

12° International Conference on Thalassaemia and the Haemoglobinopathies

Complications and Management of Thalassaemia Intermedia

Maria Domenica Cappellini, MD
University of Milan, Milano, Italy



β -Thalassemia intermedia (TI)

- “Highly diverse” group of β -thalassemia syndromes where red blood cells are sufficiently short-lived to cause anemia but not necessarily the need for regular blood transfusions.
- Clinical phenotypes lie in severity between those of β -thalassemia minor and β -thalassemia major (TM).
- Arises from defective gene(s) leading to partial suppression of β -globin protein production.

Mild

Severe



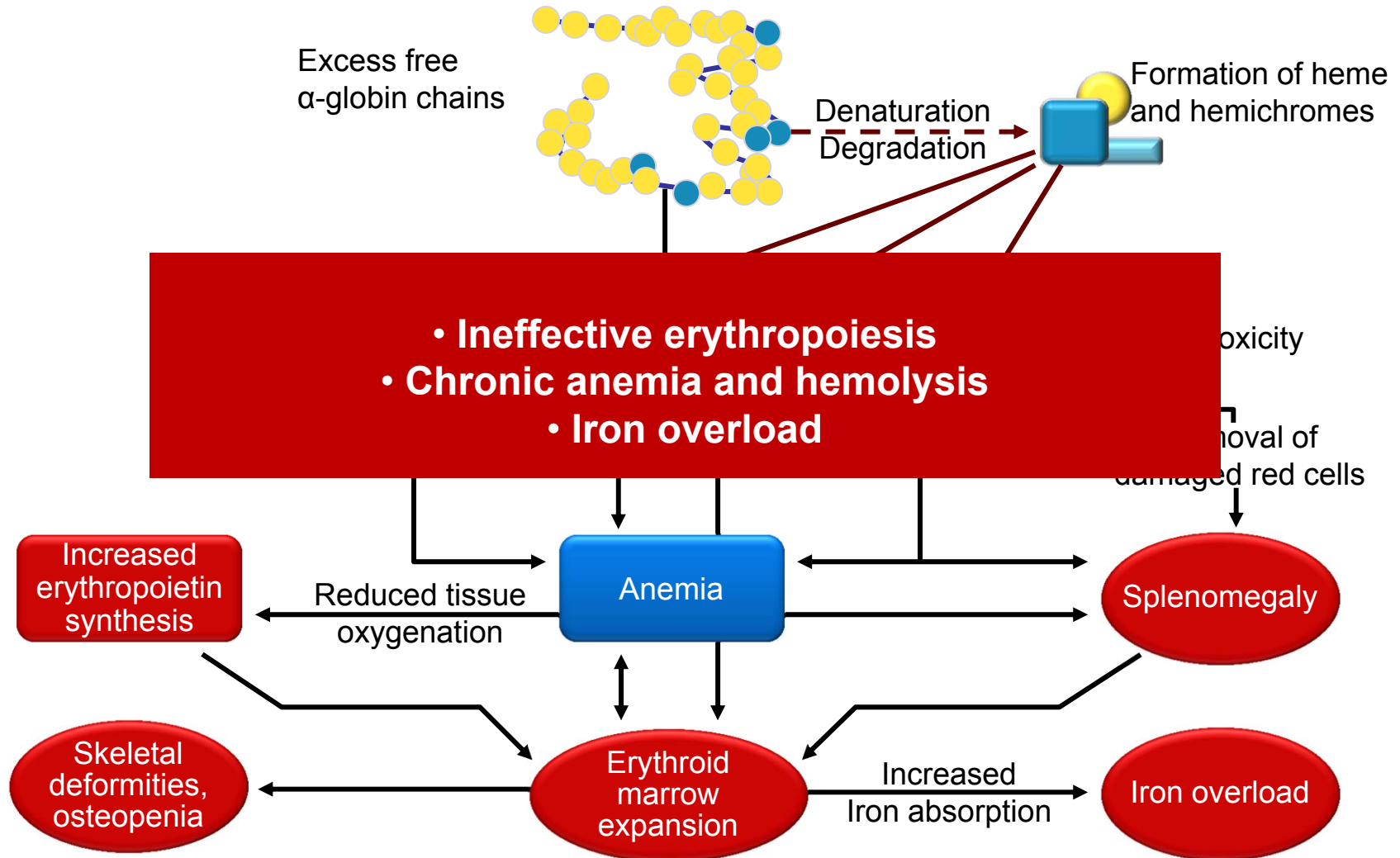
Completely asymptomatic
until adult life

Presentation at age 2–6 years
Retarded growth and development

Determinants of disease severity

- Molecular factors
 - inheritance of a mild or silent β -chain mutation
 - presence of a polymorphism for the enzyme Xmn-1 in the G α -promoter region, associated with increased HbF
 - co-inheritance of α -thalassaemia
 - increased production of α -globin chains by triplicated or quaduplicated α -genotype associated to β -heterozygosity; also from interaction of β - and $\delta\beta$ -thalassaemia
- Environmental factors may influence severity of symptoms, e.g.
 - social conditions
 - nutrition
 - availability of medical care

Pathophysiology summarized



Overview on Practices in Thalassemia Intermedia Management Aiming for Lowering Complication-rates Across a Region of Endemicity: the OPTIMAL CARE study

- Retrospective review of 584 TI patients from six comprehensive care centers in the Middle East and Italy



Overall study population

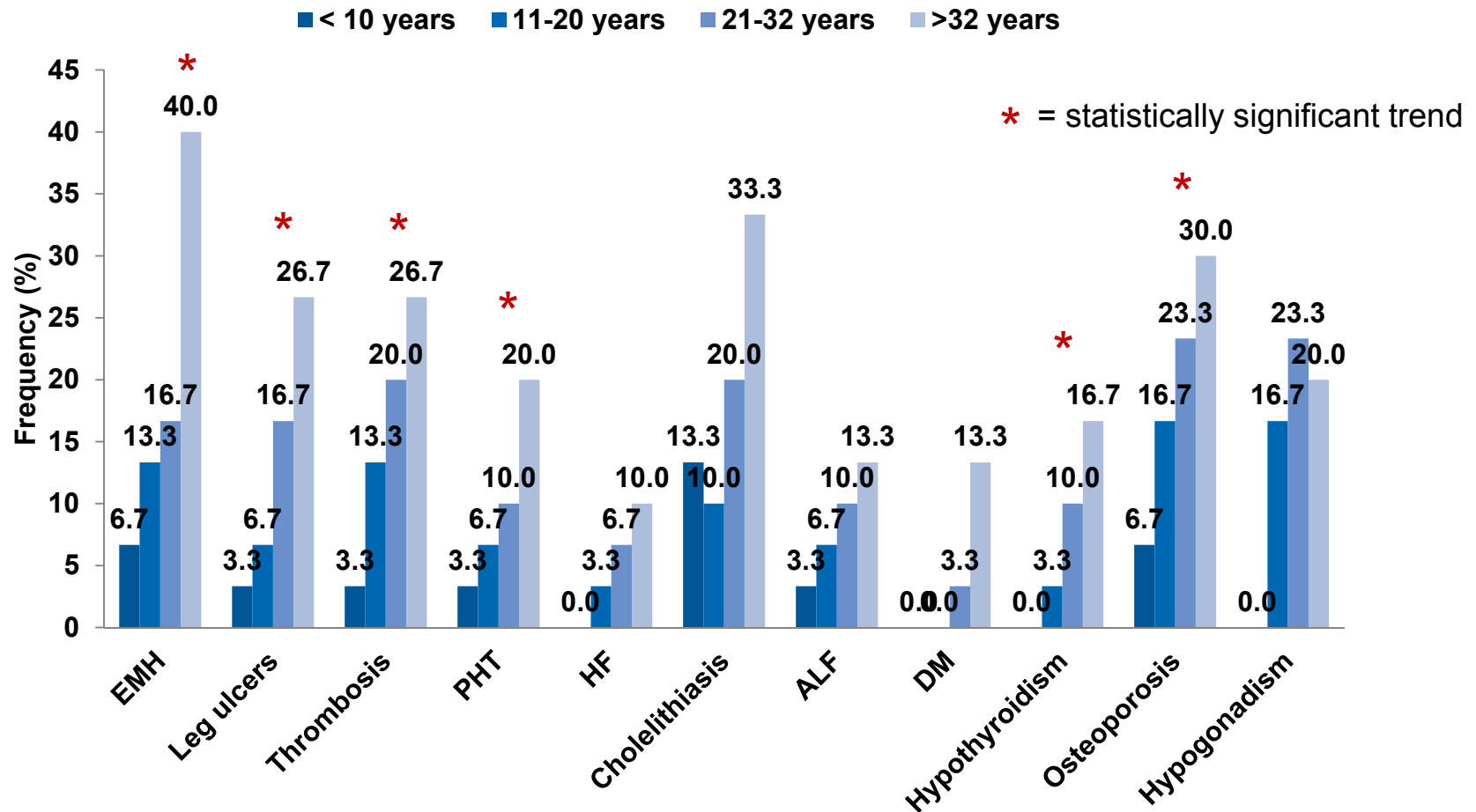
Parameter	Frequency <i>n</i> (%)
Age (yrs)	
<18	172 (29.5)
18-35	288 (49.3)
>35	124 (21.2)
Male : Female	291 (49.8) : 293 (50.2)
Splenectomized	325 (55.7)
Serum ferritin (ng/ml)	
<1000	376 (64.4)
1000-2500	179 (30.6)
>2500	29 (5)

Complications	Frequency <i>n</i> (%)
<i>Osteoporosis</i>	134 (22.9)
<i>EMH</i>	124 (21.2)
<i>Hypogonadism</i>	101 (17.3)
<i>Cholelithiasis</i>	100 (17.1)
<i>Thrombosis</i>	82 (14)
<i>Pulmonary hypertension</i>	64 (11)
<i>Abnormal liver function</i>	57 (9.8)
<i>Leg ulcers</i>	46 (7.9)
<i>Hypothyroidism</i>	33 (5.7)
<i>Heart failure</i>	25 (4.3)
<i>Diabetes mellitus</i>	10 (1.7)

EMH = extramedullary hematopoiesis

Complications vs. Age

- Complications in 120 treatment-naïve patients with TI





TREATMENT OPTIONS

Splenectomy

- Less common than in the past
 - before age 5 years it carries a high risk of infection and is therefore not generally recommended
- Main indications include
 - growth retardation or poor health
 - leukopenia
 - thrombocytopenia
 - increased transfusion demand
 - symptomatic splenomegaly
- Primarily done in regularly transfused TM patients

Splenectomy: adverse events

- Thromboembolic events
- Pulmonary hypertension
- Infection
 - 10-year follow-up of 221 splenectomized patients, 6 of whom died of sepsis
 - no need to “wait & see” in such patients with fever

In the **OPTIMAL CARE** study

splenectomized patients: 325/584

Complication	Parameter	RR	95% CI	p-value
EMH	Splenectomy	0.44	0.26-0.73	0.001
	Transfusion	0.06	0.03-0.09	<0.001
	Hydroxyurea	0.52	0.30-0.91	0.022
Pulmonary hypertension	Age > 35 yrs	2.59	1.08-6.19	0.032
	Splenectomy	4.11	1.99-8.47	<0.001
	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
Thrombosis	Age > 35 yrs	2.60	1.39-4.87	0.003
	Hb ≥ 9 g/dl	0.41	0.23-0.71	0.001
	Ferritin ≥ 1000 ng/ml	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
Cholelithiasis	Age > 35 yrs	2.76	1.56-4.87	<0.001
	Female	1.96	1.18-3.25	0.010
	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	Ferritin ≥ 1000 ng/ml	1.74	1.00-3.02	0.049

EMH = extramedullary hematopoiesis.

Taher AT, et al. Blood. 2010 ;115:1886-92.

In the **OPTIMAL CARE** study

splenectomized patients: 325/584

Complication	Parameter	RR	95% CI	p-value
Leg Ulcers	Age > 35 yrs	2.09	1.05-4.16	0.036
	Splenectomy	3.98	1.68-9.39	0.002

- Splenectomy was independently associated with an increased risk of most disease-related complications.

	Hydroxyurea	0.02	0.01-0.09	<0.001
	Iron chelation	0.40	0.24-0.68	0.001
Hypogonadism	Female	2.98	1.79-4.96	<0.001
	Ferritin ≥ 1000 ng/ml	2.63	1.59-4.36	<0.001
	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

Current evidence for the benefit of transfusions in TI

Failure to thrive in childhood in the presence of significant anemia

Increasing anemia not attributable to rectifiable factors

Delayed or poor pubertal growth spurt

Progressive splenic enlargement

Evidence of

bone deformities

clinically relevant tendency to thrombosis

leg ulcers

EMH

pulmonary hypertension

Prior to surgical procedures

In the **OPTIMAL CARE** study

Occasionally-regularly transfused patients: 445/584

Complication	Parameter	RR	95% CI	p-value
EMH	Splenectomy	0.44	0.26-0.73	0.001
	Transfusion	0.06	0.03-0.09	<0.001
	Hydroxyurea	0.52	0.30-0.91	0.022
Pulmonary hypertension	Age > 35 yrs	2.59	1.08-6.19	0.032
	Splenectomy	4.11	1.99-8.47	<0.001
	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
Thrombosis	Age > 35 yrs	2.60	1.39-4.87	0.003
	Hb ≥ 9 g/dl	0.41	0.23-0.71	0.001
	Ferritin ≥ 1000 ng/ml	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
Cholelithiasis	Age > 35 yrs	2.76	1.56-4.87	<0.001
	Female	1.96	1.18-3.25	0.010
	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	Ferritin ≥ 1000 ng/ml	1.74	1.00-3.02	0.049

In the **OPTIMAL CARE** study

Occasionally-regularly transfused patients: 445/584

Complication	Parameter	RR	95% CI	p-value
Leg Ulcers	Age > 35 yrs	2.09	1.05-4.16	0.036
	Splenectomy	3.98	1.68-9.39	0.002

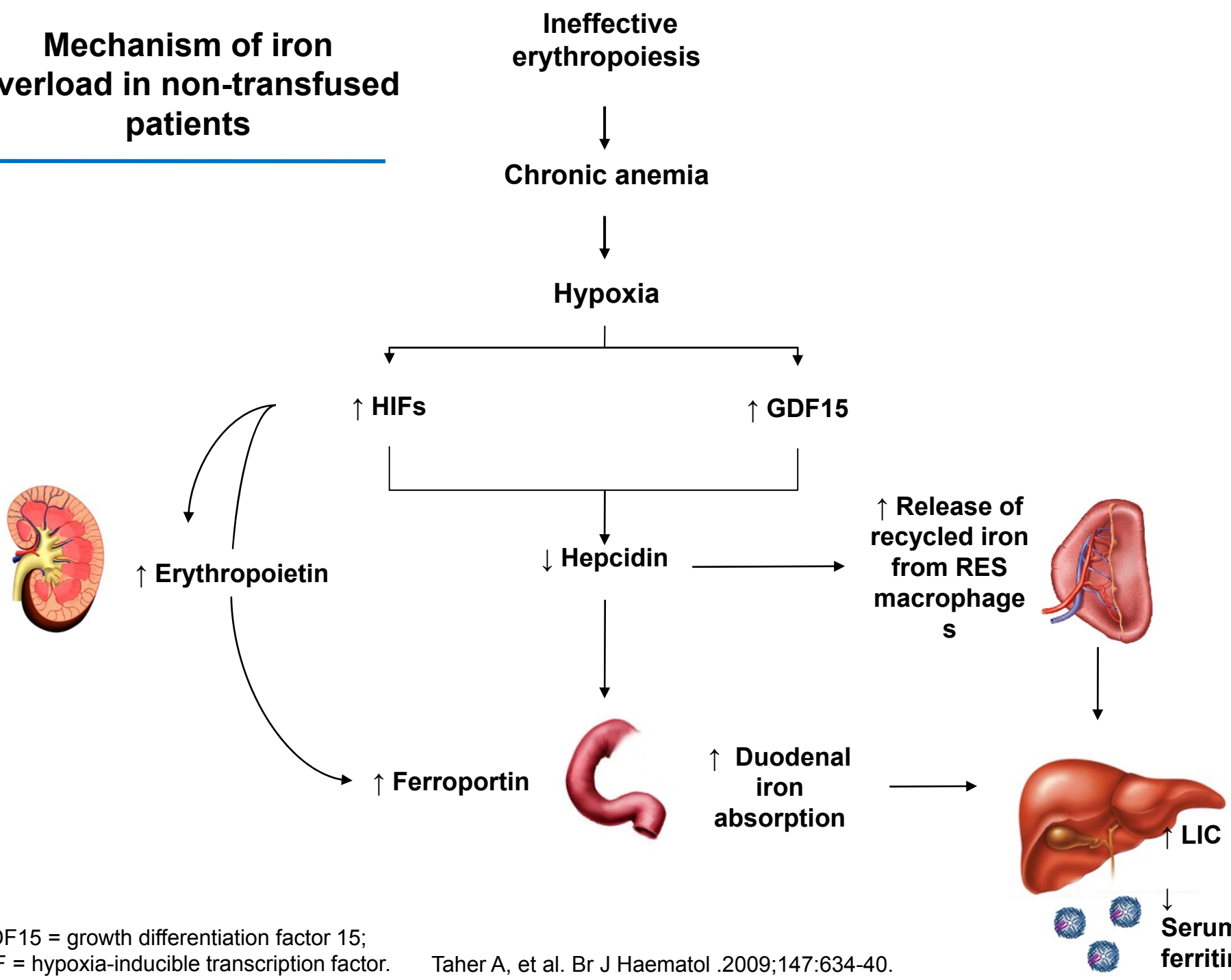
- Transfusion therapy was protective for thrombosis, EMH, PHT, HF, cholelithiasis, and leg ulcers.
- Transfusion therapy was associated with an increased risk of endocrinopathy.

Ferritin ≥ 1000 ng/ml	2.65	1.59-4.36	<0.001
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

Iron overload

- Iron overload occurs even in TI patients who have not been transfused
 - iron loading: 2–5 g Fe/year; iron toxicity develops from age 5 years
- Is much lower than in age-matched patients with transfusion-dependent TM
- Although the rate of iron loading differs between TM and TI, the consequences are apparent in both groups of patients and include
 - Liver
 - Heart (?long-term)
 - endocrine organs

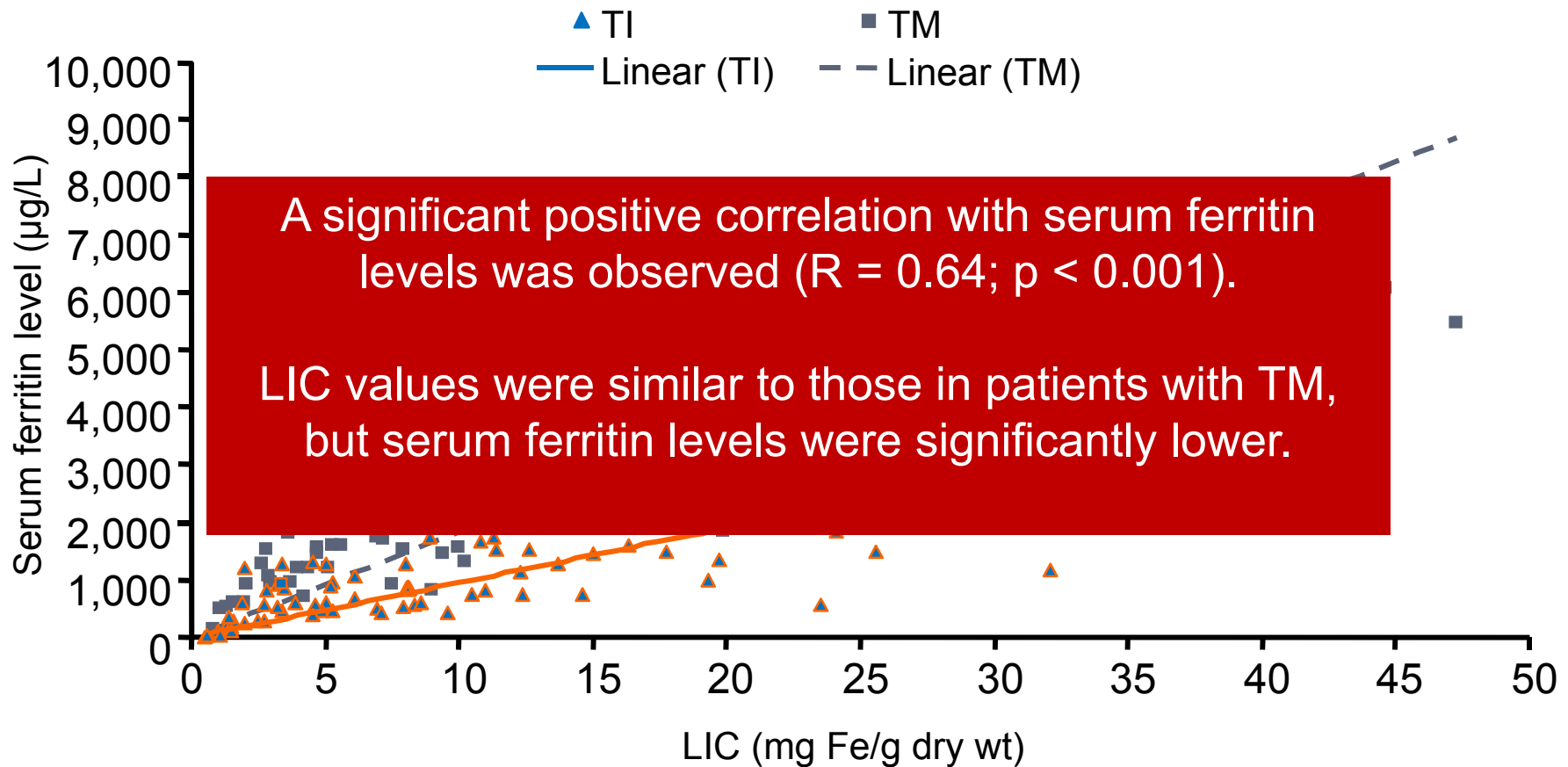
Mechanism of iron overload in non-transfused patients



GDF15 = growth differentiation factor 15;
 HIF = hypoxia-inducible transcription factor.

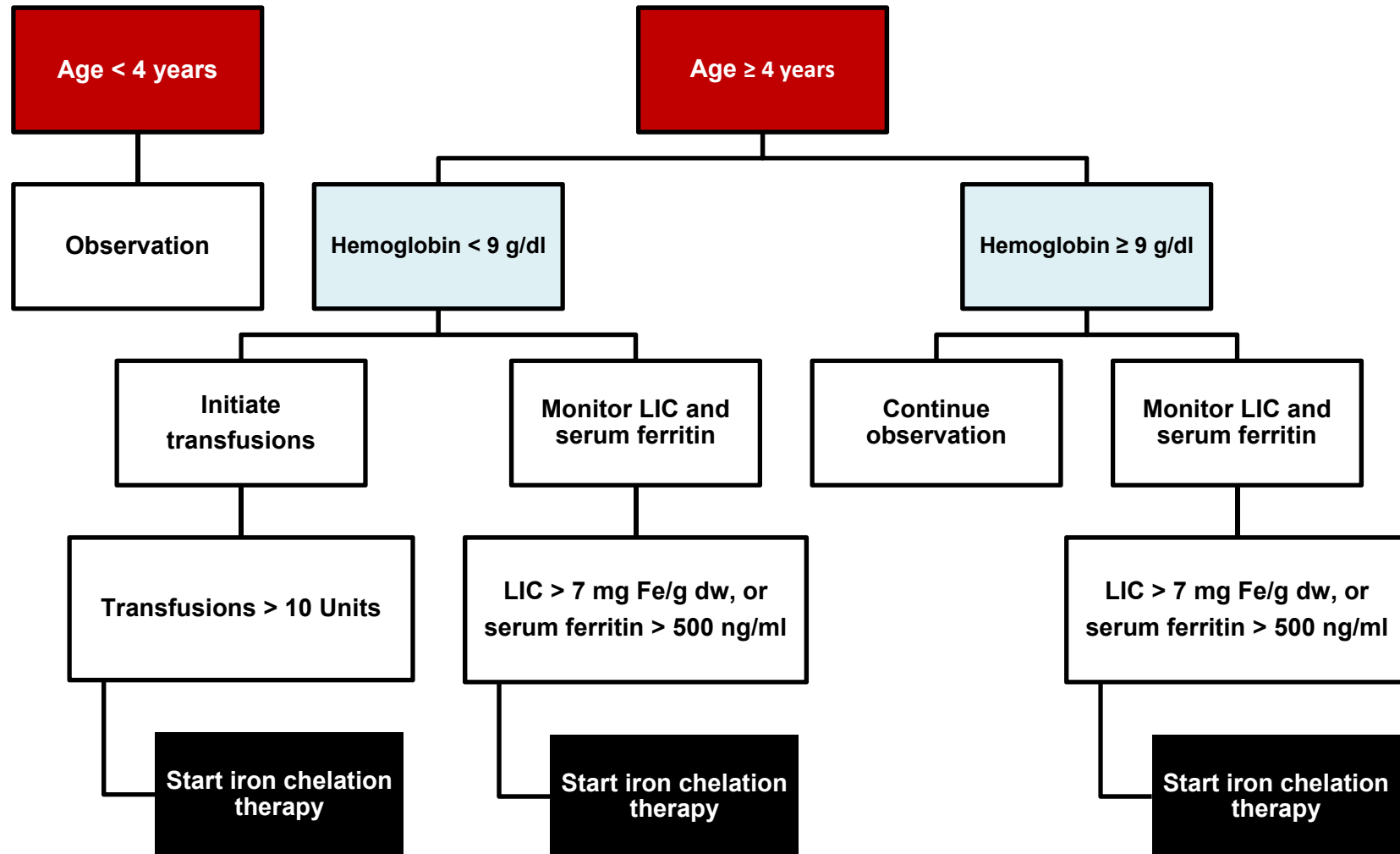
Taher A, et al. Br J Haematol .2009;147:634-40.

Serum ferritin underestimates iron burden in TI



LIC correlated with serum ferritin levels in patients with TI ($R = 0.64$; $p < 0.001$)

Recommendations for iron chelation therapy in TI



In the **OPTIMAL CARE** study

Chelated patients: 336/584

Complication	Parameter	RR	95% CI	p-value
EMH	Splenectomy	0.44	0.26-0.73	0.001
	Transfusion	0.06	0.03-0.09	<0.001
	Hydroxyurea	0.52	0.30-0.91	0.022
Pulmonary hypertension	Age > 35 yrs	2.59	1.08-6.19	0.032
	Splenectomy	4.11	1.99-8.47	<0.001
	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
Thrombosis	Age > 35 yrs	2.60	1.39-4.87	0.003
	Hb ≥ 9 g/dl	0.41	0.23-0.71	0.001
	Ferritin ≥ 1000 ng/ml	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
Cholelithiasis	Age > 35 yrs	2.76	1.56-4.87	<0.001
	Female	1.96	1.18-3.25	0.010
	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	Ferritin ≥ 1000 ng/ml	1.74	1.00-3.02	0.049

In the **OPTIMAL CARE** study

Chelated patients: 336/584

Complication	Parameter	RR	95% CI	p-value
Leg Ulcers	Age > 35 yrs	2.09	1.05-4.16	0.036
	Splenectomy	3.98	1.68-9.39	0.002
	Transfusion	0.39	0.20-0.76	0.006
	Hydroxvurea	0.10	0.02-0.43	0.002

- Iron chelation therapy was protective for hypogonadism, PHT, cholelithiasis, and osteoporosis.

Hypogonadism	Female	2.98	1.79-4.96	<0.001
	Ferritin ≥ 1000 ng/ml	2.63	1.59-4.36	<0.001
	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

Iron chelation therapy

- **Deferoxamine¹**

- significant decline in serum ferritin after 6 months of deferoxamine treatment
- significant UIE after 12 hours of continuous deferoxamine (except in patients aged < 1 year)
 - in some patients, substantial UIE despite modest serum ferritin levels
 - serum ferritin levels of no value in predicting UIE
 - no significant differences in excretion across doses

- **Deferiprone²**

- significant reductions seen in mean serum ferritin, hepatic iron, red-cell membrane iron, and serum NTBI levels
- serum ferritin \pm SD: initial 2,168 \pm 1,142 μ g/L; final 418 \pm 247 μ g/L
- significant mean increase in serum erythropoietin also observed
- increase in Hb values in 3 patients; reduction in transfusion requirements in 4 patients

Reduction in iron burden with deferasirox at year 1 in patients with TI

Mean values	Baseline	12 months	P-value
Serum ferritin, µg/L	2030 ± 1340	1165 ± 684	.02
Liver T2, ms	20.1 ± 4.1	23.7 ± 6.2	.01
Liver T2*, ms	3.4 ± 3.0	4.4 ± 3.0	.02
Cardiac T2*, ms	38.9 ± 5.9	39.8 ± 4.5	.64
LVEF, %	66.3 ± 8.1	66.9 ± 7.9	.76
Aspartate aminotransferase, U/L	64.8 ± 29.6	42.5 ± 18.1	.04
Alanine aminotransferase, U/L	63.5 ± 29.5	36.5 ± 17.6	.02
Serum creatinine, mg/dL	0.67 ± 0.15	0.75 ± 0.19	.07
Cystatin C, mg/L	0.98 ± 0.23	1.13 ± 0.27	.094

Mean cardiac T2* and LVEF (both normal at baseline), serum creatinine, and cystatin C did not significantly change after 12 months of treatment with deferasirox

Deferasirox can effectively reduce iron burden in patients with TI

Deferasirox for nontransfusional iron overload in patients with TI

11 patients with thalassemia intermedia

6 male, 5 female

Mean age 31.7 years

10 splenectomized

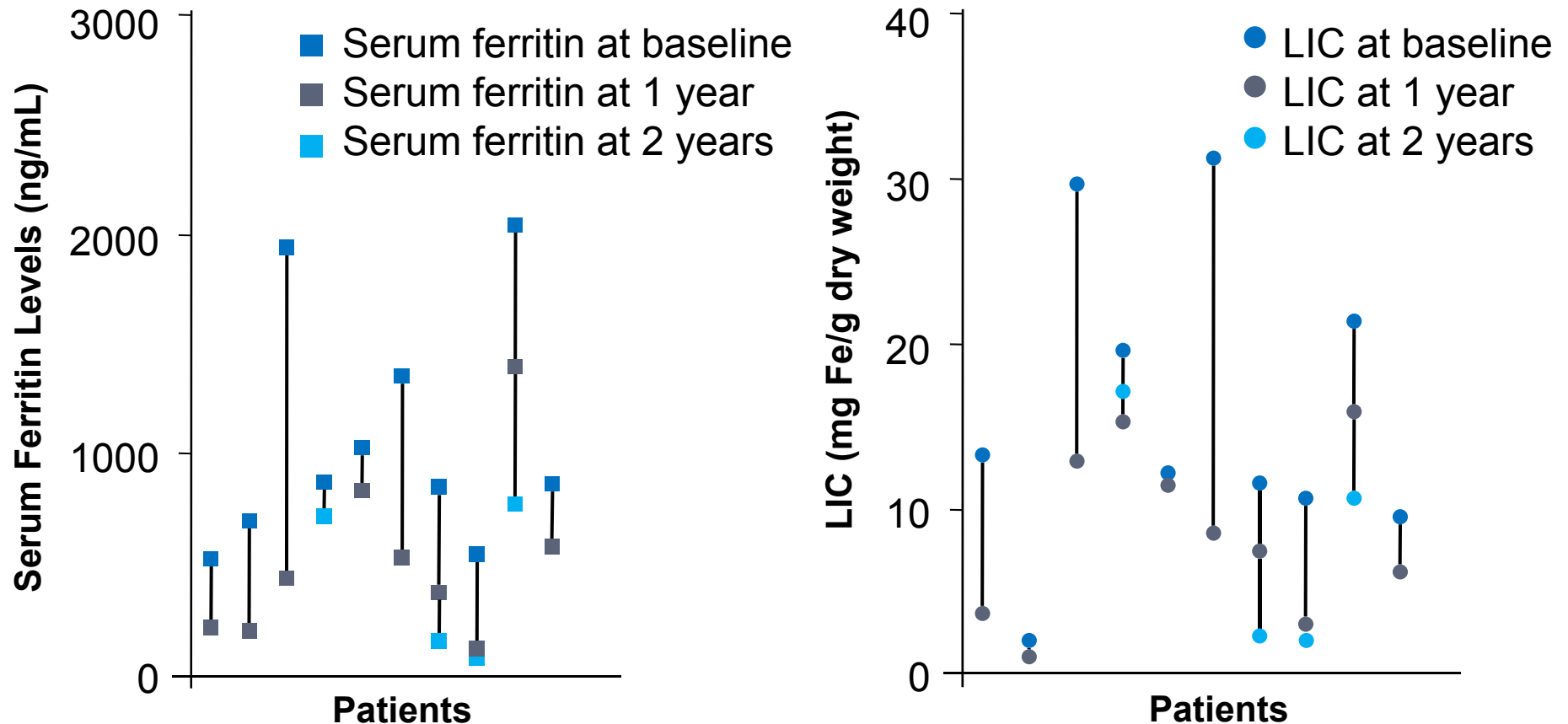
Deferasirox regimen

1 year (n = 11), 2 years (n = 4)

10 mg/kg/day (n = 7), 20 mg/kg/day (n = 4)

Dose adjustment after first year

Effect of deferasirox on serum ferritin and LIC in patients with TI and nontransfusional iron overload



1 patient, who was noncompliant, did not show decrease of iron overload and was excluded from graph

Changes in LIC and ferritin levels were related to deferasirox dose, but even patients with severe iron load, treated with 10 mg/kg/day, responded well

Safety of deferasirox during treatment of up to 2 years

Treatment was well tolerated

No serious adverse events were noted

Creatinine and cystatin C levels did not change during treatment

Transaminase levels significantly decreased in year 1 ($P = .0002$) and year 2 ($P = .024$) of treatment

This improvement probably due to decreased hepatic siderosis

Ongoing clinical evaluation of deferasirox in TI

Prospective, randomized, double-blind, placebo-controlled trial

Patients (age ≥ 10 years) with non–transfusion-dependent β -thalassemia (no transfusion required within 6 months prior to the study)

2 doses: 5 mg/kg/day and 10 mg/kg/day

Screening 4 weeks; treatment period 52 weeks

Primary objective

To assess the efficacy of deferasirox in patients with non–transfusion-dependent β -thalassemia, based on the change in LIC from baseline after 1 year of treatment compared with placebo-treated patients

Hydroxycarbamide

Experience from Iran and India

most patients were reported to have become **transfusion-independent**

in patients who were not transfused, the **Hb** concentration **increased**

the combination of hydroxycarbamide with **L-carnitine** or **magnesium** could be **more effective** in improving hematologic parameters and cardiac status in patients with TI than hydroxyurea alone

Experience from Europe

constant increase of the **erythrocyte volume** and in **HbF**, but only a modest effect on total Hb concentration

Karimi M, et al. J Pediatr Hematol Oncol. 2005;27:380-5.

Dixit A, et al. Ann Hematol. 2005;84:441-6.

Karimi M, et al. Eur J Haematol. 2010;84:52-8.

In the **OPTIMAL CARE** study

Patients on hydroxyurea: 202/584

Complication	Parameter	RR	95% CI	p-value
EMH	Splenectomy	0.44	0.26-0.73	0.001
	Transfusion	0.06	0.03-0.09	<0.001
	Hydroxyurea	0.52	0.30-0.91	0.022
Pulmonary hypertension	Age > 35 yrs	2.59	1.08-6.19	0.032
	Splenectomy	4.11	1.99-8.47	<0.001
	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
Thrombosis	Age > 35 yrs	2.60	1.39-4.87	0.003
	Hb ≥ 9 g/dl	0.41	0.23-0.71	0.001
	Ferritin ≥ 1000 ng/ml	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
Cholelithiasis	Age > 35 yrs	2.76	1.56-4.87	<0.001
	Female	1.96	1.18-3.25	0.010
	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	Ferritin ≥ 1000 ng/ml	1.74	1.00-3.02	0.049

EMH = extramedullary hematopoiesis.

Taher AT, et al. Blood. 2010 ;115:1886-92.

In the **OPTIMAL CARE** study

Patients on hydroxyurea: 202/584

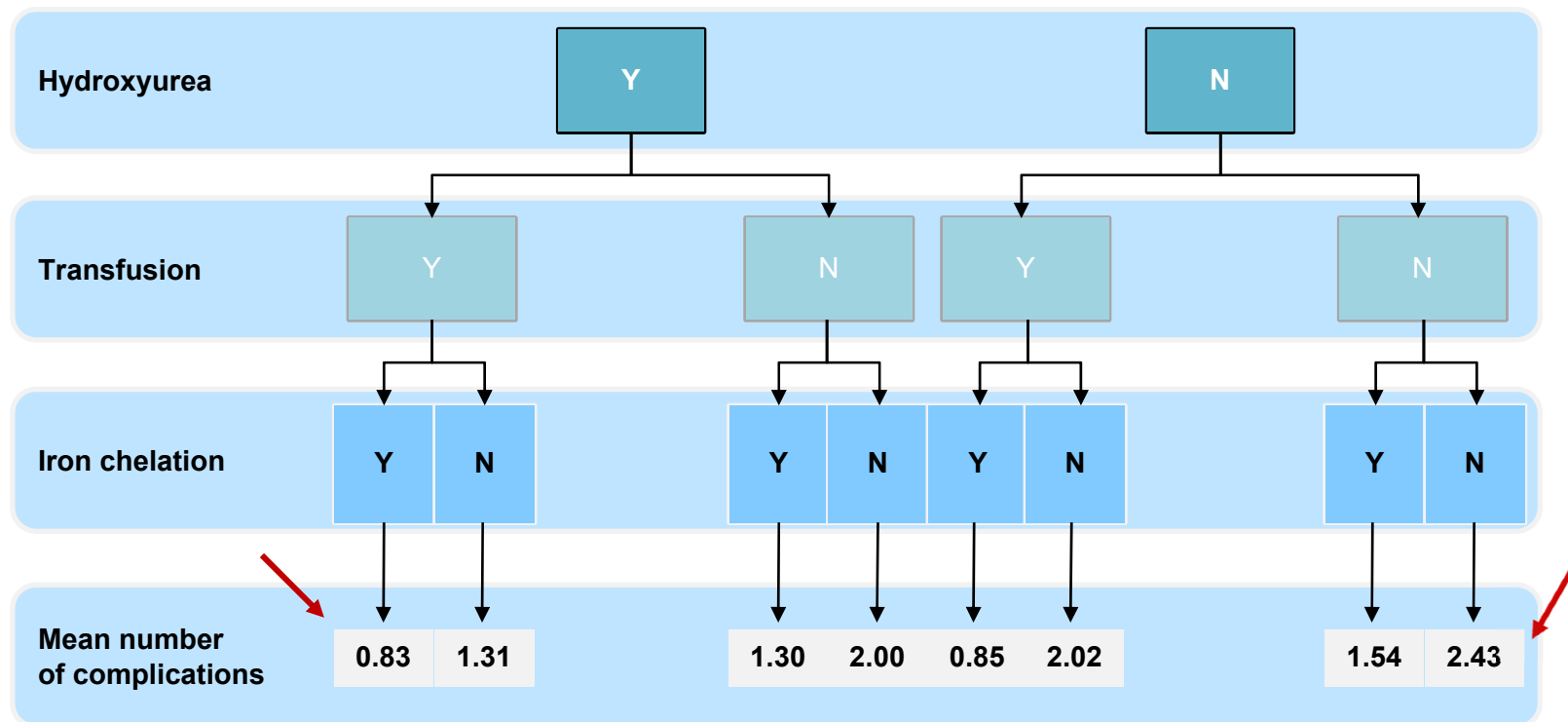
Complication	Parameter	RR	95% CI	p-value
Leg Ulcers	Age > 35 yrs	2.09	1.05-4.16	0.036
	Splenectomy	3.98	1.68-9.39	0.002
	Transfusion	0.39	0.20-0.76	0.006
	Hydroxyurea	0.10	0.02-0.43	0.002

- Hydroxyurea treatment was protective for EMH, PHT, leg ulcers, hypothyroidism, and osteoporosis.

	Transfusion	3.10	1.04-9.83	<0.001
	Hydroxyurea	0.02	0.01-0.09	<0.001
	Iron chelation	0.40	0.24-0.68	0.001
Hypogonadism	Female	2.98	1.79-4.96	<0.001
	Ferritin ≥ 1000 ng/ml	2.63	1.59-4.36	<0.001
	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

OPTIMAL CARE

Multimodality therapy



Take-home message

- Our understanding of the molecular basis and pathophysiology of TI significantly increased
- Iron overload and hypercoagulability are recently receiving increasing attention in TI
- Despite various treatment options are available, no clear guidelines exist
- Several studies are challenging the role of splenectomy yet highlighting the benefit of transfusion, iron chelation therapy, and fetal hemoglobin induction in the management of TI; thus these approaches merit large prospective evaluation
- The role of antiplatelets/anticoagulants in TI merits investigation