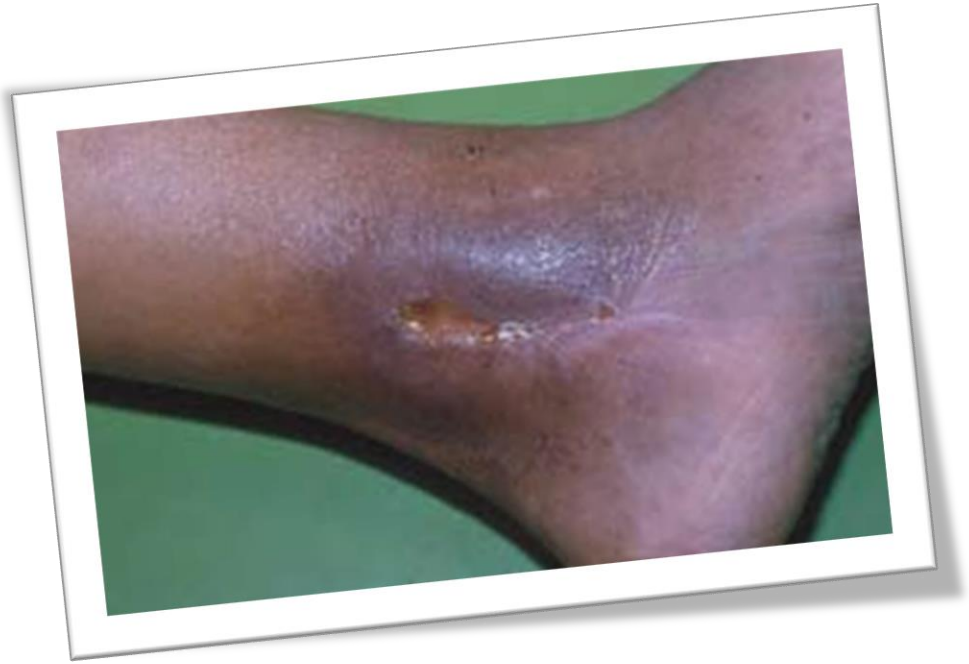


- Thoracic and lumbar regions are most commonly involved
- Symptoms develop as a result of pressure on surrounding structures
- Spinal cord compression and possible irreversible neurological damage is most significant and debilitating

Haidar R *et al. Eur Spine J* 2010;19:871–878; Castelli R *et al. Am J Med Sci* 2004;328:299–303; Chehal A *et al. Spine* 2003;28:E245–E249; Borgna-Pignatti C. *Br J Haematol* 2007;138:291–304.

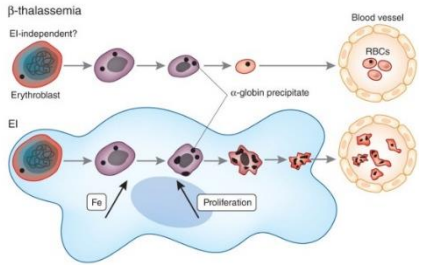
Leg ulcers in NTDT can develop in the context of anemia and tissue hypoxia

- Leg ulcers are more common in older than in younger patients with NTDT
- The skin at the extremities of elderly NTDT patients can be thin due to reduced tissue oxygenation; this makes the subcutaneous tissue fragile and increases the risk of lesions
- Ulcers are very painful and difficult to cure
- Risk factors: severe anemia, ineffective erythropoiesis, splenectomy, and hypercoagulability
- Local iron overload may play a role in the pathophysiology of leg ulcers by causing oxidative stress and not just by local accumulation



1. Taher AT *et al. Blood Cells Mol Dis* 2006;37:12-20; 2. Levin C, Koren A. *Isr Med Assoc J* 2011;13:316-318; 3. Taher AT, Musallam KM *et al. Blood* 2010;115:1886-1892; 4. Musallam KM *et al. Blood Cells Mol Dis* 2011;47:232-234; 5. Musallam KM *et al. Cold Spring Harb Perspect Med* 2012;a013482; 6. Matta BN *et al. J Eur Acad Dermatol Venere*ol. 2014;28:1245-1250; Taher AT, Musallam KM *et al. Blood Cell Mol Dis* 2015;55:108–109.

Iron overload develops even in the absence of transfusions in NTDT due to ineffective erythropoiesis

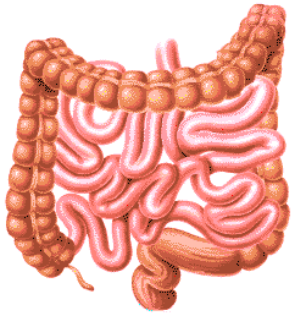


Ineffective erythropoiesis
Chronic anemia/hypoxia

Erythroferrone
PDGF-BB
GDF15?
TWSG1?

↑ Erythropoietin

↓ **Hepcidin**



↓ Ferroportin
Intestinal iron absorption

↑ Release of recycled iron
from reticuloendothelial system

Transfusions ***Minor role***

Iron overload

Bidirectional relationship established

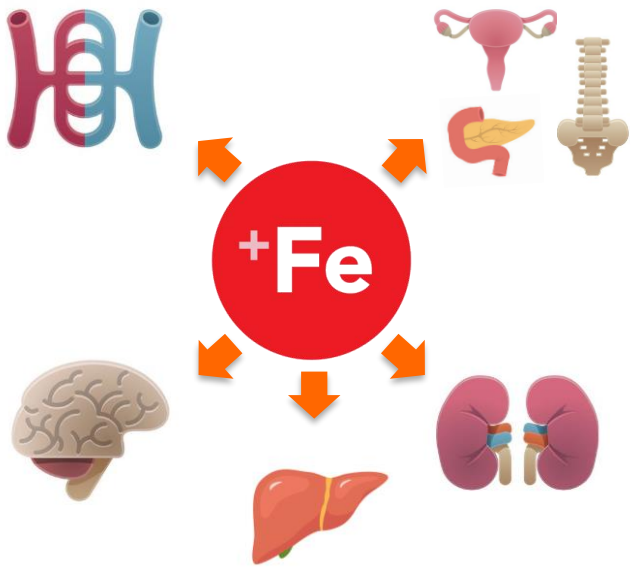
PDGF-BB, platelet-derived growth factor BB; GDF15, growth differentiation factor 15; TWSG1, twisted gastrulation 1

Musallam KM *et al. Curr Opin Hematol* 2013; 20:187-192; Rivella S. *Blood* 2019;133:51-58; Kautz L *et al. Nat Genet* 2014;46:678-684.

Iron overload is a major contributor to multiple morbidities in NTDT

Pulmonary hypertension and venous thrombosis[1–4]

Endocrinopathy and osteoporosis[1–4]



Silent cerebral infarcts (MRI), large vessel stenosis (MRA), decreased neuronal function (PET-CT)[5–7]

Proteinuria and end-stage renal disease[8,9]

Hepatic fibrosis, cirrhosis, and HCC[10,11]

OPTIMAL CARE (n = 584)

ORIENT (n = 52)

Other local and regional collaborations

Notable absence of cardiac siderosis despite elevated liver iron content[12]

HCC, hepatocellular carcinoma; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography.

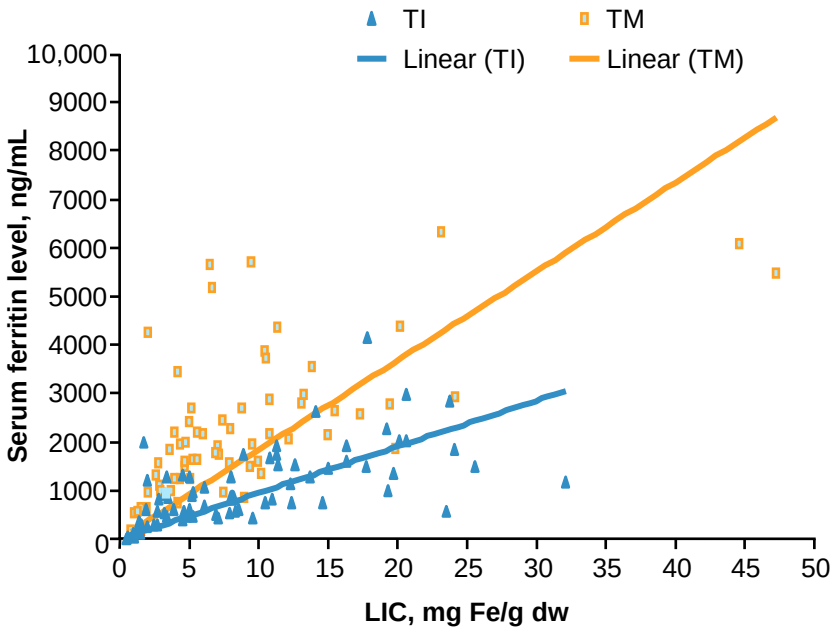
1. Musallam KM *et al. Haematologica* 2011;96:1605-1612; 2. Musallam KM *et al. Blood Cells Mol Dis* 2013;51:35-38; 3. Musallam KM *et al. Haematologica* 2014;99:e218-e221; 4. Taher AT, Musallam KM et a*l. Blood* 2010;115:1886-1892; 5. Taher AT, Musallam KM *et al. J Thrombosis Haemost* 2010;8:54-59; 6. Musallam KM *et al. Eur J Haematol* 2011;87:539-546; 7. Musallam KM *et al. Ann Hematol* 2012;91:235-241; 8. Ziyadeh FN, Musallam KM *et al. Nephron Clin Pract* 2012;121:c136-143; 9. Mallat NS, Musallam KM *et al. Blood Cells Mol Dis* 2013;51:146-148; 10. Musallam KM *et al. Blood Cells Mol Dis* 2012;49:136-139; 11. Moukhadder HM *et al. Cancer* 2017;123:751-758; 12. Taher AT, Musallam KM *et al. Am J Hematol* 2010;85:288-290.

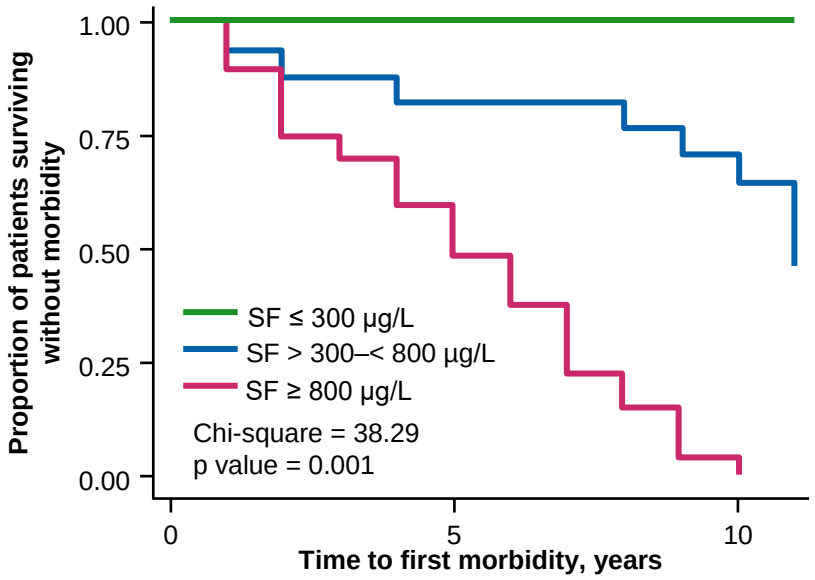
Defining iron overload thresholds to inform management needs specific to NTDT vs TDT

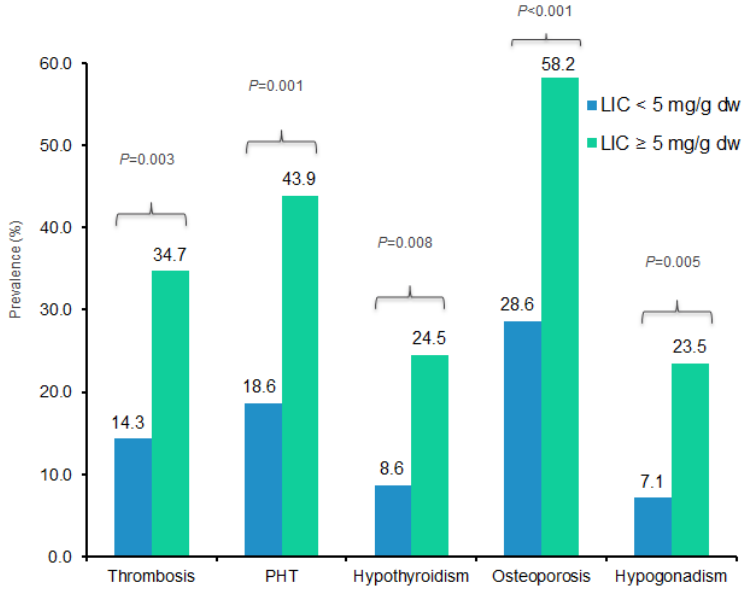
Iron accumulates slowly over time[1,2] but SF values remain lower than TDT for the same LIC[3]

SF values > 800 ng/mL are associated with considerable morbidity[2]

LIC values > 5 mg/g are associated with considerable morbidity[4]





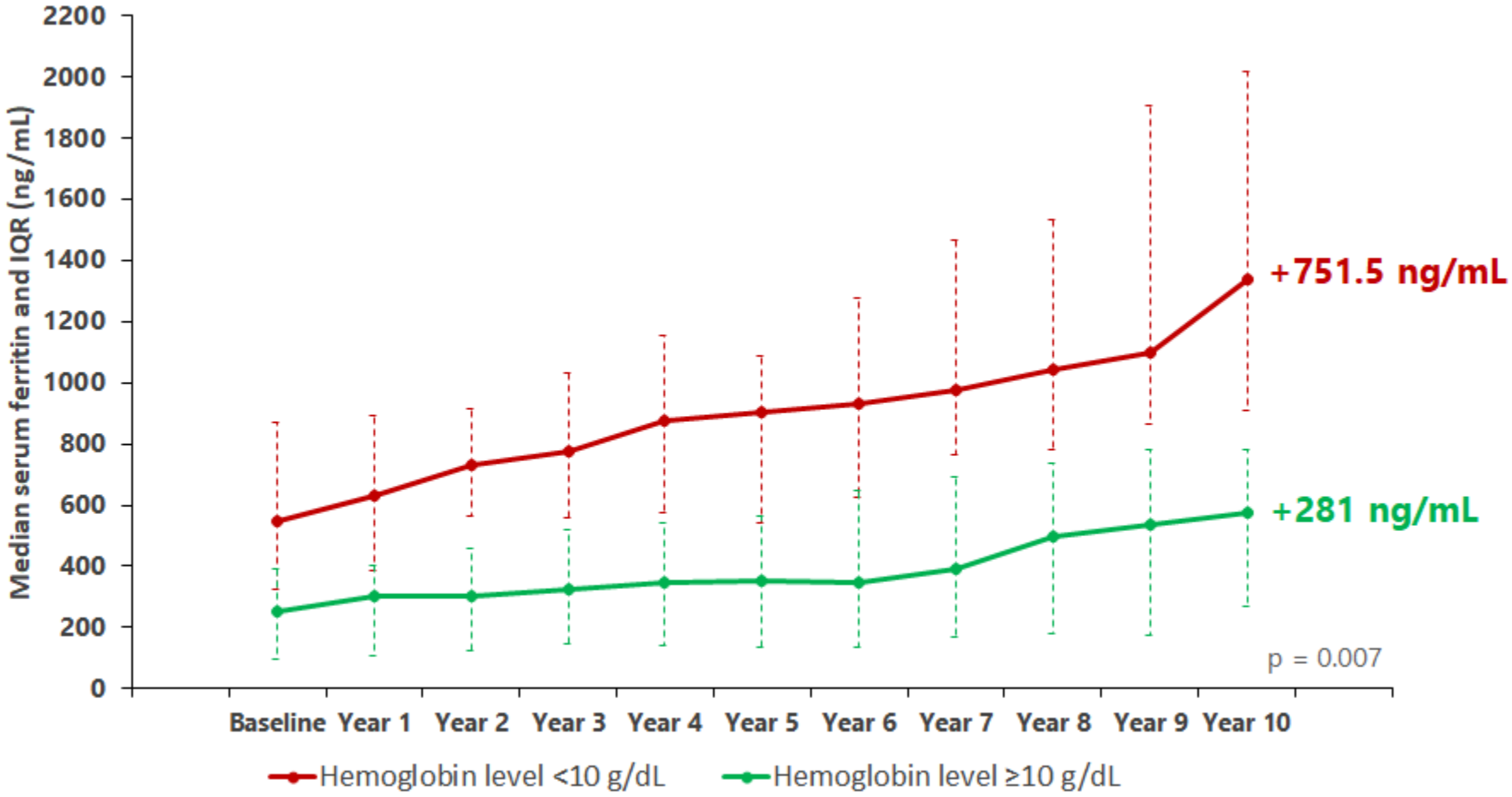


Iron chelation thus became recommended for patients > 10 years of age with SF > 800 ng/mL or LIC > 5 mg/g[5]

LIC, liver iron concentration; PHT, pulmonary hypertension; SF, serum ferritin.

1. Taher AT, Musallam KM *et al*. *Br J Haematol* 2010;150:486–489; 2. Musallam KM *et al. Haematologica* 2014;99:e218–e221; 3. Taher A *et al. Haematologica* 2008;93:1584–1586; 4. Musallam KM *et al. Blood Cells Mol Dis* 2013;51:35–38; 5. Taher AT, Musallam KM, Cappellini MD. TIF NTDT Guidelines 2023.

Anemia severity affects magnitude and rate of primary iron overload in NTDT

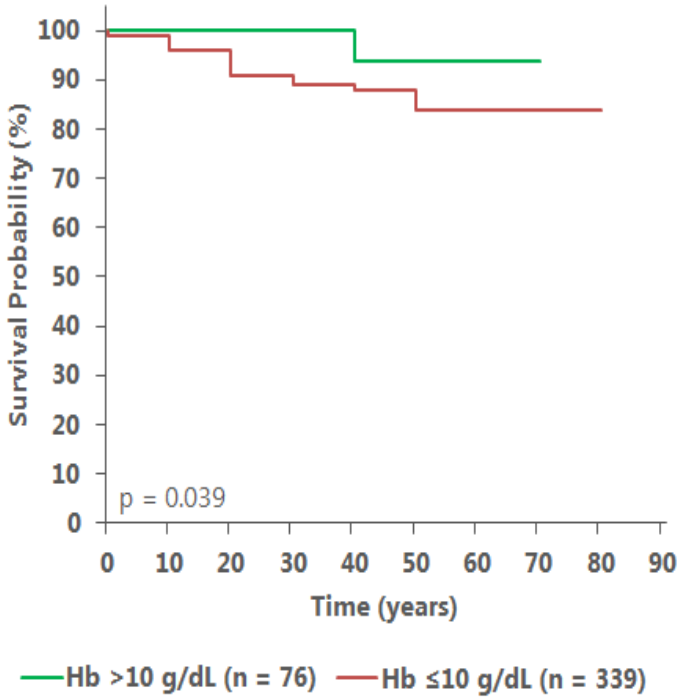


52 patients

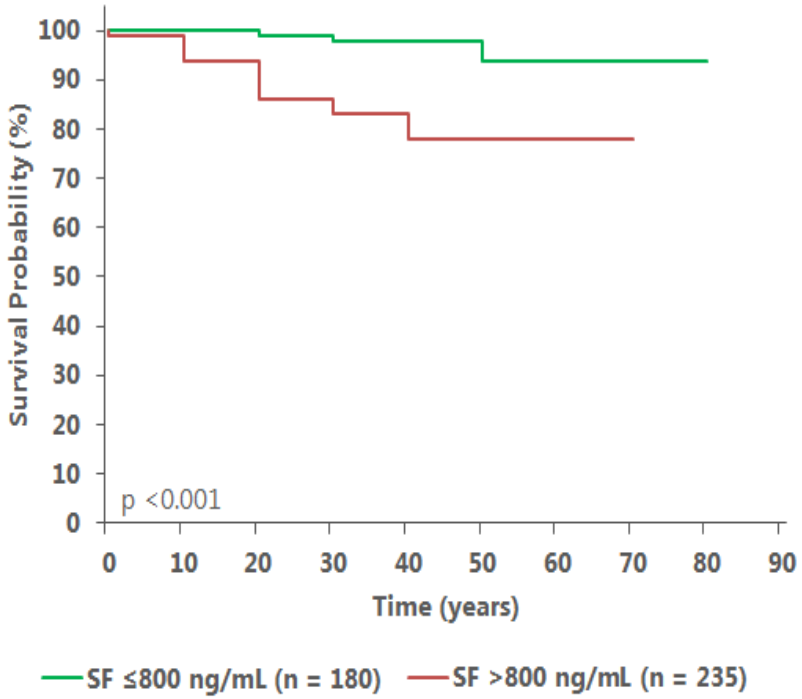
Musallam KM *et al. Ann Hematol* 2023;102:467-469.

Risk of mortality from anemia and iron overload in NTDT

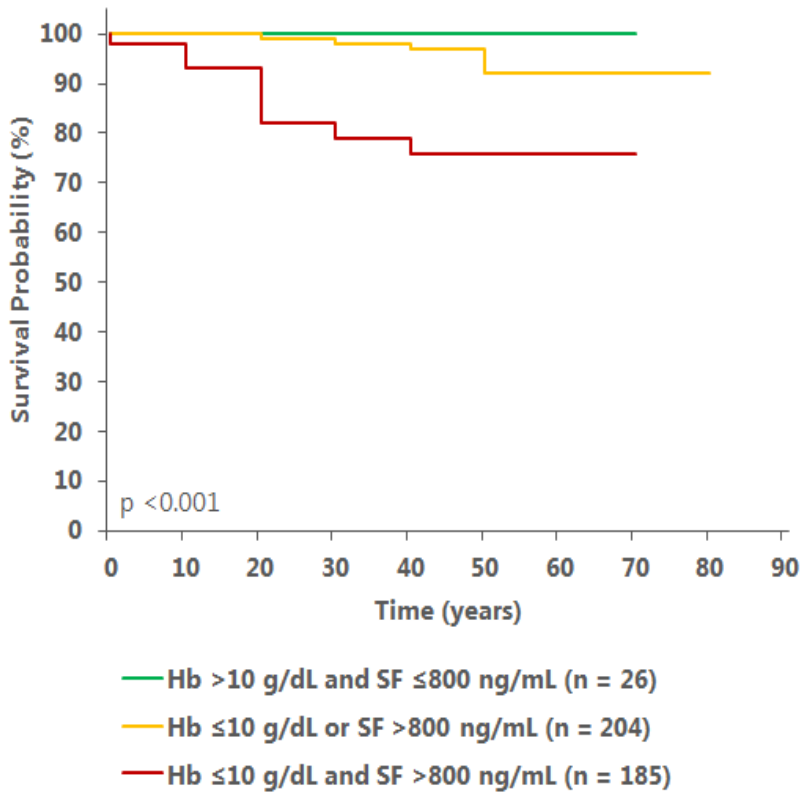
Kaplan–Meier survival curve for mortality according to Hb level



Kaplan–Meier survival curve for mortality according to SF level

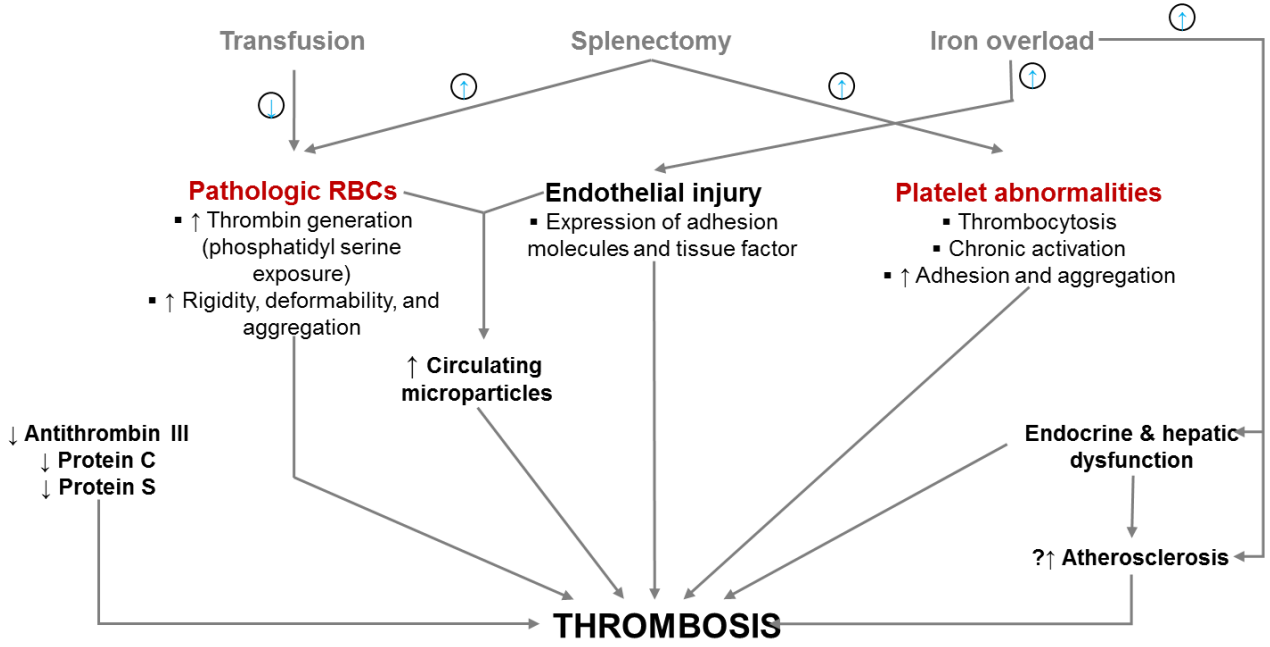


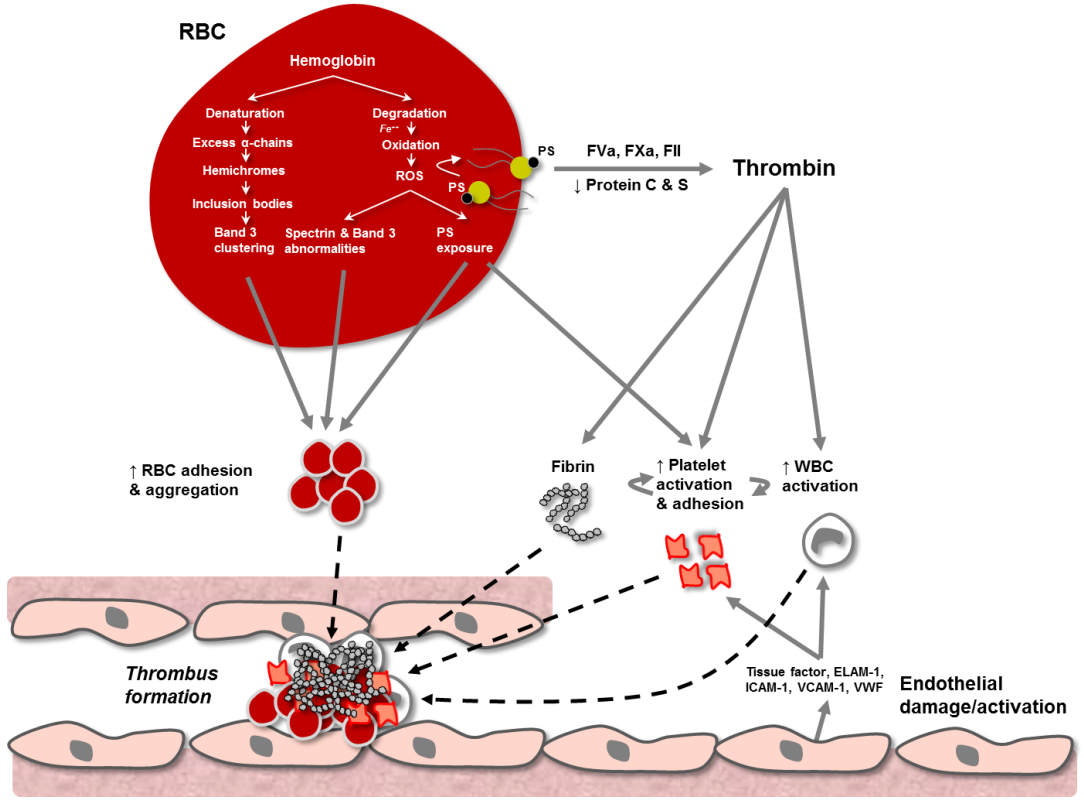
Kaplan–Meier survival curve for mortality according to both Hb and SF levels



Musallam KM *et al. Am J Hematol* 2022;97:E78-E80.

Hypercoagulability and vascular disease are another source of morbidity in NTDT

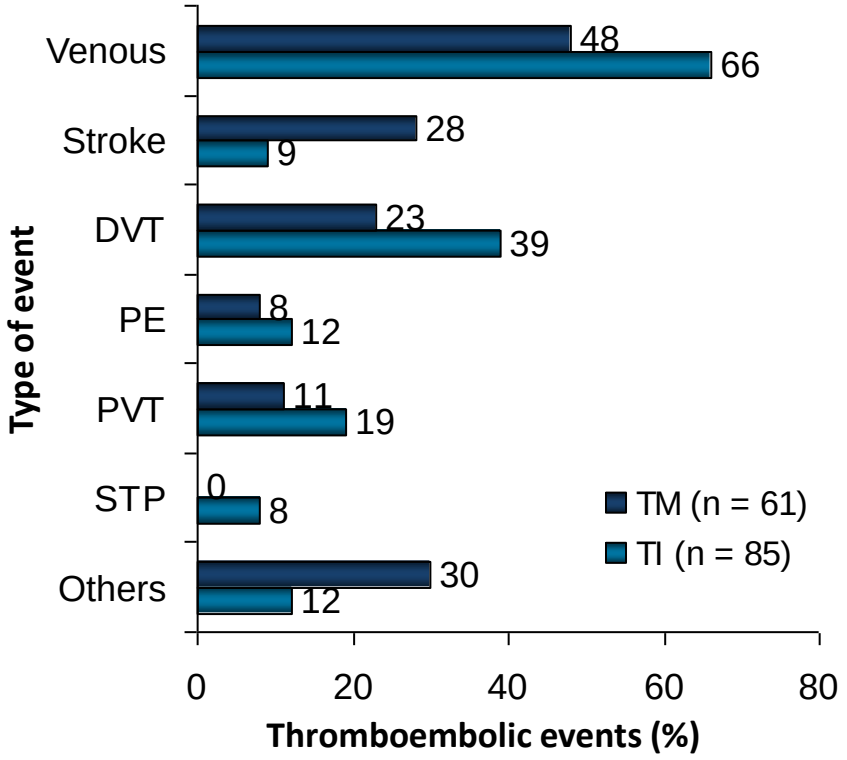




Musallam KM *et al. Haematologica.*2013;98:833-844; Musallam KM *et al. Thromb Res* 2012;130:695-702.

Thromboembolic events in a large cohort of patients with β-thalassemia

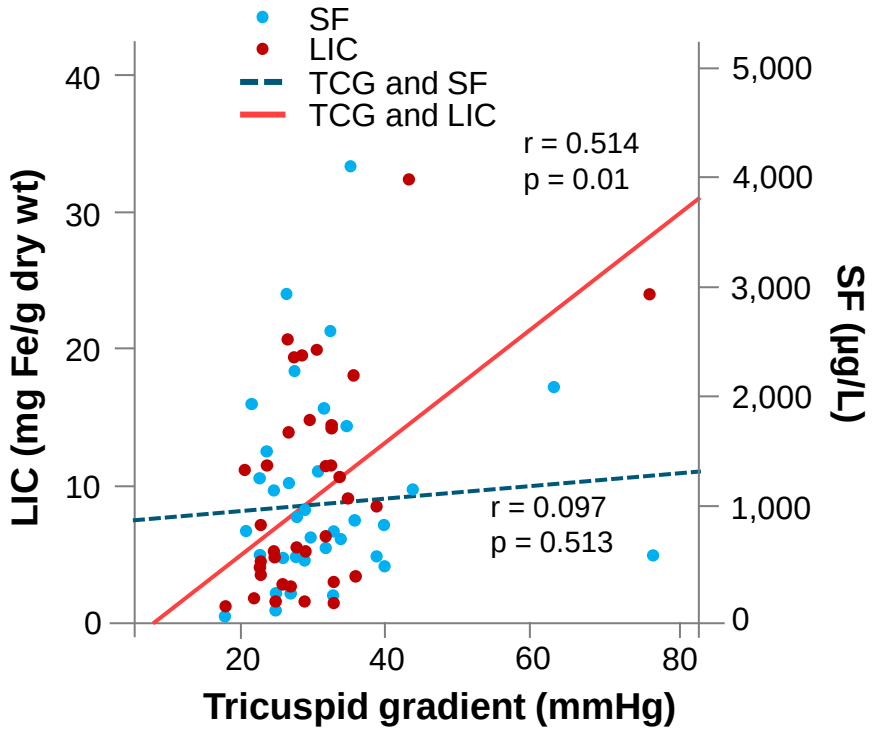
- Patients (N = 8,860)
  - 6,670 with β-TM
  - 2,190 with β-TI
- 146 (1.65%) thrombotic events
  - 61 (**0.9%**) with β-TM
  - 85 (**3.9%**) with β-TI
- Risk factors for developing thrombosis in β-TI were
  - age (> 20 years)
  - previous thromboembolic event
  - family history
  - splenectomy



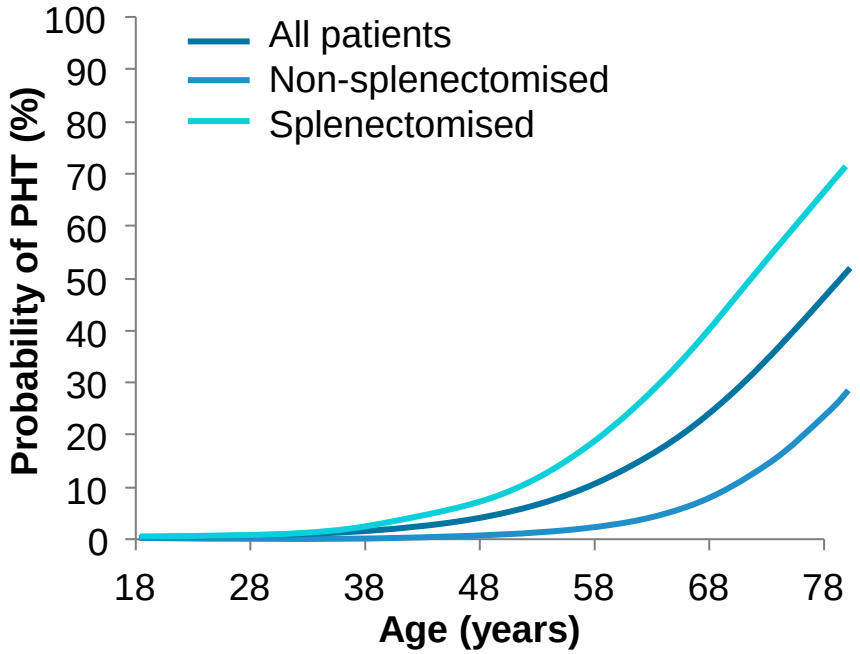
DVT, deep vein thrombosis; PVT, portal vein thrombosis; STP, superficial thrombophlebitis.

Taher A *et al. Thromb Haemost* 2006;96:488-491.

Risk of pulmonary hypertension in NTDT increases with advancing age, splenectomy, anemia and iron overload[1-3]



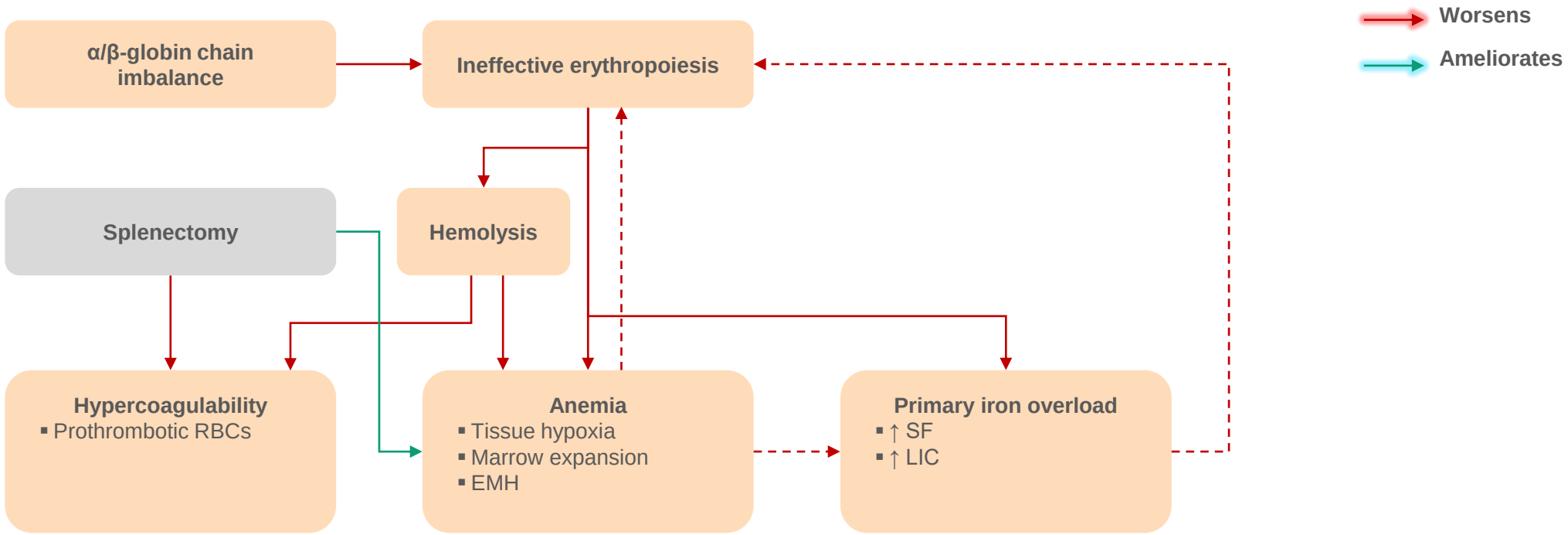
ECHO: PHT (defined as PASP ≥ 30 mmHg) present in 38.5%[1]



CATH: PHT prevalence in thalassaemia was 2.1% (TI 4.8%, TM 1.1%)[2]

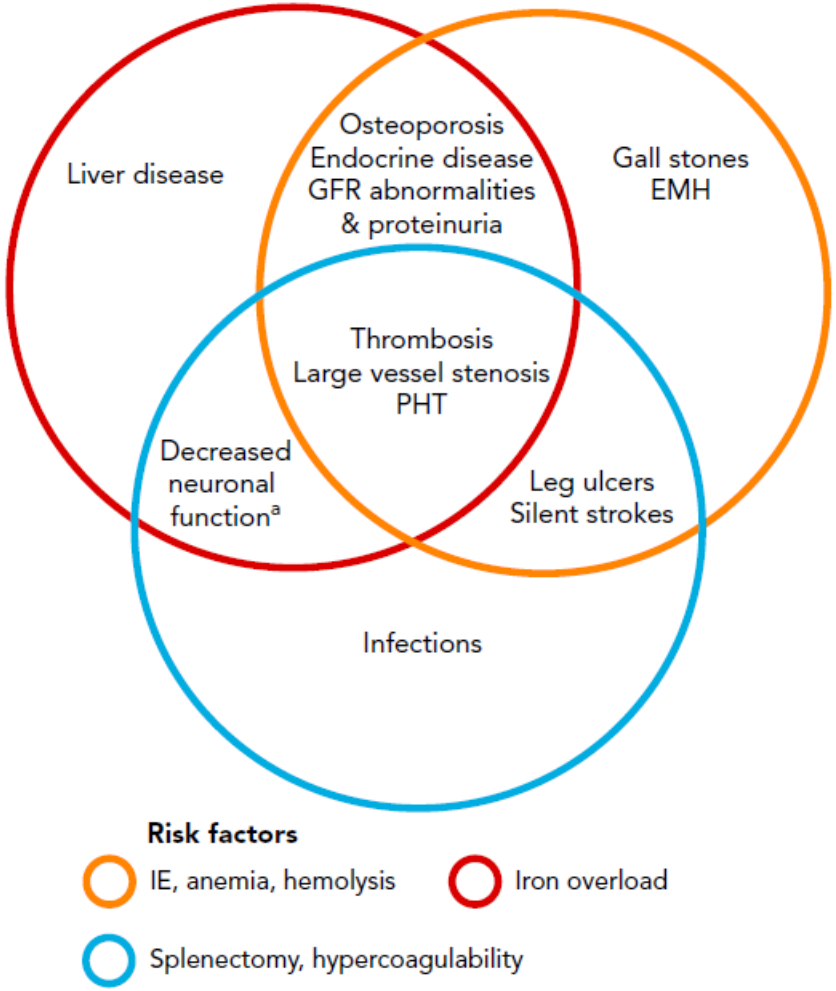
1. Isma'eel H *et al. Am J Cardiol* 2008;102:363-367; 2. Derchi G *et al. Circulation* 2014;129:338-345; 3. Karimi M *et al. Eur J Intern Med* 2011;22:607-610.

Splenectomy, once commonly performed especially in NTDT, is now mainly reserved to cases of symptomatic splenomegaly or hypersplenism due to associated morbidity (infections, thrombotic disease); and now mainly recognized as a high-risk patient characteristic



Taher AT, Musallam KM, Cappellini MD. *N Engl J Med* 2021;384:727-743.

Interaction of multiple risk factors for morbidity in NTDT

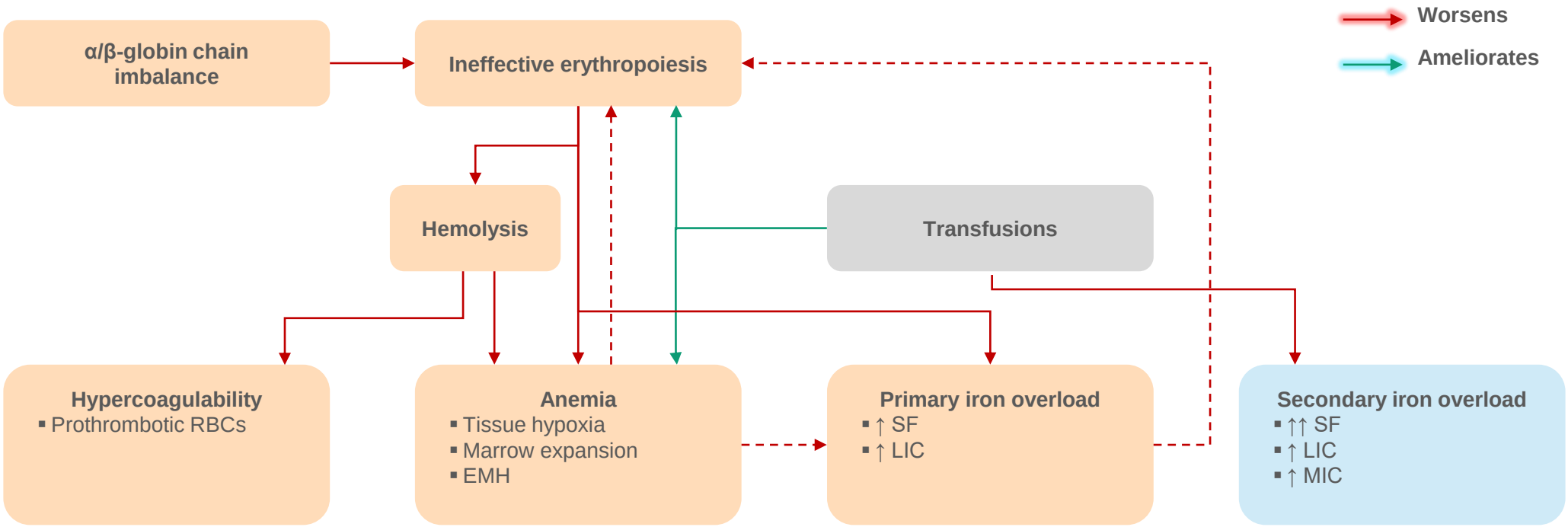


[a]As evident on PET-CT.

Taher AT, Cappellini MD. *Blood* 2018;132:1781-1791.

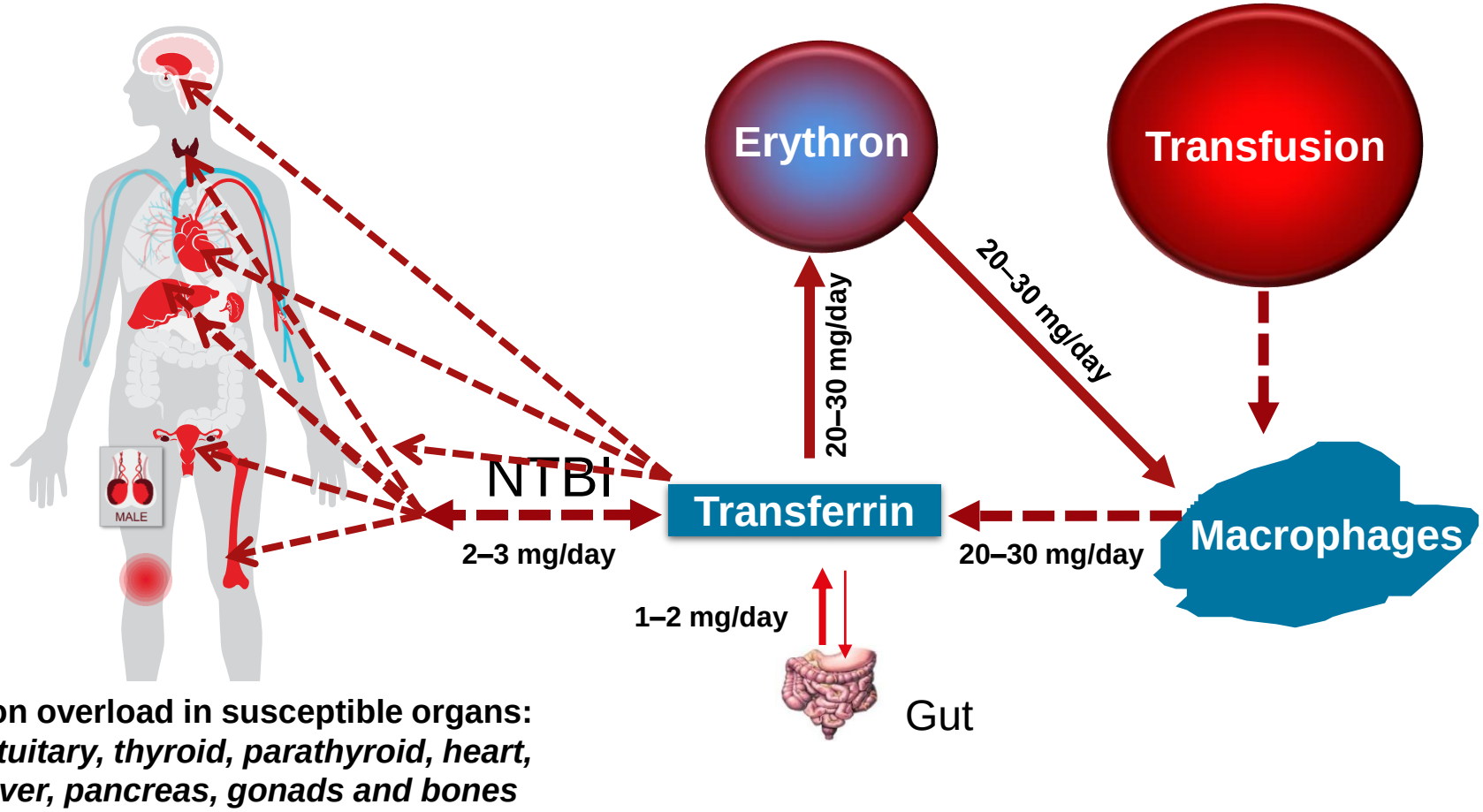
Pathogenesis in Transfused Patients (TDT)

In patients with TDT, transfusional iron overload is the key driver for morbidity



Taher AT, Musallam KM, Cappellini MD. *N Engl J Med* 2021;384:727-743.

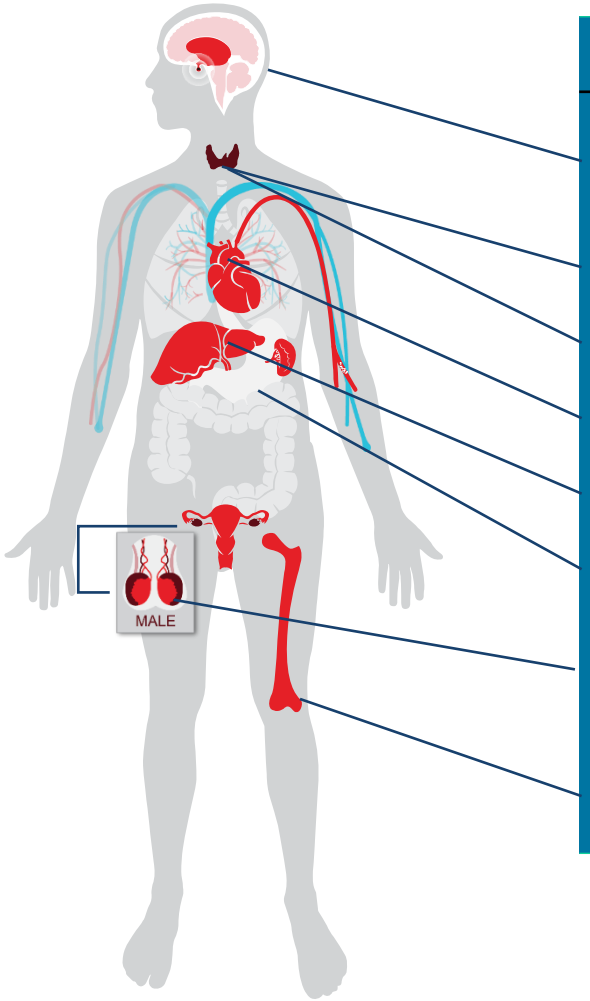
Transfusional iron in TDT patients affects iron distribution



NTBI, non-transferrin-bound iron.

Porter J. *Hematol Oncol Clin* 2005;19(suppl 1):7.

Iron deposition eventually occurs in different organs

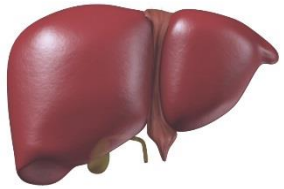


Organ[1,2]	Consequences
Pituitary	Hypogonadotropic Hypogonadism
Thyroid	Hypothyroidism
Parathyroid	Hypoparathyroidism
Heart	Cardiomyopathy
Liver	Cirrhosis, carcinoma
Pancreas	Diabetes
Gonads	Hypogonadotropic Hypogonadism
Bones	Osteomalacia Osteoporosis

These tissues share L-type calcium-dependent channels for NTBI uptake[3]

1. Taher A *et al. Semin Hematol* 2007;44:S2–S6; 2. Ebrahimpour L *et al. Hematology* 2012;17:297–301; 3. Oudit GY *et al. Nat Med* 2003;9:1187–1194.

Hepatic and cardiac iron levels associated with morbidity and mortality are now recognized

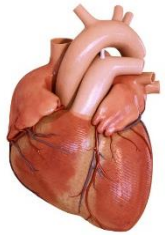


LIC >7 mg/g

- Increased risk of morbidity and liver disease[1]
- Increased risk of cardiac disease for LIC 7–15 mg/g dw (28.6% within 13 years)[2]

LIC >15 mg/g

- Increased risk of hepatic fibrosis, cirrhosis and HCC[3,4]
- Increased risk of cardiac disease (50% within 13 years)[2]



T2* <20 ms

- Increased risk of cardiac arrythmia[5]

T2* <10 ms

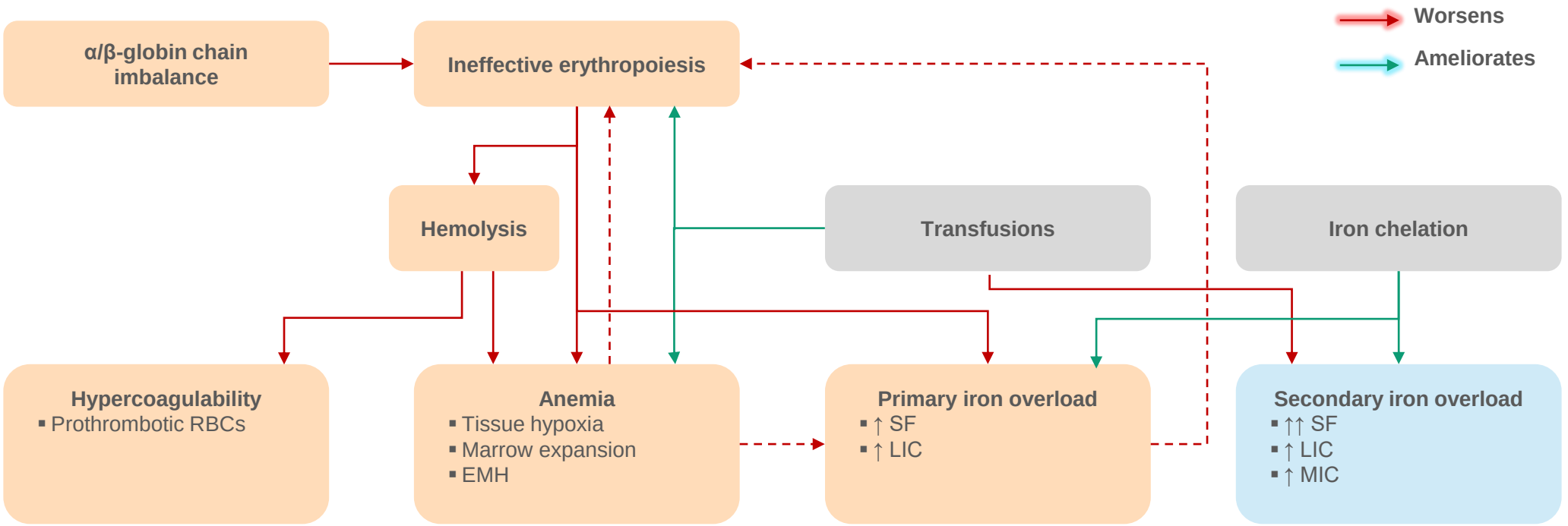
- Increased risk of heart failure and death[5,6]

Patient iron overload profile recognized as combinations of low/high liver/heart iron

1. Olivieri NF. *N Engl J Med* 1999;341:99-109; 2. Telfer PT *et al. Br J Haematol* 2000;110:971–977; 3. Angelucci E *et al. Blood* 2002;100:17-21; 4. Borgna Pignatti C *et al. Br J Haematol* 2004;124: 114-117; 5. Kirk P *et al. Circulation* 2009;120:1961-1968; 2. Carpenter JP *et al. Haematologica* 2013;98:1368-1374.

Management of TDT

Transfusion and iron chelation have been the mainstay of therapy in patients with TDT



Taher AT, Musallam KM, Cappellini MD. *N Engl J Med* 2021;384:727-743.

Standard transfusion regimen for TDT

Transfusion frequency

- Every 2 to 5 weeks, taking into account patient's lifestyle issues

Pre-transfusion hemoglobin level

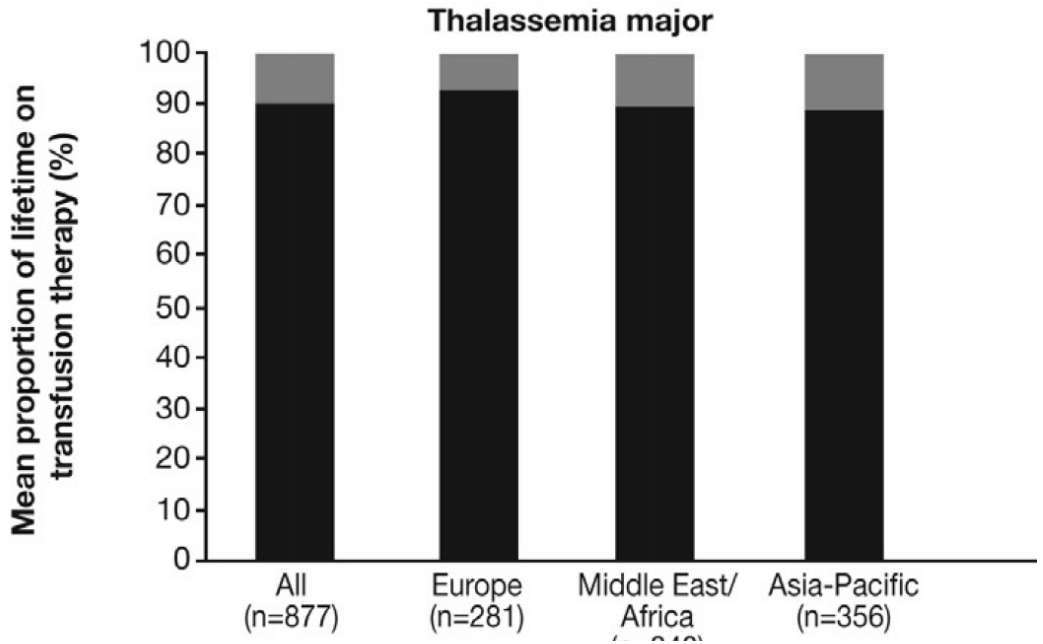
- > 9–10.5 g/dL
- 11–12 g/dL for patients with heart disease or other medical conditions and for those who do not achieve adequate suppression of bone marrow activity at the lower hemoglobin level

Post-transfusion hemoglobin level

- > 14–15 g/dL
- Monitor occasionally to allow assessment of the rate of fall in the hemoglobin level between transfusions

Cappellini MD *et al.* TIF TDT Guidelines 2021.

Regional variations in transfusion practices in TDT



	All regions	Europe	Middle East/Africa	Asia-Pacific
Mean ± SD number of transfusion sessions in the year prior to study entry, n				
TM	17.5±8.8 (n=935)	22.7±10.6 (n=279)	15.8±8.3 (n=240)	14.9±5.5 (n=416)
Mean ± SD volume blood transfused in the year prior to study entry, mL/kg				
TM	189.8±139.3 (n=917)	190.9±210.3 (n=263)	141.4±76.9 (n=240)	217.2±97.2 (n=414)

Viprakasit V *et al. Blood Transf* 2013;11:108-122.

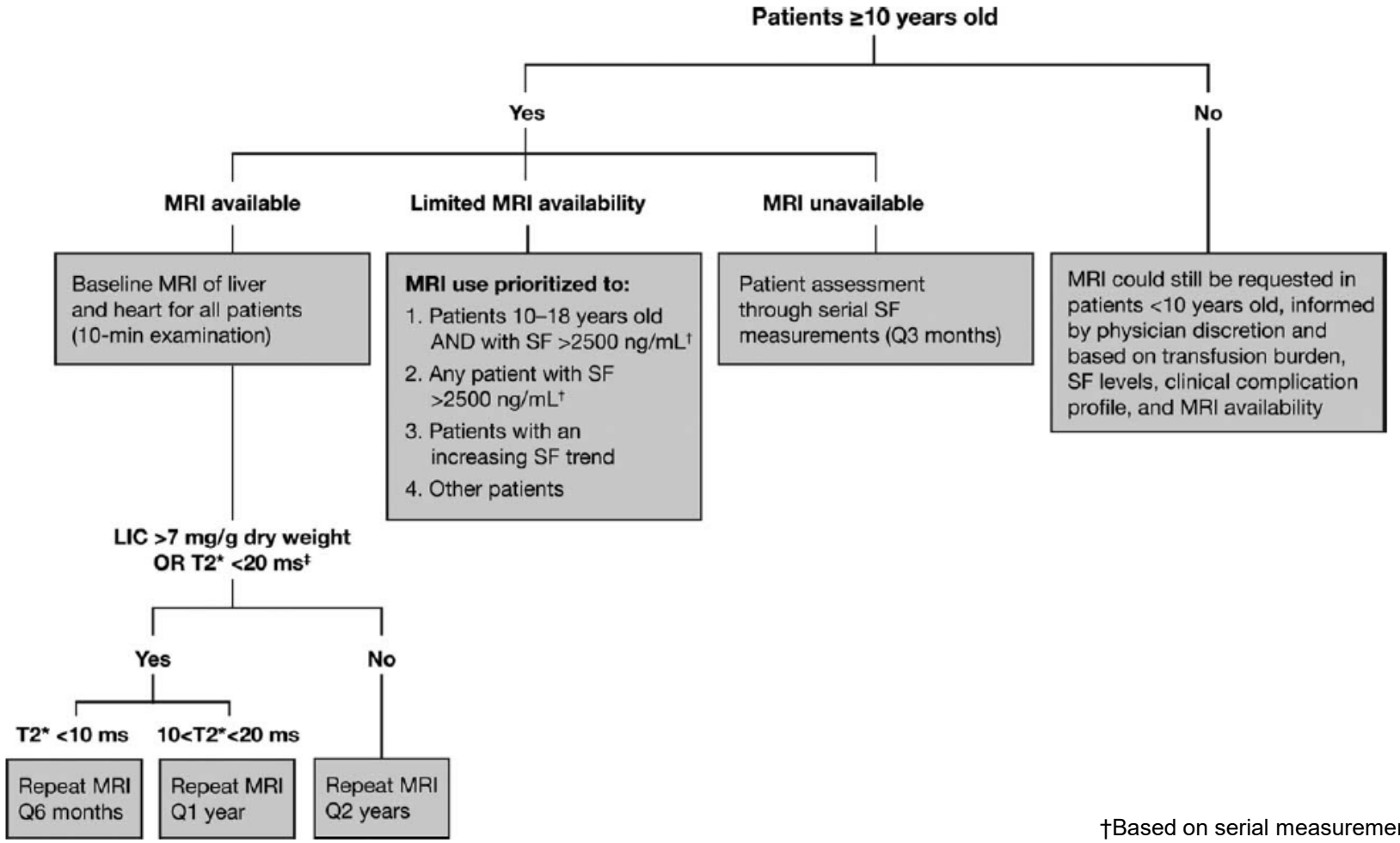
Thalassaemia International Federation recommendations for iron overload monitoring in TDT

Measurement	Screening frequency (months)					
	1	3	6	12	24	As needed
Volume of packed red blood cells transfused			X	X		
Serum ferritin		X				
Liver iron				X		X
Iron, TIBC						X
Transferrin saturation						X
Myocardial T2*				X		

Monitoring liver and cardiac iron by MRI can be started at 8–10 years or earlier if feasible without sedation.

Cappellini MD *et al*. TIF TDT Guidelines 2021.

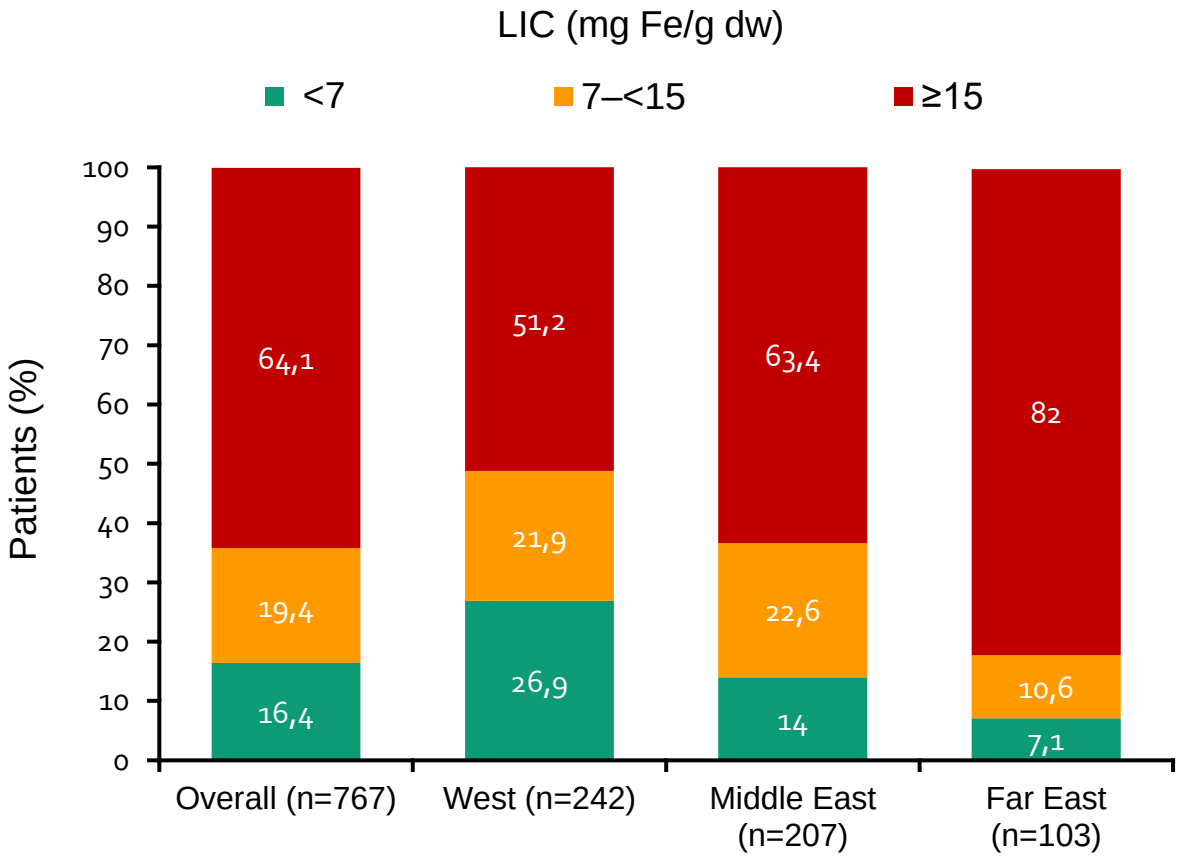
In resource-limited settings

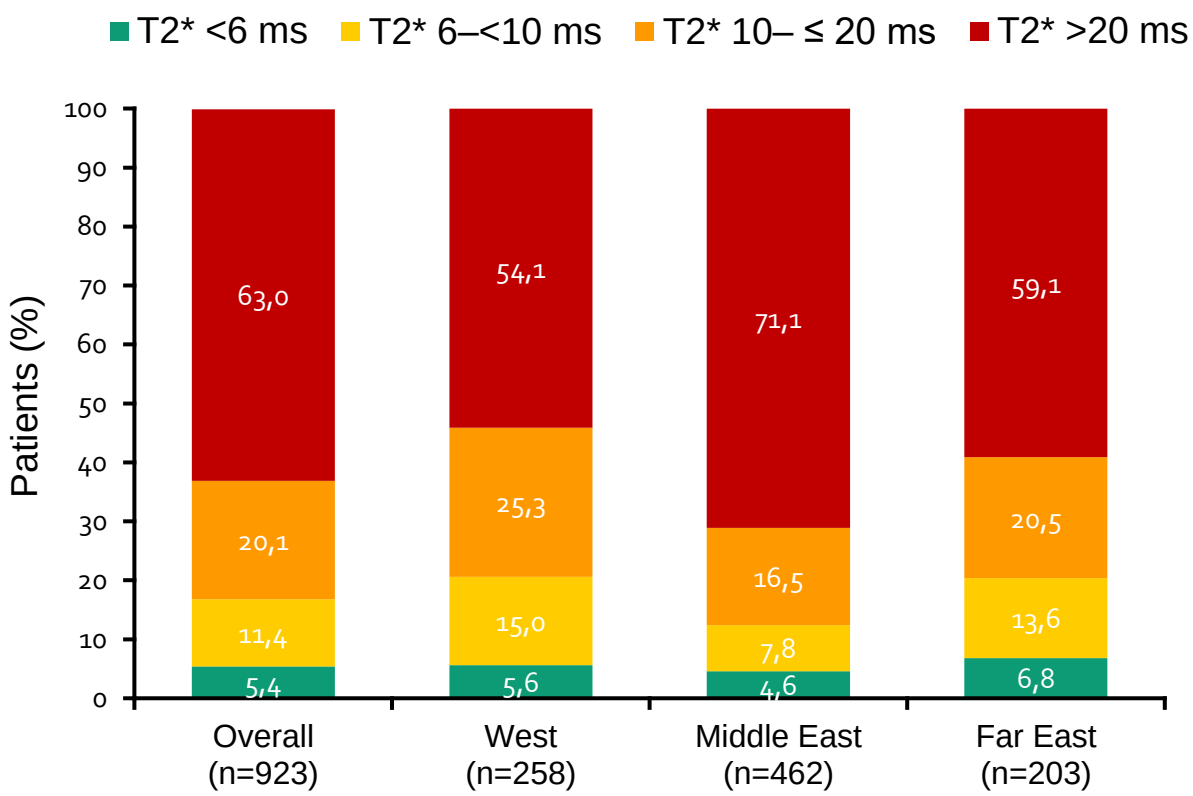


†Based on serial measurements of at least three SF readings;
‡Irrespective of SF levels and heart-failure status.

Viprakasit V *et al*. *Am J Hematol* 2018;93:E135-E137.

Regional variations in iron overload profiles





Aydinok Y *et al. Eur J Haematol* 2015;95:244-253.

Aims of iron chelation therapy

Prevention	• Maintain safe levels of body iron by balancing iron intake with iron excretion
Rescue	• Remove excess stored iron that has accumulated after blood transfusion
Emergency	• Intense treatment to remove excess iron quickly to reverse the effects of heart failure

Cappellini MD *et al*. TIF TDT Guidelines 2021.

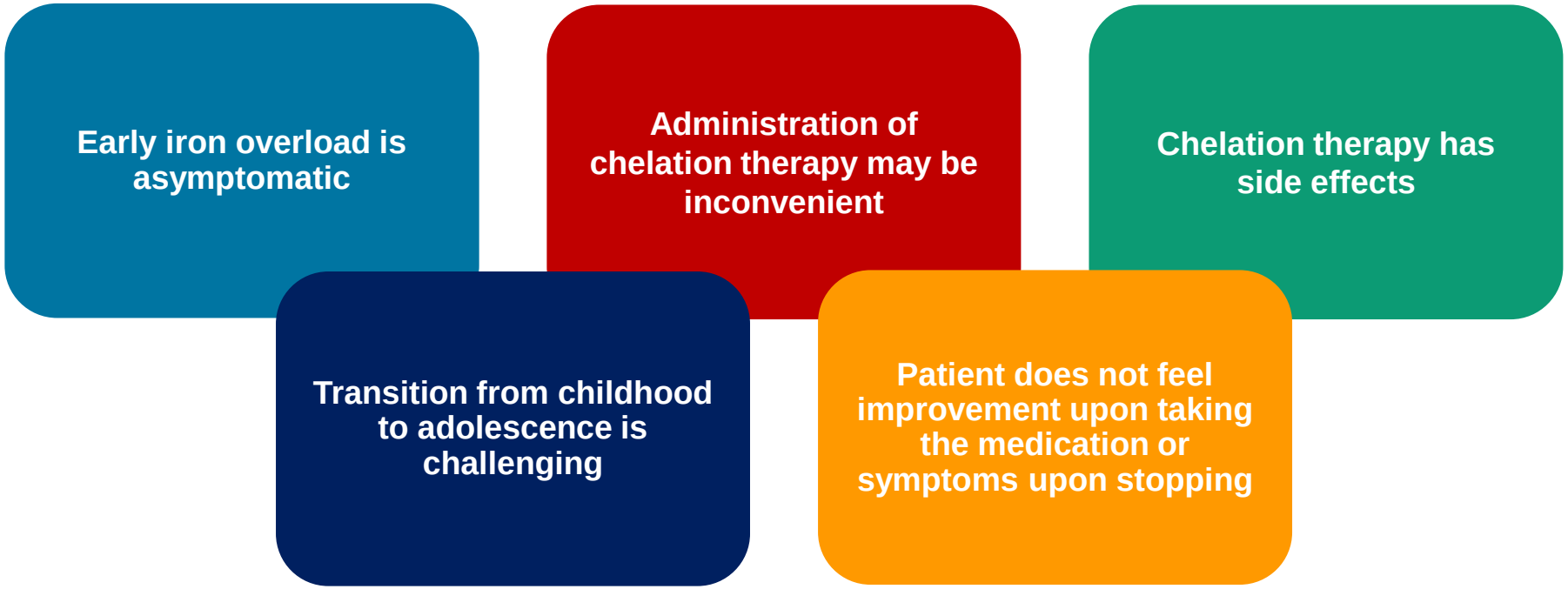
Efficacy and safety of current iron chelators

Parameter	Deferoxamine	Deferiprone	Deferasirox
Efficacy[1]	• Reduction in SF and LIC[2] • Improvement in cardiac T2*[2,3] • Improvement in cardiac dysfunction with continuous infusion[4,5]	• Relative reductions in SF and LIC[6,7] • Improvement of cardiac T2* in monotherapy or combination with deferoxamine (higher doses that commonly used in clinical practice)[7,8] • Improvement in cardiac dysfunction in combination with deferoxamine[9] • Improvement in endocrine dysfunction in combination with deferoxamine or deferasirox[10,11]	• Reduction in SF and LIC up to five years and cardiac T2* up to three years of therapy even in severely loaded patients[12-15] • Non-inferior to deferoxamine for improvement of cardiac T2*[16] • Improvement in hepatic fibrosis and inflammation[2] • Stabilization of heart function[2,12] • Stabilization of endocrine function[17]
Main adverse events[1]	Ocular, auditory, bone growth retardation, local reactions, allergy	Gastrointestinal, arthralgia, agranulocytosis/neutropenia	Gastrointestinal, increased creatinine, increased hepatic enzymes
Pregnancy[1]	Contraindicated (but has been used in third trimester)	Contraindicated	Contraindicated

Lack of large head-to-head comparison trials for oral chelators

1. Cappellini MD *et al.* TIF TDT Guidelines 2014; 2. Pennell DJ *et al. Blood* 2014;123:1447-1454; 3. Mamtani M, Kulkarni H. *Br J Haematol* 2008;141:882-890; 4. Davis BA, Porter JB. *Blood* 2000;95:1229-1236; 5. Porter JB *et al. J Cardiovasc Magn Reson* 2013;15:38; 6. Viprakasit V et al. *Am J Hematol* 2013;88:251-260; 7. Pennell DJ *et al. Blood* 2006;107:3738-3744; 8. Tanner MA *et al. Circulation* 2007;115:1876-1884; 9. Tanner MA *et al. J Cardiovasc Magn Reson* 2008;10:12; 10. Farmaki K *et al. Br J Haematol* 2010;148:466-475; 11. Farmaki K et al. Blood Cells Mol Dis 2011;47:33-40; 12. Pennell DJ et al. Haematologica 2012;97:842-848;131; 13. Cappellini MD et al. Blood 2011;118:884-893; 14. Pathare A et al. Ann Hematol 2010;89:405-409; 15. Taher A et al. Br J Haematol 2009;147:752-759; 16. Deugnier Y *et al. Gastroenterology* 2011;141:1202-1211; 17. Casale M *et al. Am J Hematol* 2014;89:1102-1106.

Barriers to adherence in iron chelation therapy



Cappellini MD *et al*. TIF TDT Guidelines 2021.

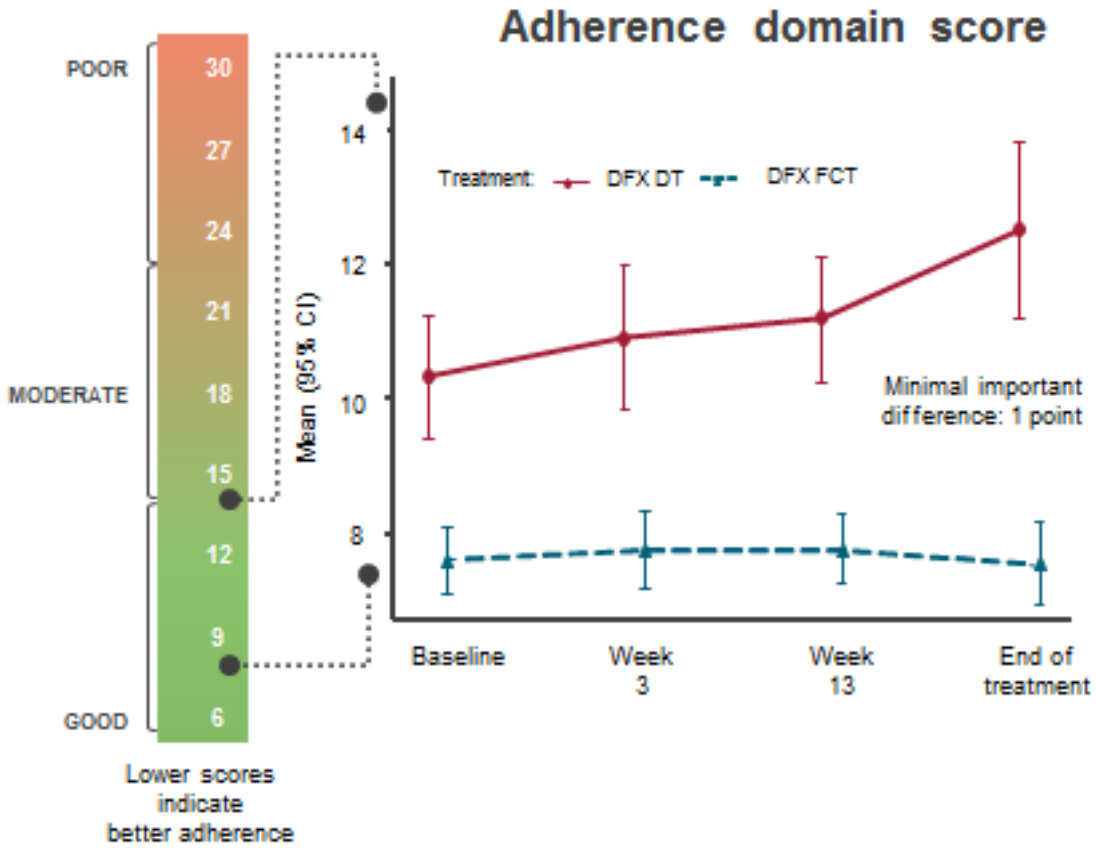
Deferasirox film-coated tablet (FCT)

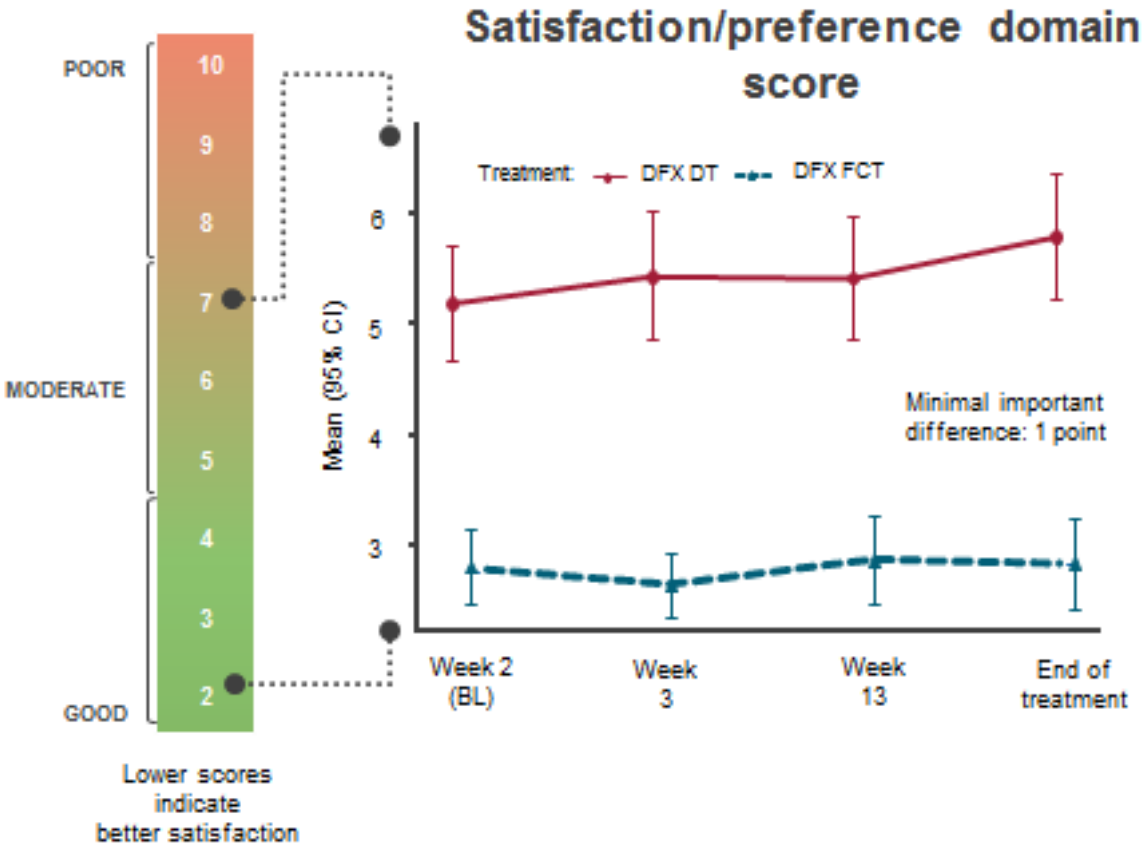
	Dispersible tablet (DT)	Film-coated tablet (FCT)
Starting dose (mg/kg/day)		
pRBC <7 mL/kg/month (<2 pRBC units/month)	10	7
pRBC 7–14 mL/kg/month (2–4 pRBC units/month) pRBC	20	14
>14 mL/kg/month (>4 pRBC units/month)	30	21
Titrating increments (mg/kg/day)	5–10	3.5–7.0
Maximum dose (mg/kg/day)	4	28
Dose strengths (mg)	125 →	90
	250 →	180
	500 →	360

For easy conversion, patients can take the same number of tablets at the same dose level
Be sure to recalculate the dose in case of dose adjustment or change in patient weight

Taher A *et al*. *Am J Hematol* 2017;92:420–428.

ECLIPSE trial: patients on DFX FCT reported greater adherence and satisfaction than those on DFX DT

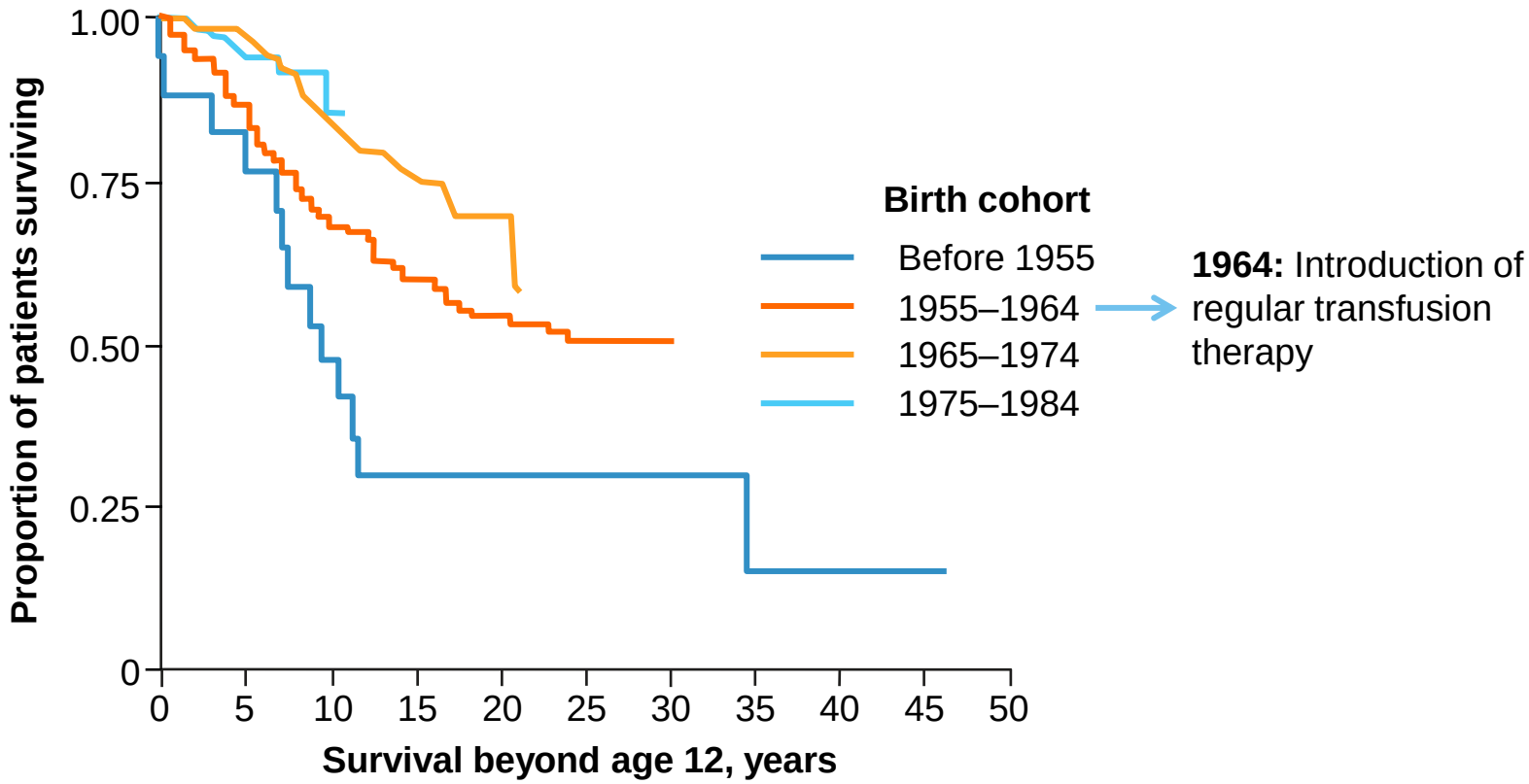




Taher A *et al*. *Am J Hematol* 2017;92:420–428.

The introduction of transfusions improved (ensured) survival in TDT patients[1,2]

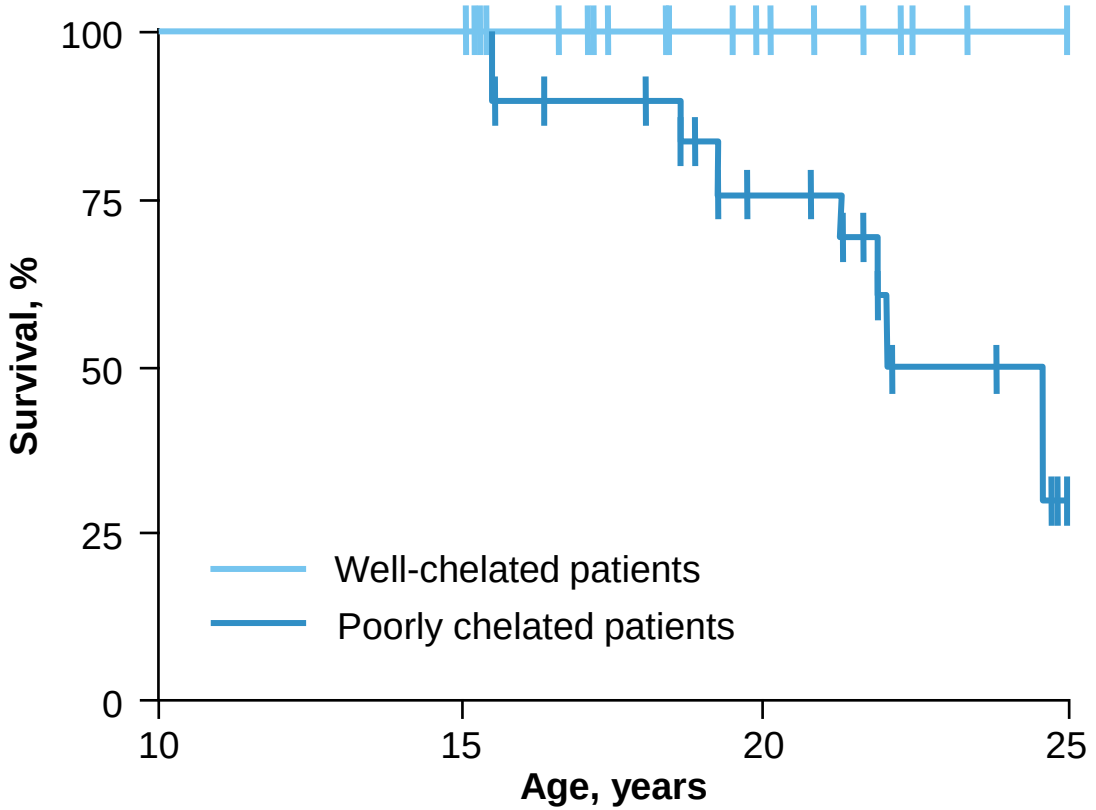
Left untreated, patients would die within a few years of birth[1]



1. Cao A. *Haematologica* 2004;89:1157–1159; 2. Modell B et al. *Lancet* 2000;355:2051–2052.

The introduction of iron chelation therapy improved survival in TDT

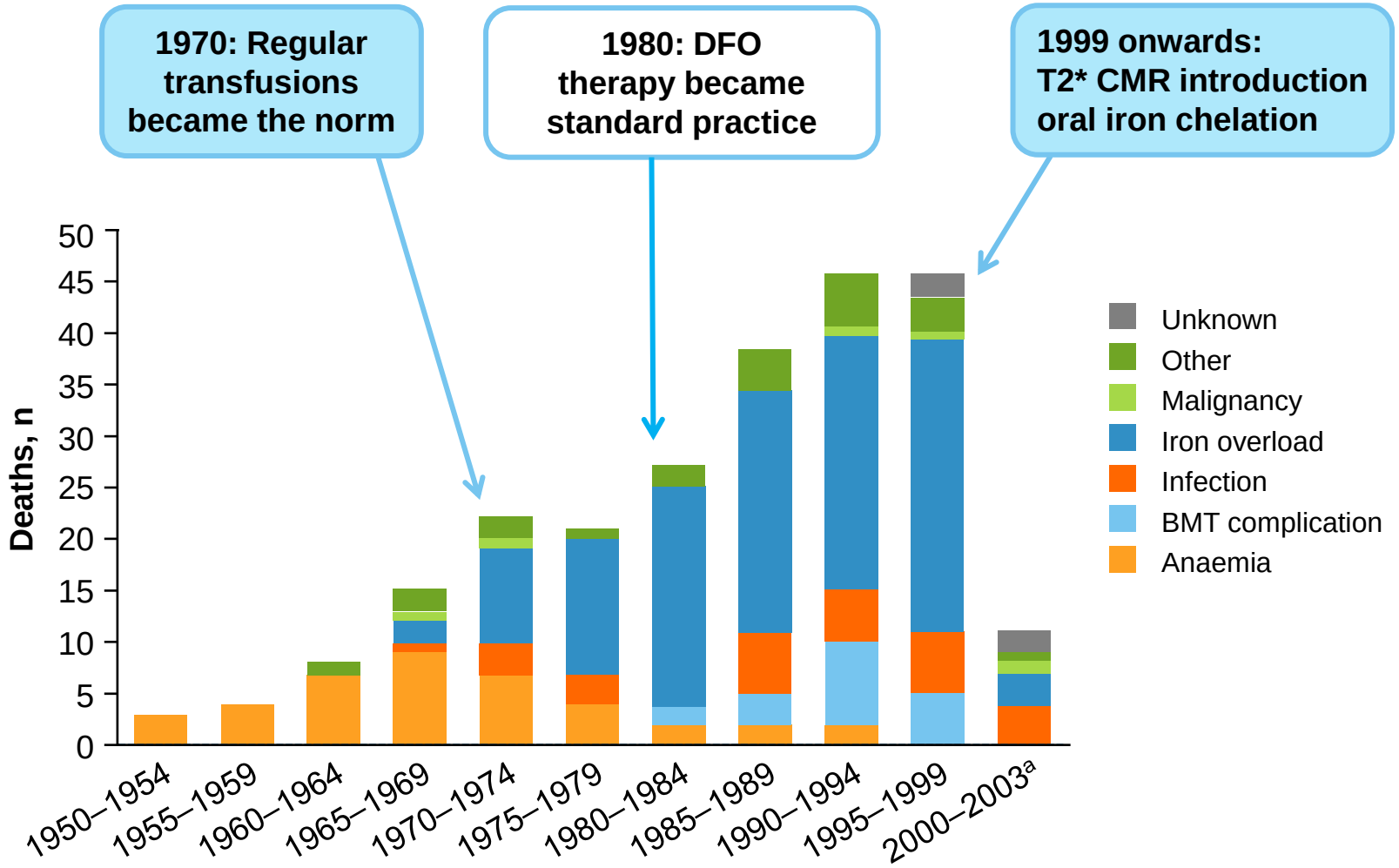
Probability of survival to at least 25 years of age in poorly chelated patients was just one-third that of patients whose iron levels were well managed



TDT patients (n = 59) treated with DFO

Brittenham GM *et al. N Engl J Med* 1994;331:567–573.

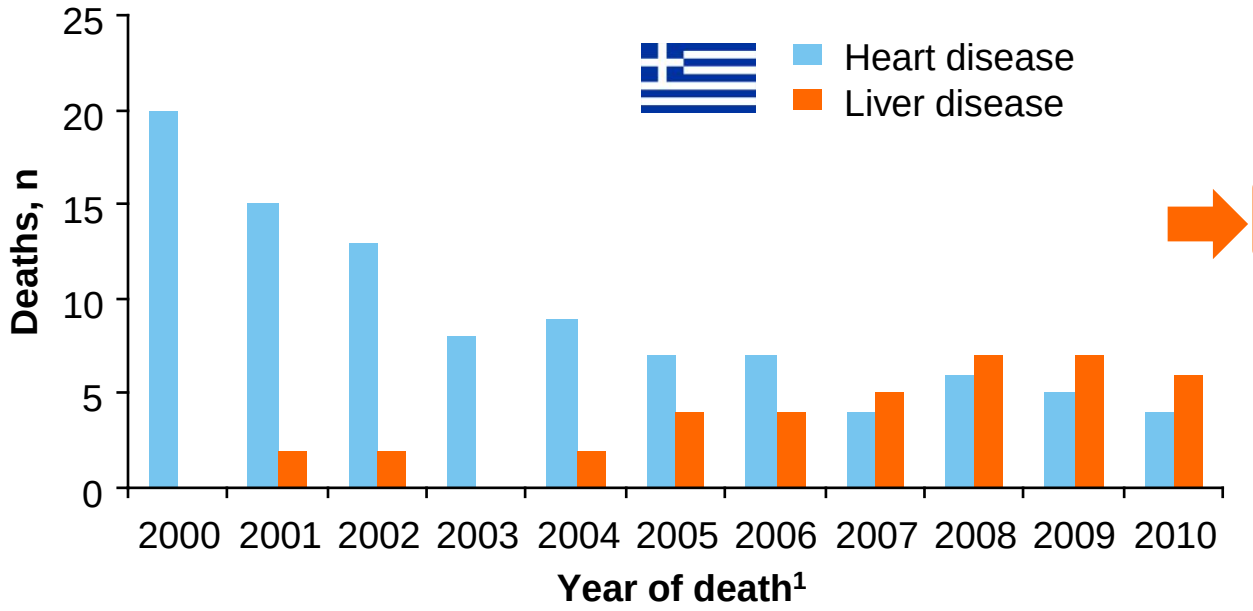
Advances in MRI to detect iron overload coupled with the introduction of oral chelation transformed survival and causes of death in the UK



[a]The number of deaths in the 2000–2003 interval represents deaths over 4 years, and in all the other groups the number of deaths is over 5 years.
BMT, bone marrow transplant; CMR, cardiovascular magnetic resonance; DFO, deferoxamine; MRI, magnetic resonance imaging.

Modell B *et al. J Cardiovasc Magn Reson* 2008;10:42.

Trends in mortality from Greece, Cyprus, and Thailand



Causes of death among thalassemia and sickle cell disease[2]

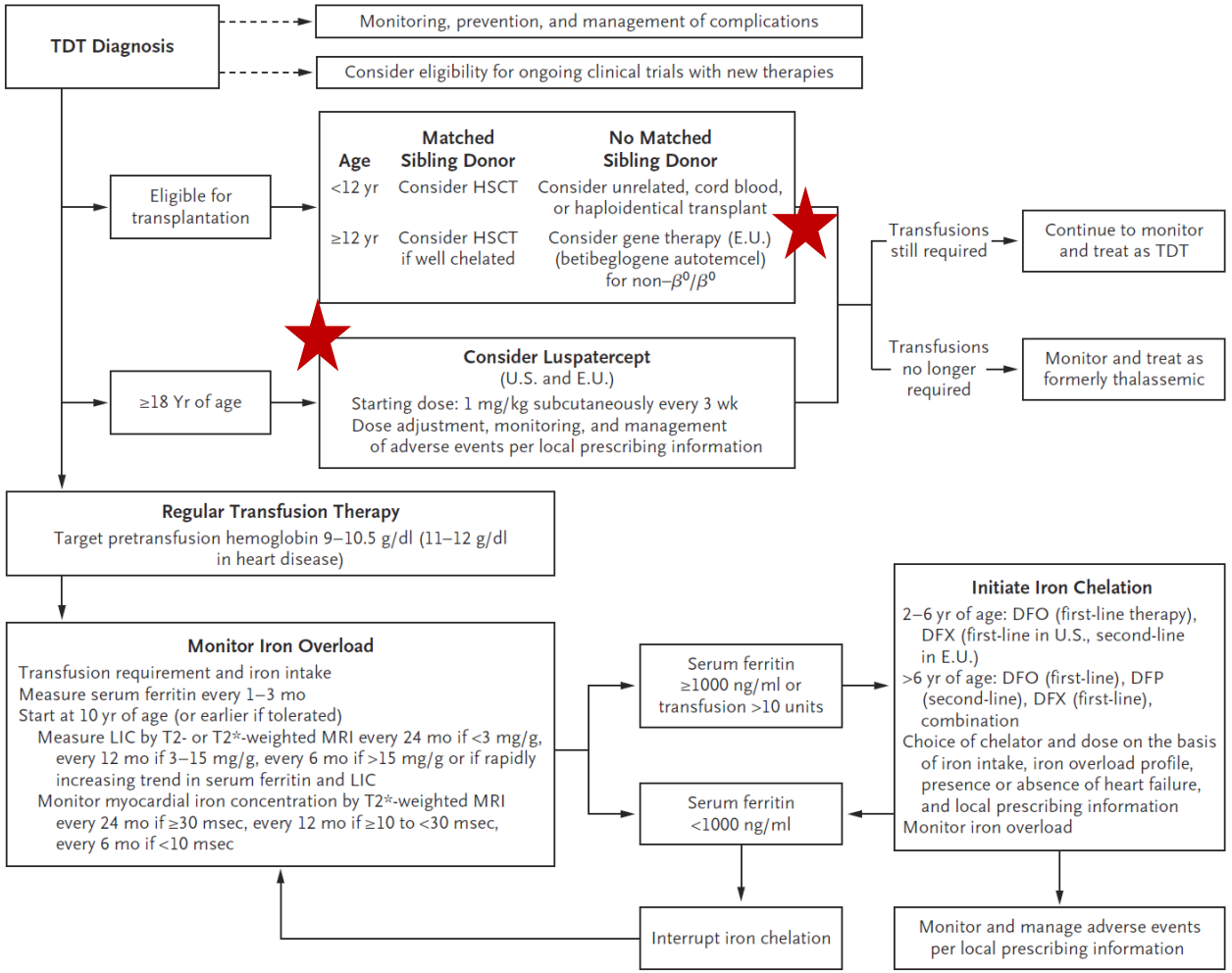
	THAL 2000–2010		SCD 2000–2010		THAL 2010–2015		SCD 2010–2015	
	n	%	*n*	%	*n*	%	*n*	%
Pulmonary embolism	5	3.31	10	11.1	8	4.79	5	7.46
Acute chest syndrome	1	0.66	0	0	0	0	4	5.97
Heart disease	77	50.99	8	8.89	47	28.14	10	14.93
HCC	19	12.58	9	10	28	16.77	2	2.99
Liver failure	9	5.96	13	14.44	11	6.59	8	11.94
Stroke	7	4.64	14	15.56	5	2.99	9	13.43
Renal failure	1	0.66	4	4.44	8	4.79	6	8.96
Sickle cell crisis	0	0	3	3.33	0	0	0	0
Multiorgan failure	1	0.66	2	2.22	2	1.20	1	1.49
Microbial infections	10	6.62	7	7.78	12	7.19	5	7.46
Malignancy other than HCC	8	5.30	7	7.78	10	6.00	4	5.97
Other causes (HIV, car accident)	9	5.96	7	7.78	14	8.38	5	7.46
Unknown causes: cardiac arrest	0	0	0	0	17	10.18	6	8.96
Unknown causes	4	2.66	6	6.68	5	2.98	2	2.98
Total	151	100	90	100	167	100	67	100

In Cyprus, survival to the age of 30 years increased by 8% in the period from 2000 to 2018, as compared with the period from 1980 to 1999[3]

In Thailand, only 20% of patients with β-thalassemia major reached their fourth decade of life, mainly because they received inadequate blood transfusions and iron chelation therapy in the past[4,5]

1. Voskaridou E *et al. Ann Hematol* 2012;91:1451–1458; 2. Voskaridou E *et al. Ann Hematol* 2019;98:55–66; 3. Telfer P *et al. HemaSphere* 2019;3(suppl):346–347; 4. Viprakasit V et al. Presented at: 20th Congress of the European Hematology Association; June 11-14, 2012; Vienna, Austria. Abstract 383; 5. Kattamis A *et al. Eur J Haematol* 2020;105:692–703.

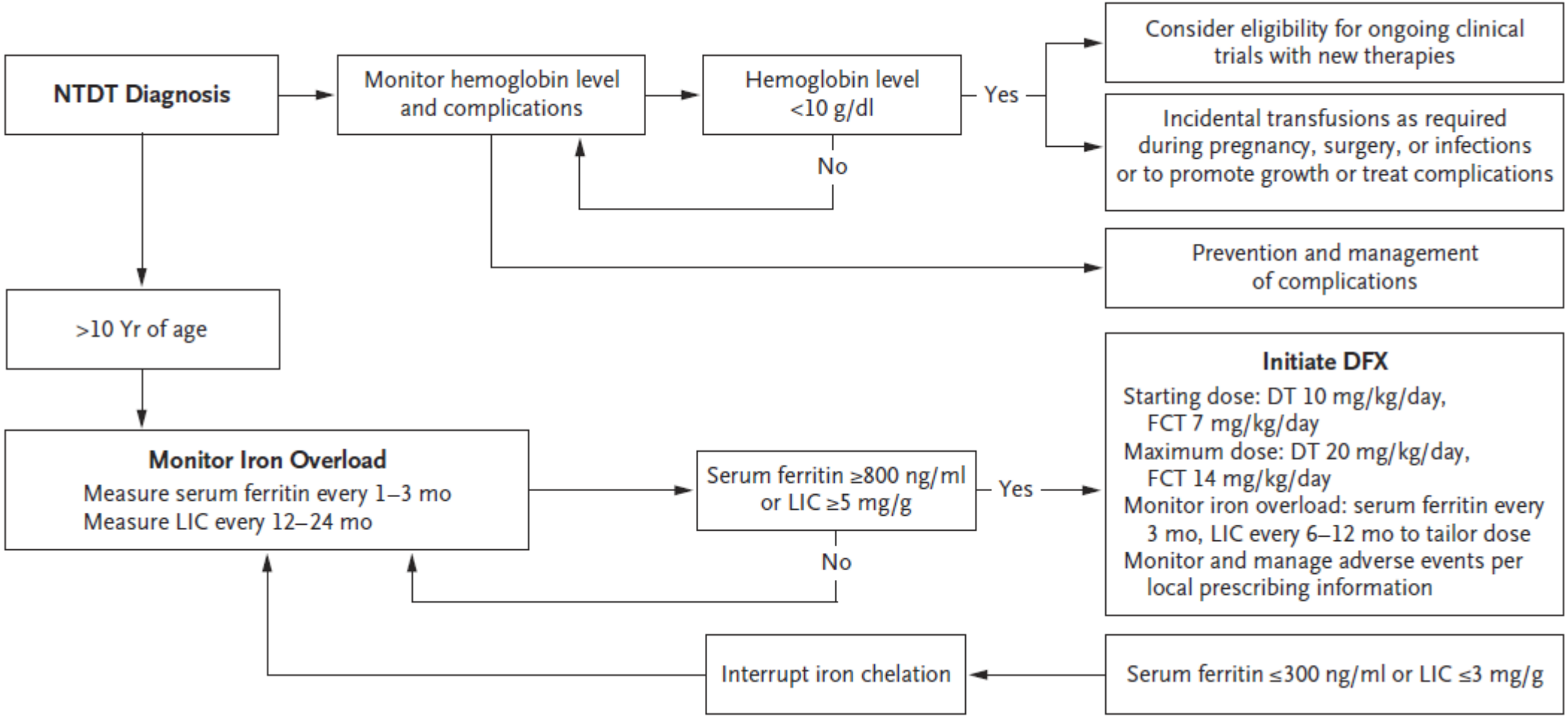
Novel therapies are now gradually being integrated into standard of care for TDT



Taher AT, Musallam KM, Cappellini MD. *N Engl J Med* 2021;384:727-743.

Management of NTDT

Until recently: considerable advances in management of iron overload in NTDT, but limited options to address anemia



Taher AT, Musallam KM, Cappellini MD. *N Engl J Med* 2021;384:727-743.

Approach to management of anemia and IOL in NTDT

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How I treat non-transfusion-dependent β-thalassemia

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The intricate interplay of anemia and iron overload under the pathophysiological umbrella of ineffective erythropoiesis in non-transfusion-dependent β-thalassemia (NTDT) results in a complex variety of clinical phenotypes that are challenging to diagnose and manage. In this article, we use a clinical framework rooted in pathophysiology to present 4 common scenarios of patients with NTDT. Starting from practical considerations in the diagnosis of NTDT, we delineate our strategy for the longitudinal care of patients who exhibit different constellations of symptoms and complications. We highlight the use of transfusion therapy and novel agents, such as luspatercept, in the patient with anemia-related complications. We also describe our approach to chelation therapy in the patient with iron overload. Although tackling every specific complication of NTDT is beyond the scope of this article, we touch on the management of the various morbidities and multisystem manifestations of the disease.

Introduction

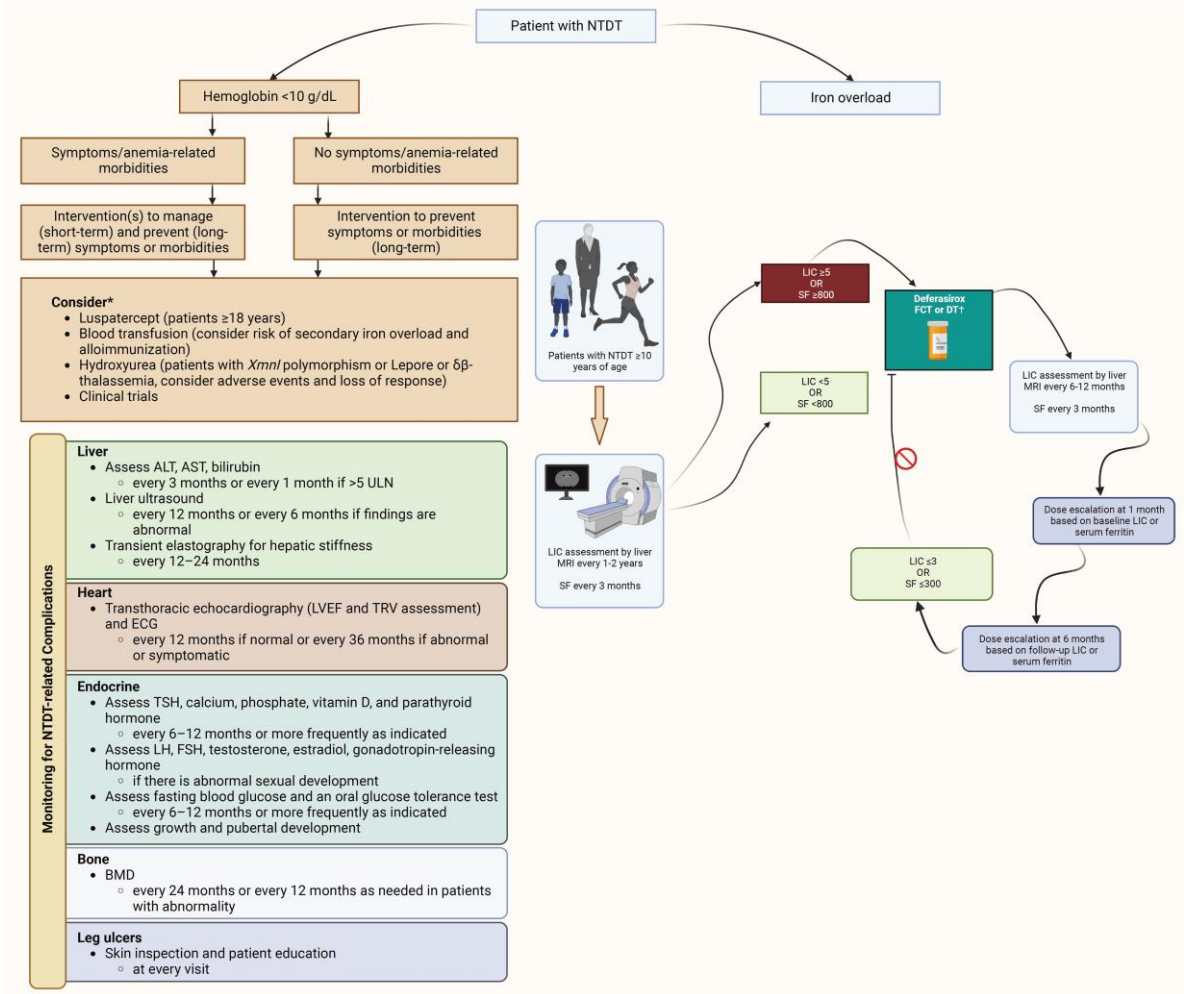
Since the previous How I Treat articles focusing on the thalassemias were published in *Blood* in 2011 and 2018, our armamentarium for the management of these disorders has expanded.[1,2] In this article, we present 4 cases as examples of the most contemporary clinical approaches to the diagnosis and management of non-transfusion-dependent β-thalassemia (NTDT), specifically β-thalassemia intermedia. Although some aspects of care continue to be extrapolated from transfusion-dependent β-thalassemia (TDT), the approach for patients with NTDT should be individualized while considering opportunities for interventions with the potential of improving short-term or long-term outcomes, such as blood transfusion, iron chelation therapy (ICT), hydroxyurea, and luspatercept. The distinction between TDT and NTDT may vary with time because a patient with NTDT may increasingly depend on regular transfusion support or a patient with TDT may require a less intensive transfusion program with certain interventions.[3]

Therefore, we describe special situations in which the clinical phenotypes merge and highlight opportunities to use conventional and novel therapies to address the underlying pathophysiology based on emerging evidence or otherwise practical considerations for the hematologist.[2,4]

Patient 1: diagnosing non-transfusion-dependent β-thalassemia, the intricate interplay of genotype and phenotype

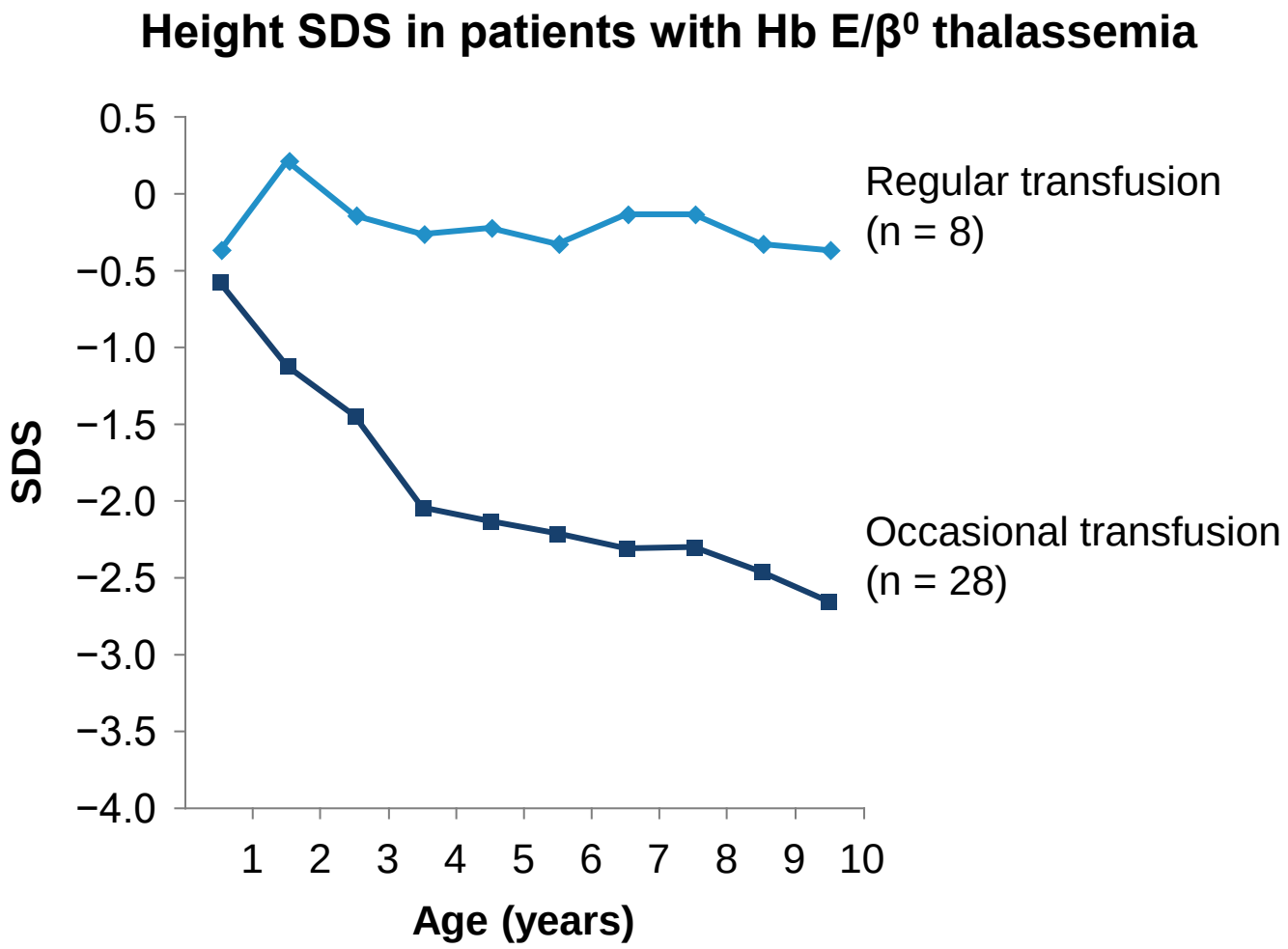
A 25-year-old woman was referred to our clinic for moderate chronic microcytic anemia. The hemoglobin (Hb) concentration was 9.5 g/dL, and the mean corpuscular volume was 69 fL. The red-cell distribution width was normal, and the mean corpuscular Hb concentration was low. Before she was referred to us, she was initially treated empirically for iron deficiency anemia with oral ferrous sulfate without improvement. Lactate dehydrogenase level, reticulocyte count, and indirect bilirubin level were mildly elevated; haptoglobin was suppressed. Hb electrophoresis showed an elevated HbA2 fraction at 4.5% and a normal HbF fraction at 0.7%. She was initially thought to have a severe manifestation of heterozygous β-thalassemia. Her ferritin level was elevated at 780 ng/mL. α-Globin gene analysis demonstrated the presence of an additional α-globin gene in a DNA insert of 3.7 kb. This patient had β-thalassemia intermedia, resulting from increased α/β-globin chain imbalance in the setting of 1 defective β-globin gene (IVSI-110 G>A) and a triplicated α-globin gene locus.

In β-thalassemia intermedia, as the name implies, the disease is characterized by a clinical severity that is intermediate when compared with β-thalassemia major and the asymptomatic carrier (trait/minor) state. Practically, this usually manifests as delayed age at presentation (commonly >2 years of age) with mild-to-moderate anemia (commonly 7-10 g/dL).[4-7] The β-thalassemia intermedia phenotype can result from a variety of genetic alterations that lead to an α/β-globin chain imbalance of sufficient magnitude to promote ineffective erythropoiesis and subsequent anemia of such intermediate severity. This includes various homozygous or compound heterozygous states for β-thalassemia mutations or in some instances, such as the patient described in this study, heterozygous β-thalassemia mutations combined with α-globin gene duplications. The variety of mutations that may affect the β-globin gene in the homozygous or compound heterozygous state is the primary modifier of phenotype. These β-globin gene mutations include mild promoter mutations that cause a mild reduction in β-globin



Saliba AN, Musallam KM *et al. Blood* 2023;142:949-960.

Children's growth and height development can be restored by regular transfusions in NTDT



Viprakasit V *et al. J Med Assoc Thai* 2001;84:929-941.

Benefits of (occasional/regular) transfusions: the OPTIMAL CARE study in NTDT patients

Complication	Parameter	RR	95% CI	p value
	Splenectomy	0.44	0.26–0.73	0.001
EMH	Transfusion	0.06	0.03–0.09	< 0.001
	Hydroxyurea	0.52	0.30–0.91	0.022
	Age > 35 years	2.59	1.08–6.19	0.032
	Splenectomy	4.11	1.99–8.47	< 0.001
Pulmonary hypertension	Transfusion	0.33	0.18–0.58	< 0.001
	Hydroxyurea	0.42	0.20–0.90	0.025
	Iron chelation	0.53	0.29–0.95	0.032
Heart failure	Transfusion	0.06	0.02–0.17	< 0.001
	Age > 35 years	2.60	1.39–4.87	0.003
	Hb ≥ 9 g/dL	0.41	0.23–0.71	0.001
Thrombosis	SF ≥ 1,000 µg/L	1.86	1.09–3.16	0.023
	Splenectomy	6.59	3.09–14.05	< 0.001
	Transfusion	0.28	0.16–0.48	< 0.001
	Age > 35 years	2.76	1.56–4.87	< 0.001
	Female	1.96	1.18–3.25	0.010
Cholelithiasis	Splenectomy	5.19	2.72–9.90	< 0.001
	Transfusion	0.36	0.21–0.62	< 0.001
	Iron chelation	0.30	0.18–0.51	< 0.001
Abnormal liver function	SF ≥ 1,000 µg/L	1.74	1.00–3.02	0.049

Taher AT, Musallam KM *et al. Blood* 2010;115:1886-1892.

Benefits of (occasional/regular) transfusions: the OPTIMAL CARE study in NTDT patients (cont.)

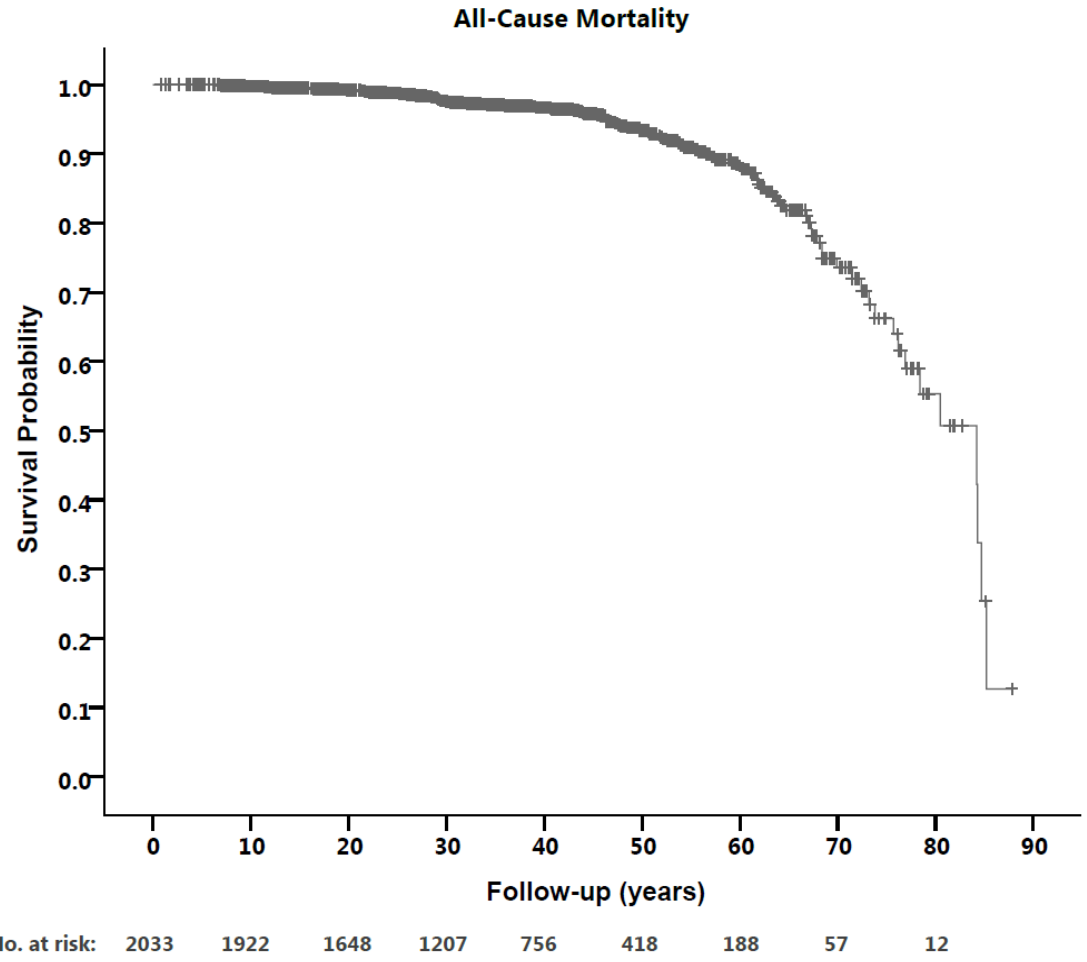
Complication	Parameter	RR	95% CI	p value
	Age > 35 years	2.09	1.05–4.16	0.036
	Iron chelation	0.40	0.24–0.68	0.001
	Female	2.98	1.79–4.96	< 0.001
	SF ≥ 1,000 µg/L	2.63	1.59–4.36	< 0.001
Hypogonadism	Transfusion	16.13	4.85–52.63	< 0.001
	Hydroxyurea	4.32	2.49–7.49	< 0.001
	Iron chelation	2.51	1.48–4.26	0.001

Transfusion therapy was protective for thrombosis, EMH, PHT, HF, cholelithiasis, and leg ulcers

Transfusion therapy was associated with an increased risk of endocrinopathy

Taher AT, Musallam KM *et al. Blood* 2010;115:1886-1892.

Survival in 2033 Patients with NTDT: IWG-THAL Global Registry

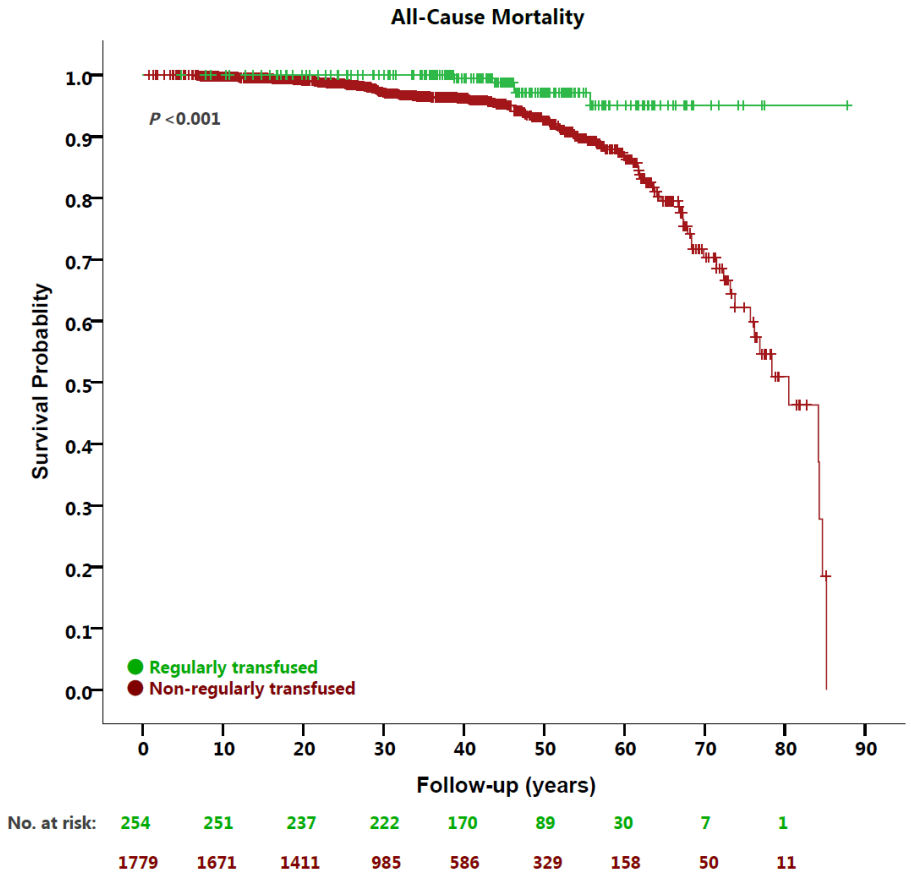


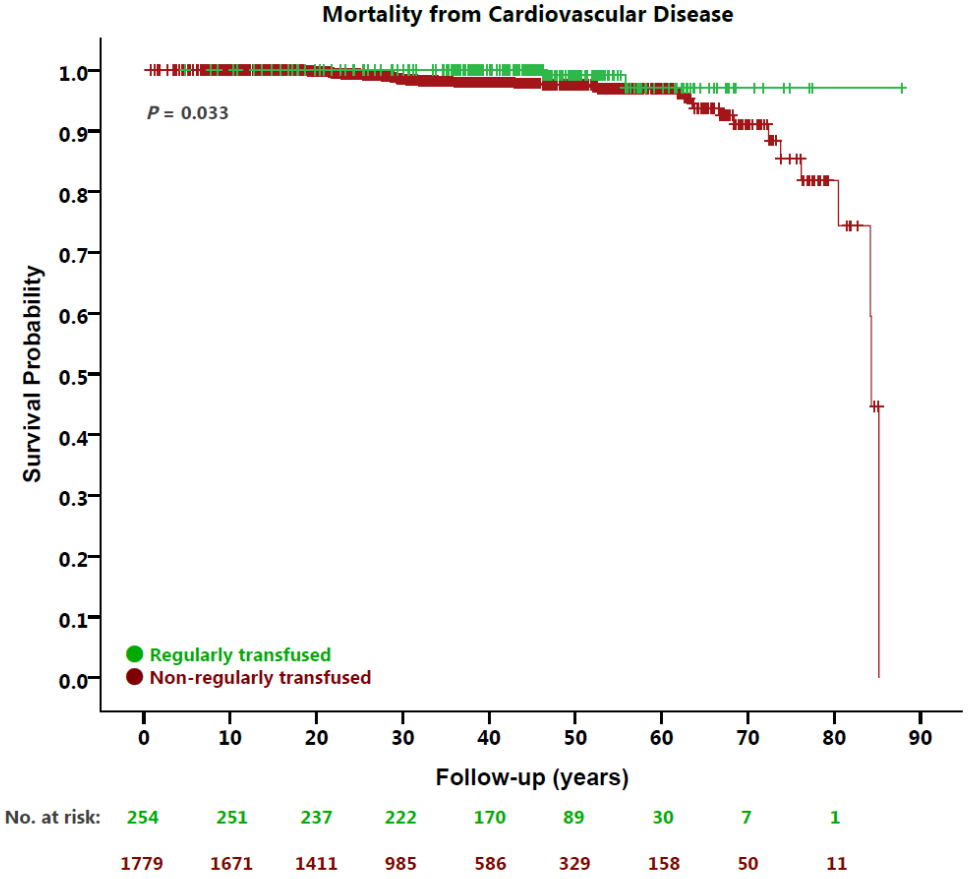
Cause	n	% among deaths (n = 113)	% among population (n = 2033)	Median age at death (min-max), years
Cardiovascular disease *(iron-related cardiomyopathy, n = 2; other cardiomyopathy, n = 14; myocardial infarction, n = 1; valvular disease, n = 1; pulmonary hypertension, thrombosis or peripheral vascular disease, n = 23)*	41	36.3	2.0	34.2 (19-85)
Hepatic disease *(fibrosis or cirrhosis, n = 10; HCC, n = 13)*	23	20.4	1.1	55.4 (26-76)
Cancer *(solid or hematologic malignancy excluding HCC)*	14	12.4	0.7	54.0 (12-85)
Infection	13	11.5	0.6	44.1 (12-68)
Unclassified thalassemia-related complications	17	15.0	0.8	19.8 (7-64)
Non-thalassemia related causes	5	4.4	0.2	62.0 (27-73)

HCC, hepatocellular carcinoma.

Musallam KM *et al. Haematologica* 2021;106:2489-2492.

Regular transfusion was associated with reduced all-cause and cardiovascular disease related mortality





Regular transfusion starting at a median age of 10 years (IQR: 4-28.3)

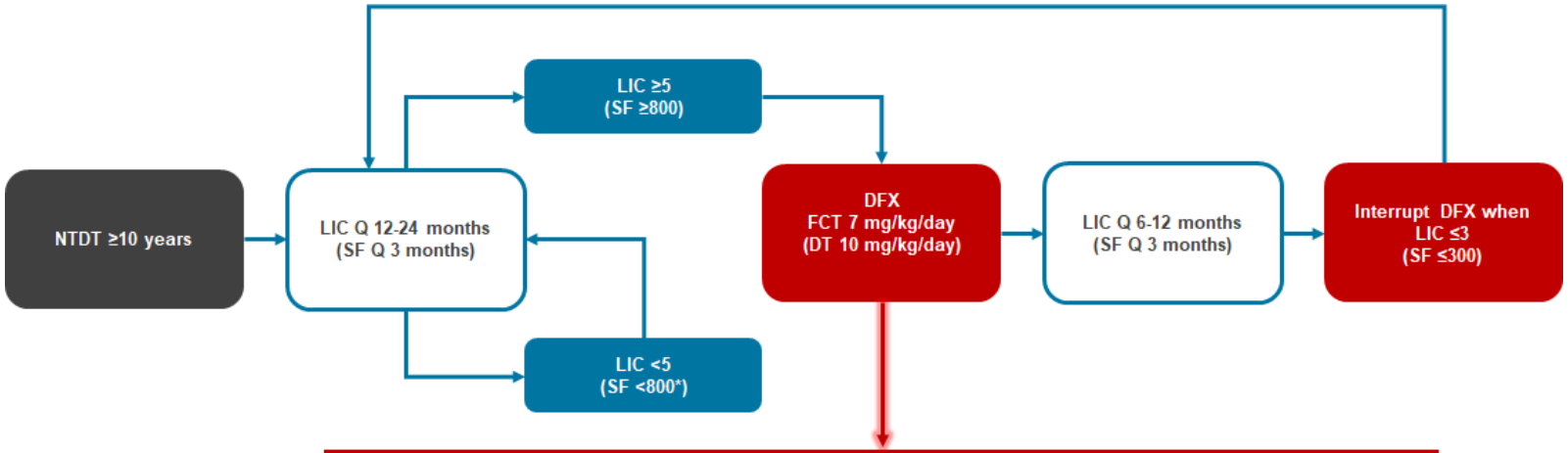
Musallam KM *et al. Haematologica* 2021;106:2489-2492.

Historic experience with HbF inducers in β-thalassemia were not encouraging

Agent	Main positive findings	Limitations
DNA methylation inhibitiors		
5-azacytidine	• Marked hematological responses achieved	• Few studies • Small sample sizes • Safety concerns
Decitabine	• Hematological responses achieved • Favorable effects on red cell indices • Well-tolerated	• Few studies • Small sample sizes
Hydroxyurea	• Hematological responses achieved • Favorable effects on red cell, hemolysis, and hypercoagulability indices • Favorable effects on clinical morbidities • Well-tolerated	• Heterogonous phenotypes studied together • Heterogeneous study endpoints evaluated together • Ideal dose and duration of therapy still controversial • Lack of efficacy on long-term therapy • Data on predictors of response remain inconsistent
Short-chain fatty acids	• Hematological responses achieved • Favorable effects on red cell and hemolysis indices • Well-tolerated	• Small sample sizes • Lack of efficacy on long-term therapy
Erythropoietic stimulating agents	• Hematological responses achieved • Favorable effects on combination with hydroxyurea • Well-tolerated	• Few studies • Small sample sizes • High doses required • No additive effects with short-chain fatty acids
Thalidomide and derivatives	• Hematological responses achieved • Well-tolerated	• Few studies • Small sample sizes

Musallam KM *et al. Blood* 2013;121:2199-2212.

Guidelines for iron overload assessment and chelation therapy in NTDT



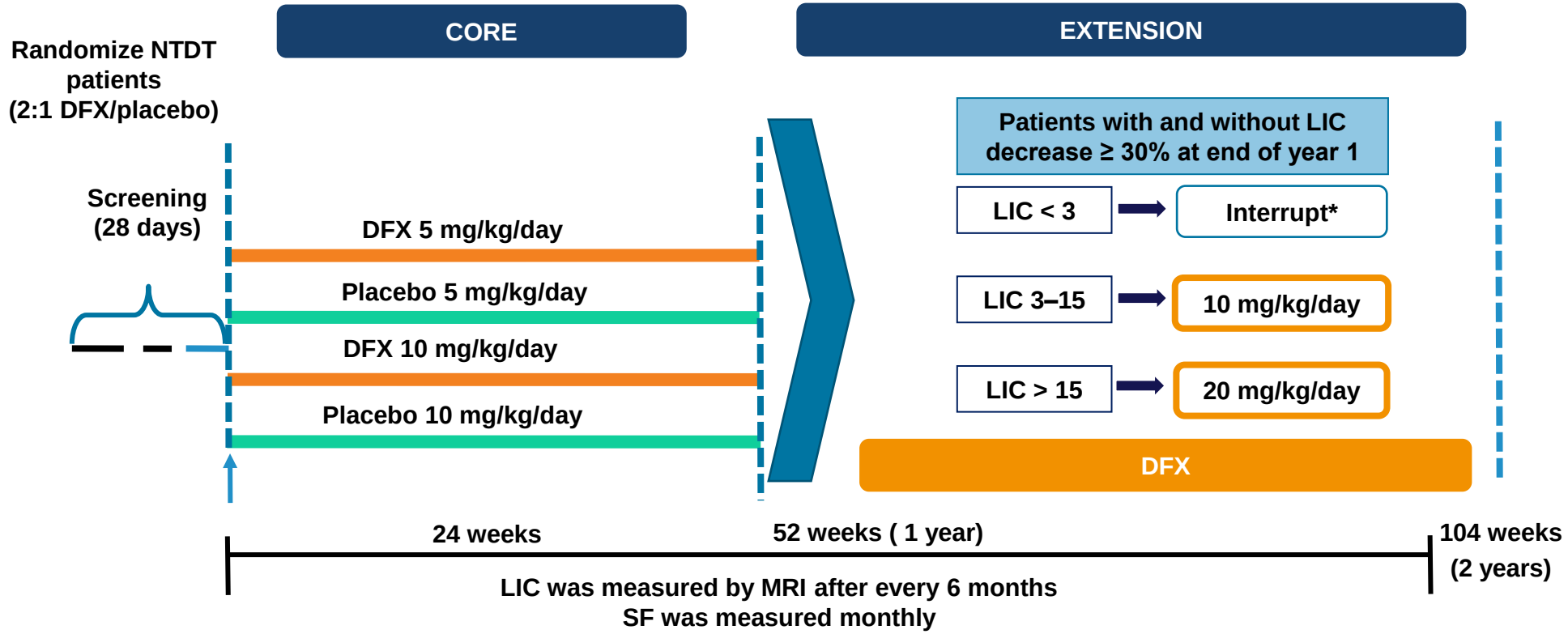
DFX dose escalation after 1 month			
Baseline LIC	≥5 to ≤7	>7 to ≤15	>15
Baseline SF	≥800 to ≤1500	>1500 to ≤3000	>3000
Dose modification	None	Escalate to FCT 11.5 or DT 15 mg/kg/day	Escalate to FCT 14 or DT 20 mg/kg/day
DFX dose escalation after 6 months			
6 months LIC	≥3 to ≤7	>7 to ≤15	>15
6 months SF	≥300 to ≤1500	>1500 to ≤3000	>3000
Dose modification	Same dose (max FCT 7 or DT 10 mg/kg/day)	Escalate by FCT 3.5 or DT 5 mg/kg/day (max FCT 14 or DT 20 mg/kg/day)	Escalate by FCT 3.5-7 or DR 5-10 mg/kg/day (max FCT 21.5 or DT 30 mg/kg/day)†

*If serum ferritin level >300 to <800 ng/ml and liver iron concentration measurement is not possible, initiate chelation if other clinical or laboratory measures are indicative of iron overload. †Deferasirox is not currently approved at doses higher than 20 mg/kg/day in patients with NTDT; the recommendation is based on clinical expert opinion guided by data from the THETIS trial.

Taher AT, Musallam KM, Cappellini MD. TIF NTDT Guidelines 2023.

THALASSA study: the first double-blind clinical trial of iron chelation with DFX in NTDT

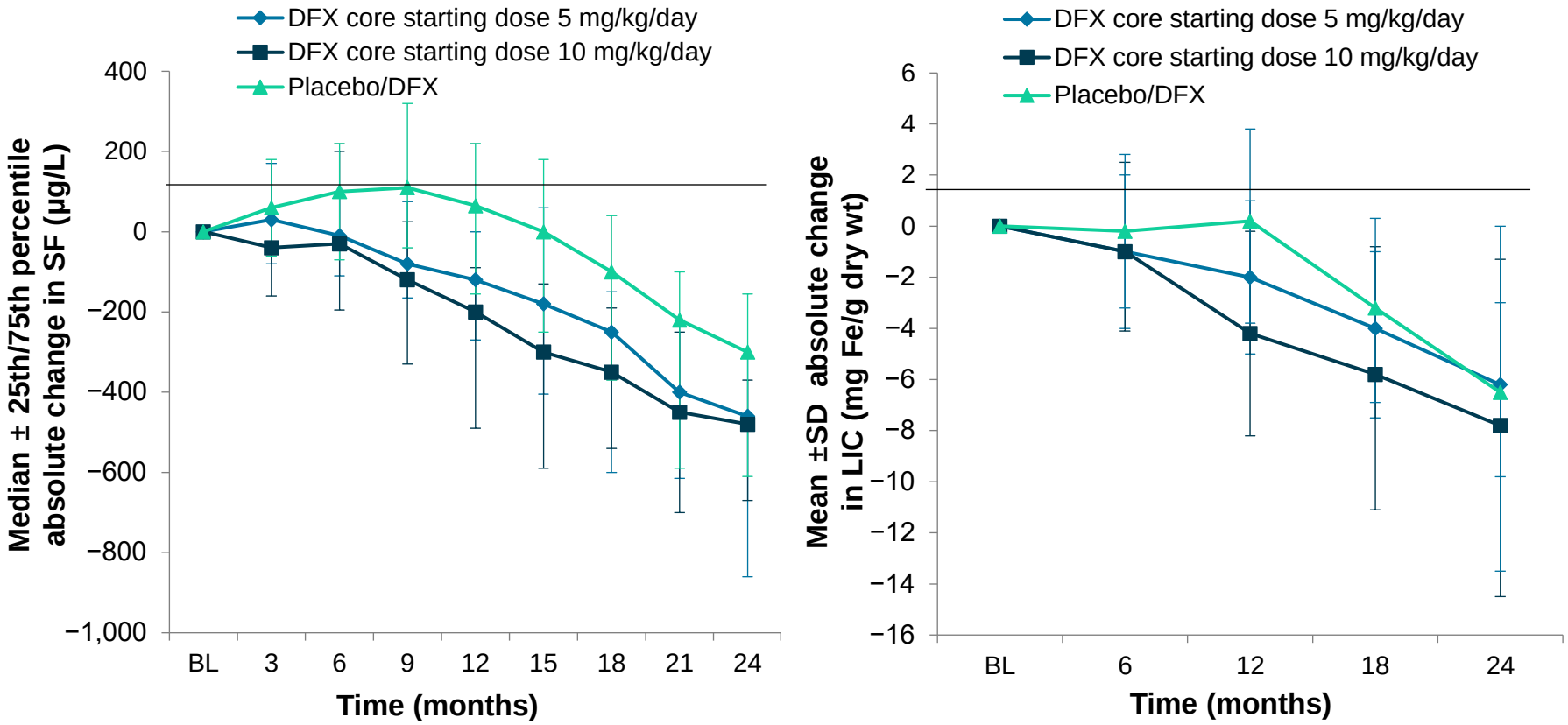
- The efficacy of two DFX regimens (5 and 10 mg/kg/day) was evaluated in NTDT patients
- Changes in LIC from baseline where compared between DFX groups and placebo group



The THALASSA study demonstrated a significant reduction in LIC in both deferasirox arms with a greater reduction in the 10 mg/kg/day group

Taher AT *et al. Blood* 2012;120:970-977; Taher AT *et al. Am J Hematol* 2013;88:409-415.

Deferasirox reduced iron burden over 2 years

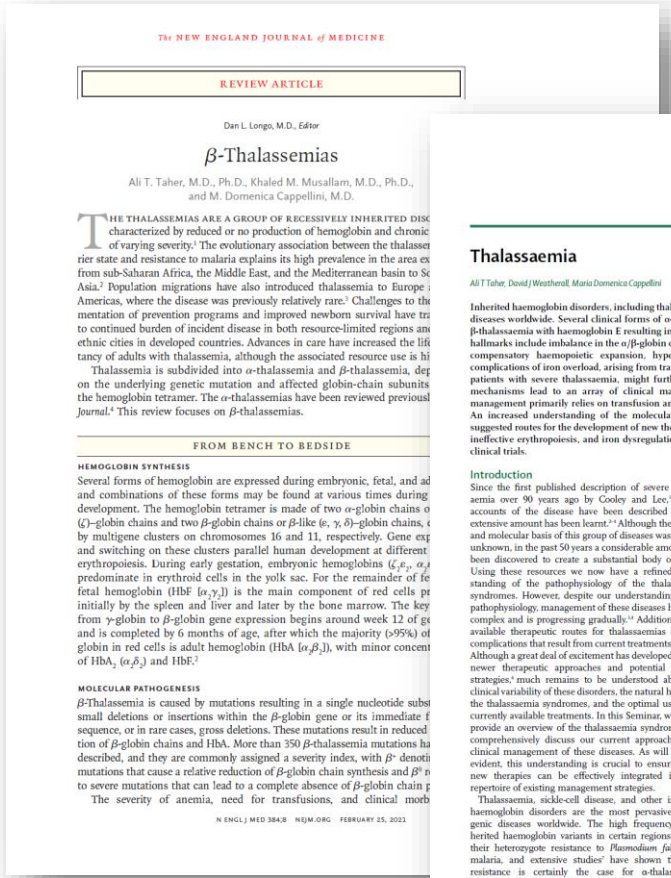


DFX core + extension: median dose = 9.5 mg/kg/day
DFX extension: median dose = 10.8 mg/kg/day
Placebo/DFX: median dose = 14.0 mg/kg/day

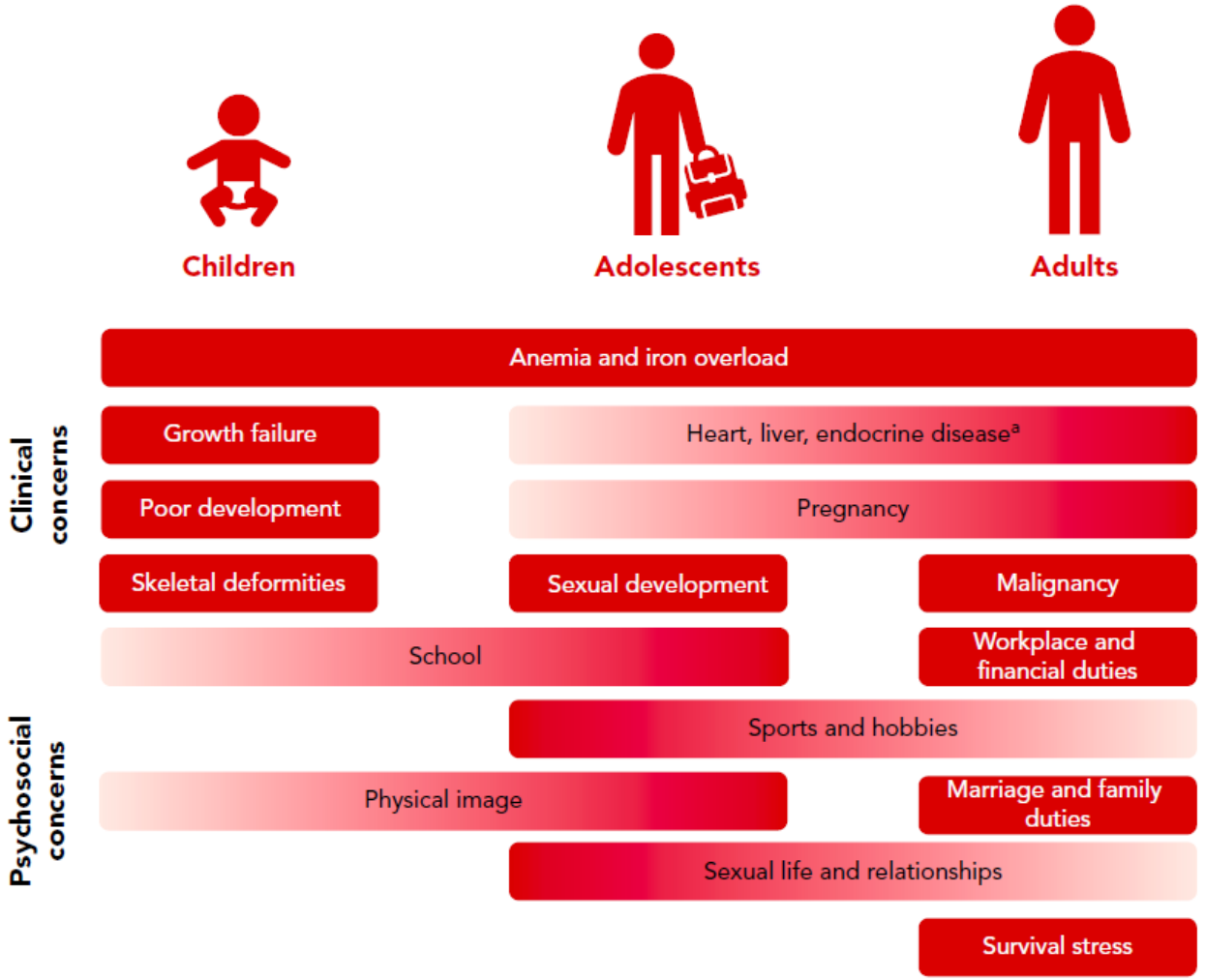
Taher AT *et al. Blood* 2012;120:970-977; Taher AT *et al. Am J Hematol* 2013;88:409-415.

Holistic Care

Management of β-thalassemia extends beyond transfusion and ICT: monitoring and management of complications



β-Thalassemia is becoming a disease of adulthood



Taher AT, Cappellini MD. *Blood* 2018;132:1781–1791.

Management of β-thalassemia requires a multidisciplinary approach and team

Psychiatrist, psychologist, social worker:
- Provide emotional support
- Facilitate personal development
- Ease pediatric to adult care transition

Nurse specialist:
- Interdisciplinary patient care
- Nursing leadership

Transplant specialist:
- Performs bone marrow transplantation from HLA-identical siblings, including post-transplant clinical follow-up

Hepatologist:
- Manages complications associated with elevated hepatic iron stores and HCV/HBV infection

Cardiologist:
- Monitors and manages cardiac complications

Thalassemia physician:
- Transfusion and chelation

Reproduction endocrinologist, gynecologist:
- Prepregnancy counseling
- Management of fertility and pregnancy

Diabetes specialist:
- Treats impaired glucose metabolism

Cappellini MD *et al*. TIF TDT Guidelines 2021; Taher AT, Musallam KM, Cappellini MD. TIF NTDT Guidelines 2023.

Novel Therapies

Novel therapies that have been recently or are being currently considered for β-thalassemia

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UPDATES IN CLINICAL TRIALS FOR HEMATOLOGICAL DISEASES

2021 update on clinical trials in β-thalassemia

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Abstract

The treatment landscape for patients with β-thalassemia is witnessing a swift evolution, yet several unmet needs continue to persist. Patients with transfusion-dependent β-thalassemia (TDT) primarily rely on regular transfusion and iron chelation therapy, which can be associated with considerable treatment burden and cost. Patients with non-transfusion-dependent β-thalassemia (NTDT) are also at risk of significant morbidity due to the underlying anemia and iron overload, but treatment options in this patient subgroup are limited. In this review, we provide updates on clinical trials of novel therapies targeting the underlying pathology in β-thalassemia, including the α/non-α-globin chain imbalance, ineffective erythropoiesis, and iron dysregulation.

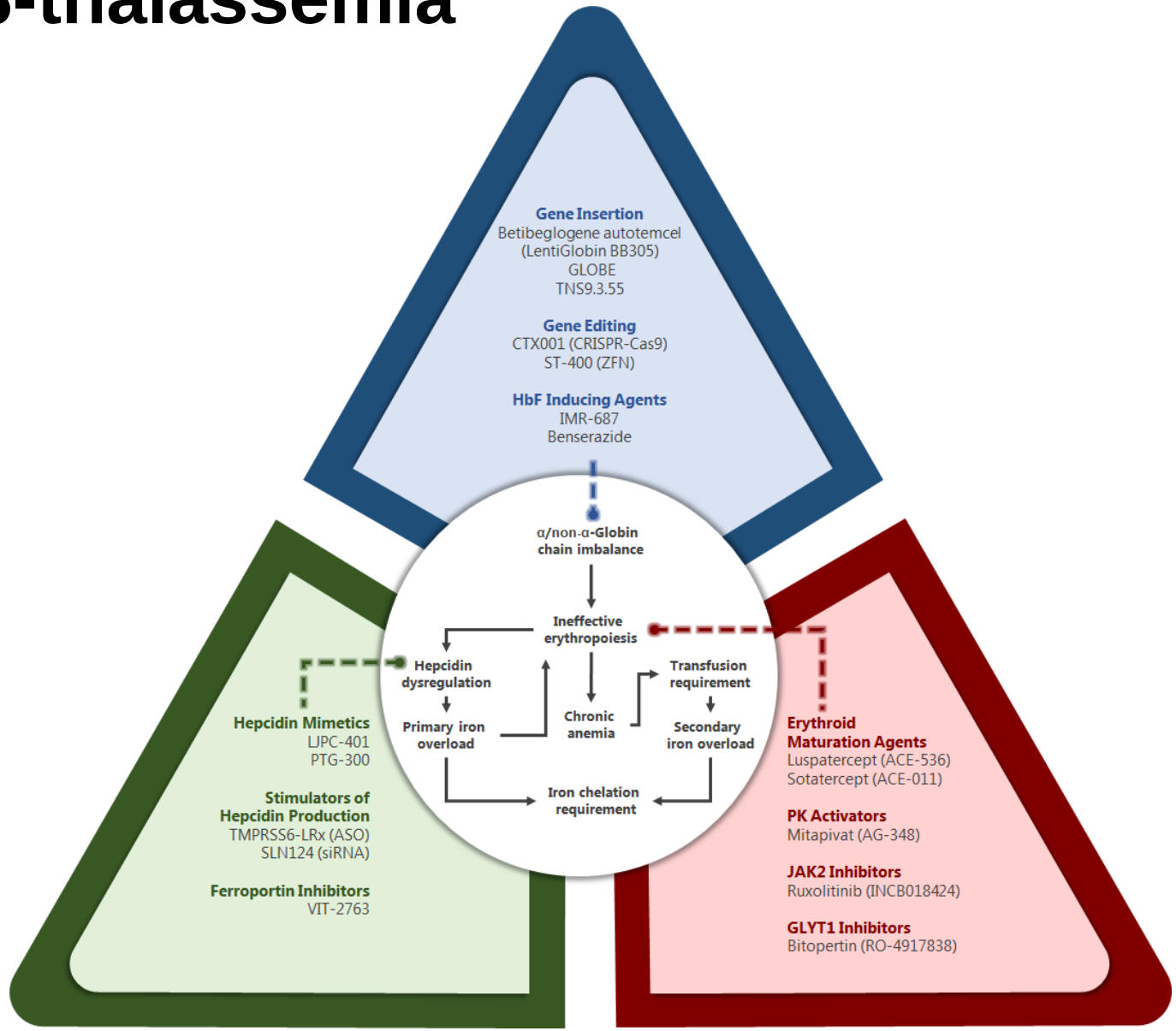
1 | INTRODUCTION

The β-thalassemias are a group of inherited disorders of hemoglobin (Hb) synthesis characterized by chronic anemia of varying severity. The degree of anemia relies on several genetic and environmental factors and determines the need for regular transfusion therapy. It is now common practice to classify patients as having transfusion-dependent β-thalassemia (TDT) or non-transfusion-dependent β-thalassemia (NTDT).[1]

The TDT patients (β-thalassemia major and severe forms of HbE/β-thalassemia) are those who commonly present in early childhood with severe anemia and require lifelong transfusion therapy for survival.[1] Although the introduction of transfusions improved survival in TDT patients, it did not come without its own side-effect, systemic iron overload leading to end-organ damage and increased mortality from cardiac or hepatic disease.[2–4] Advances in iron chelation therapy and the introduction of MRI techniques to detect organ-specific iron overload have led to improved management and patient outcomes.[5,6] Still, TDT comes with considerable burden to the patient, clinician, and overall healthcare system owing to persistent morbidity and high healthcare utilization, poor access to optimal care and high treatment cost especially in resource-limited countries, and several unmet needs in terms of efficacy, safety and adherence to conventional therapies.[7] Allogeneic hematopoietic stem-cell transplantation (HSCT) has been used successfully for the past few decades to offer curative therapy for patients with TDT, but is only available to a minority of patients with compatible donors.[1]

Patients with NTDT (β-thalassemia intermedia and mild–moderate forms of HbE/β-thalassemia) usually present later in childhood or even in adolescence with mild–moderate anemia that does not require immediate placement on a regular transfusion program.[1,8] Progress made over the past few decades has indicated that the diagnosis of NTDT carries greater morbidity than previously recognized. Ineffective erythropoiesis and anemia have been linked to an array of morbidities stemming from chronic hypoxia and an established hypercoagulable state.[1] Patients with Hb levels < 10 g/dl are at an increased risk of morbidity development, and variations of 1 g/dl can change a patient's morbidity risk.[9,10] There are currently no approved agents for the management of anemia in NTDT.[11] Transfusions are used in settings of expected drop in Hb such as pregnancy, infection or surgery; and some physicians also elect to use short courses of regular transfusions to promote growth in childhood or prevent/treat morbidity in adulthood in view of evidence of benefit from observational studies.[12–14] Even in the absence of transfusions, NTDT

Khaled M. Musallam and Rayan Bou-Fakhredin contributed equally as first authors.



Musallam KM *et al. Am J Hematol* 2021;96:1518-153.

Takeaways

- β-thalassemia is a disease of multiple risk factors and multiple morbidities, which logically implies the need for a multidisciplinary management team.
- This becomes particularly essential for older patients with comorbidities who require the attention of internists and specialists alongside their primary care.
- The ideal treatment strategy will always be an individualized one.
- The transition from child into adult care facilities becomes more essential for older patients.

Takeaways

- Unmet needs in the treatment of β-thalassaemia remain
- Currently, many novel pharmacological treatment options for β-thalassaemia are currently being tested in clinical trials
- The current standard of care (RBC transfusions and iron chelation therapy) is associated with complications
- There is a great unmet need for therapies that reduce patient reliance on RBC transfusions and iron chelation therapy