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# Iron Overload Disorders and Iron Chelation Therapy

T. Lodewyck

BHS seminar – November 2014

# Outline

- Iron overload (IO) disorders
- Mechanisms and pathophysiology of IO
- Clinical impact of IO
- Assessment of IO
- Treatment of IO, Iron Chelation Therapy (ICT)

# Classification of iron overload disorders

- Primary iron overload
  - Hereditary hemochromatosis
  - Genetic aberrations
  - Increased intestinal iron uptake

- Secondary iron overload
  - Thalassemia
  - Sickle cell disease
  - Myelodysplastic syndrome
  - Rare congenital anemias, eg. DBA

# Types of Hereditary Hemochromatosis

| Type | Mutation |
|---|---|
| 1 | HFE gene (C282Y mutation) |
| 2A | Hemojuvelin |
| 2B | Hepcidin |
| 3 | Transferrin receptor 2 |
| 4 | Ferroportin |

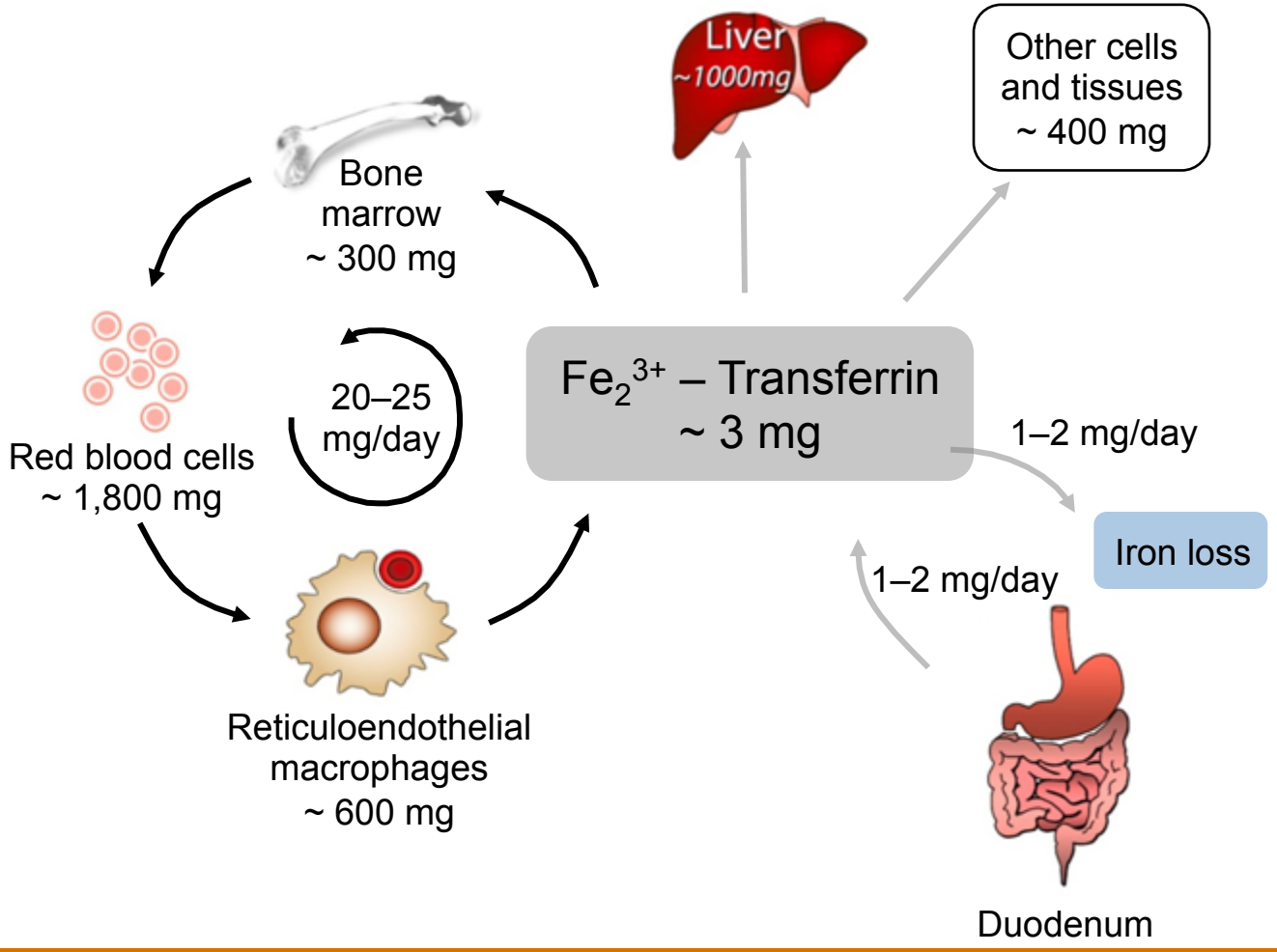
# Treatment Hereditary Hemochromatosis

- Phlebotomy
  - Initially: weekly or twice weekly
  - Maintenance: as needed, on average every 3 months
  - Target serum ferritin <50 microg/L and transferrin saturation <50%
- Iron chelation therapy
  - Intolerance of phlebotomy

# Chronic transfusion therapy is the main cause of secondary iron overload (IO)

- 1 unit contains 200 - 250 mg iron
- IO occurs after 10–20 transfusions

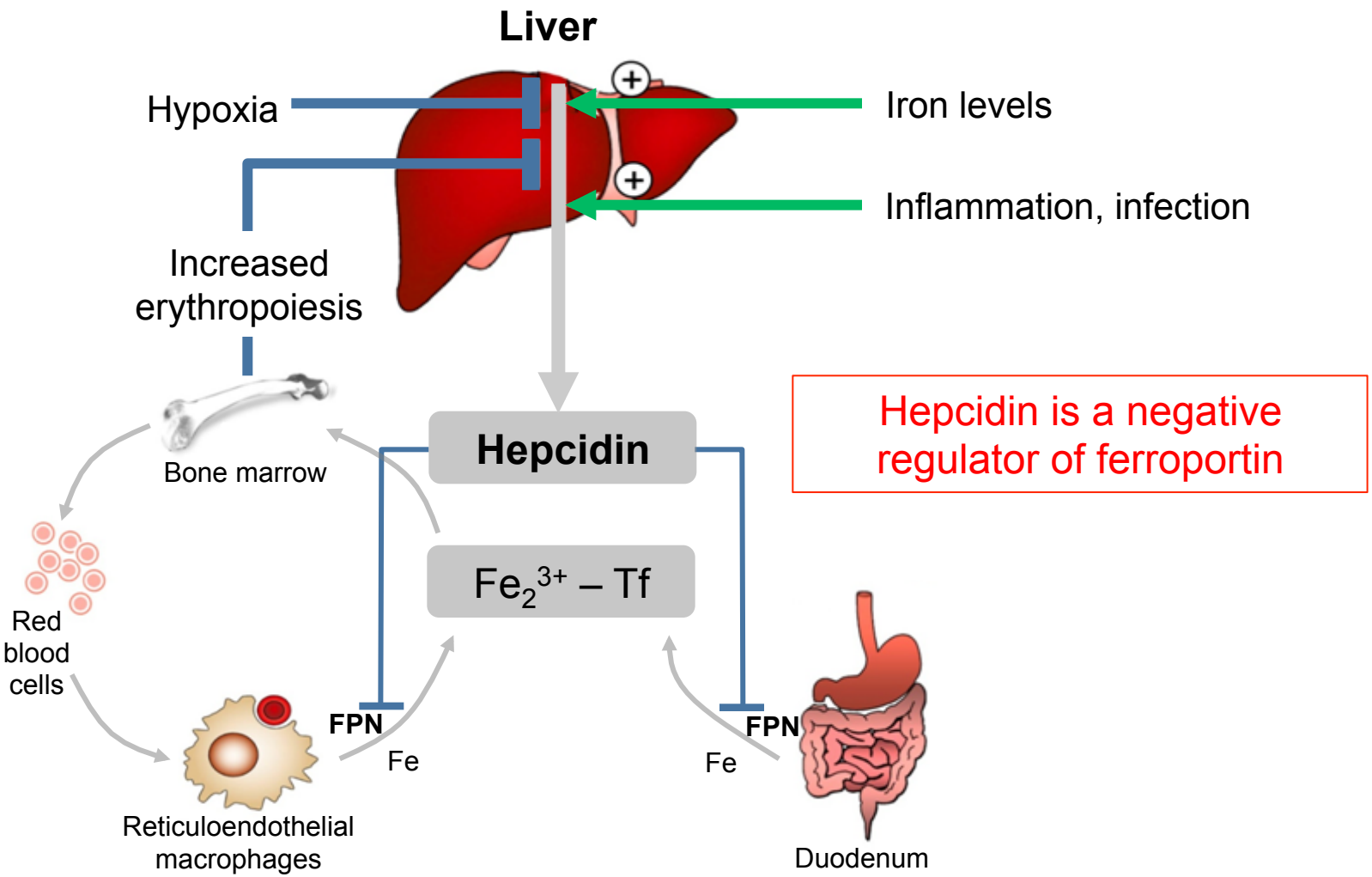
# Body iron homeostasis: (almost) perfect recycling system




**The human body has mechanisms to absorb, transfer, store iron, but none to excrete it**

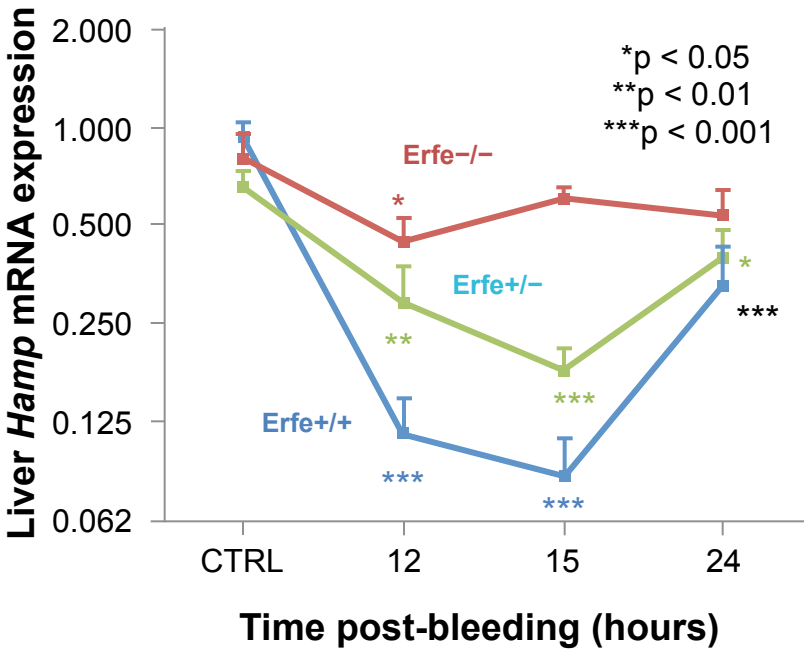
Tf, 97.

# The hepcidin/ferroportin (FPN) regulatory system controls systemic iron homeostasis




Modified from Hentze MW, et al. Cell. 2004;117:285-97.

# Erythroferrone may be the erythroid regulator of hepcidin during increased erythropoietic activity

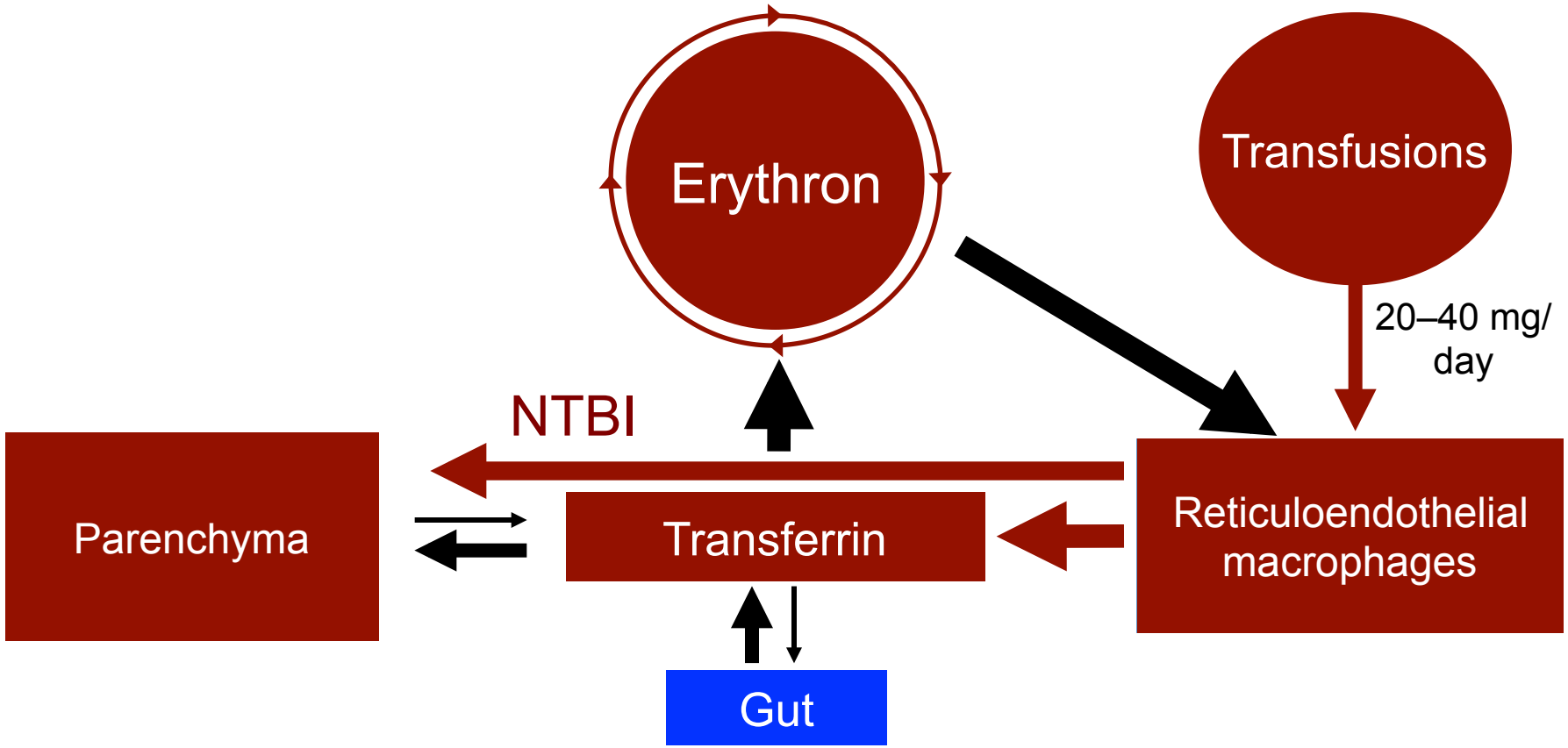



- *Erfe* mRNA expression is increased in the bone marrow and the spleen 4 hours after phlebotomy or EPO stimulation, preceding hepcidin suppression
- *Erfe*-deficient mice failed to suppress hepcidin after phlebotomy or EPO and recovered more slowly from the anaemia compared with Erfe+/− and Erfe+/+ mice
- In addition, treatment of mouse primary hepatocytes with supernatants of HEK293T cells overexpressing Erfe led to a significant decrease in hepcidin expression suggesting that Erfe can act directly on the liver to suppress hepcidin

CTRL, control; EPO, erythropoietin; Erfe, erythroferrone.

Kautz L, et al. Blood. 2013;122:abstract 4.

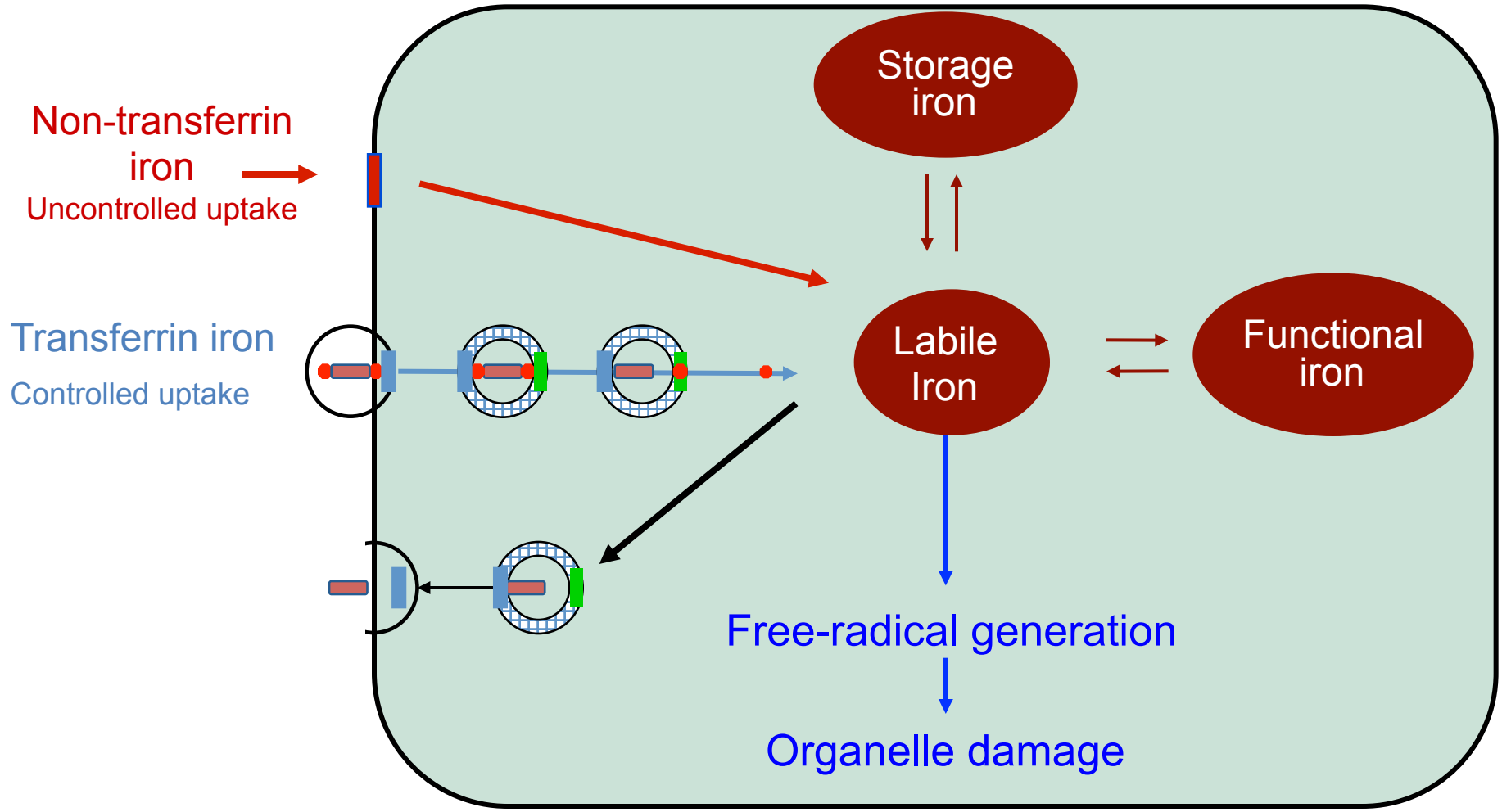
# Iron overload leads to production of NTBI




NTBI, non-transferrin-bound iron

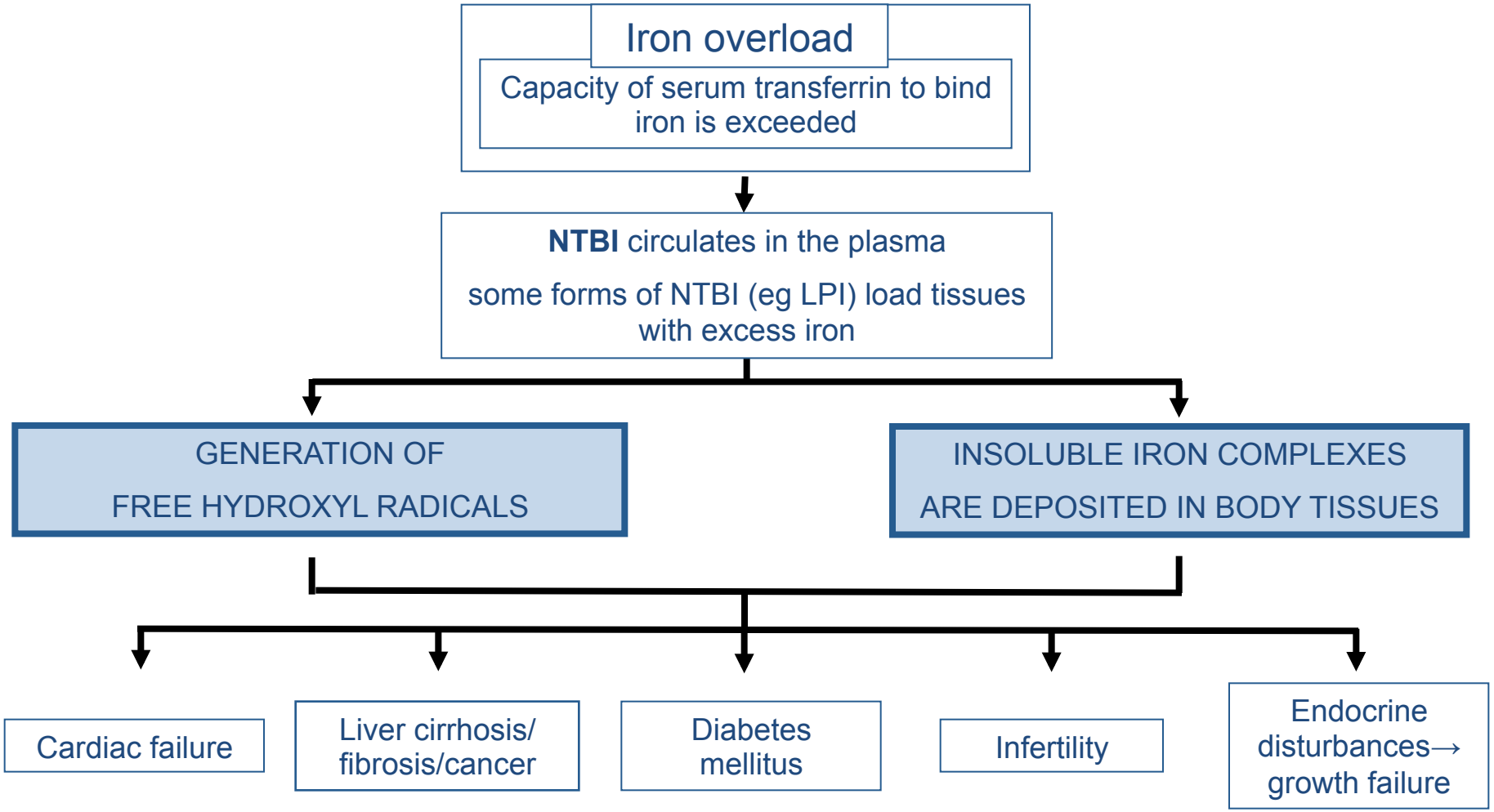
Hershko C et al. Pathophysiology of iron overload. Ann NY Acad Sci 1998;850:191–201

# Non-Transferrin Bound Iron




Porter JB. *Am J Hematol* 2007;82:1136–1139

# Non-Transferrin Bound Iron

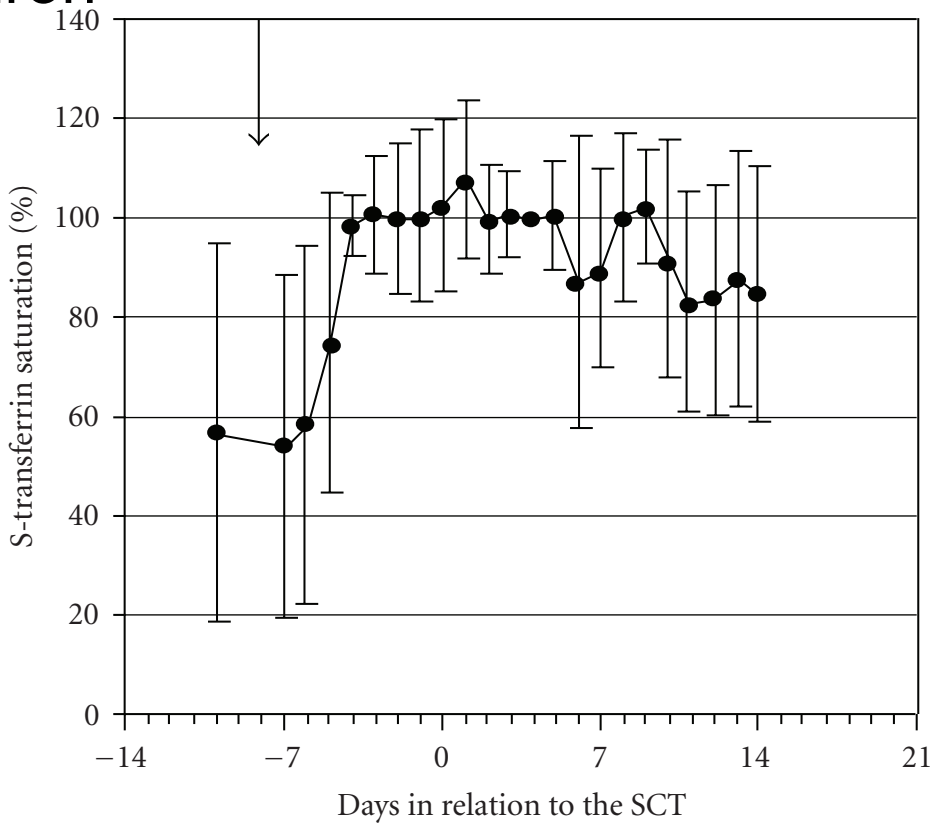


# Treatment and iron toxicity

- Myelosuppressive treatment

➔Underutilization of plasma iron

➔Release of cellular iron



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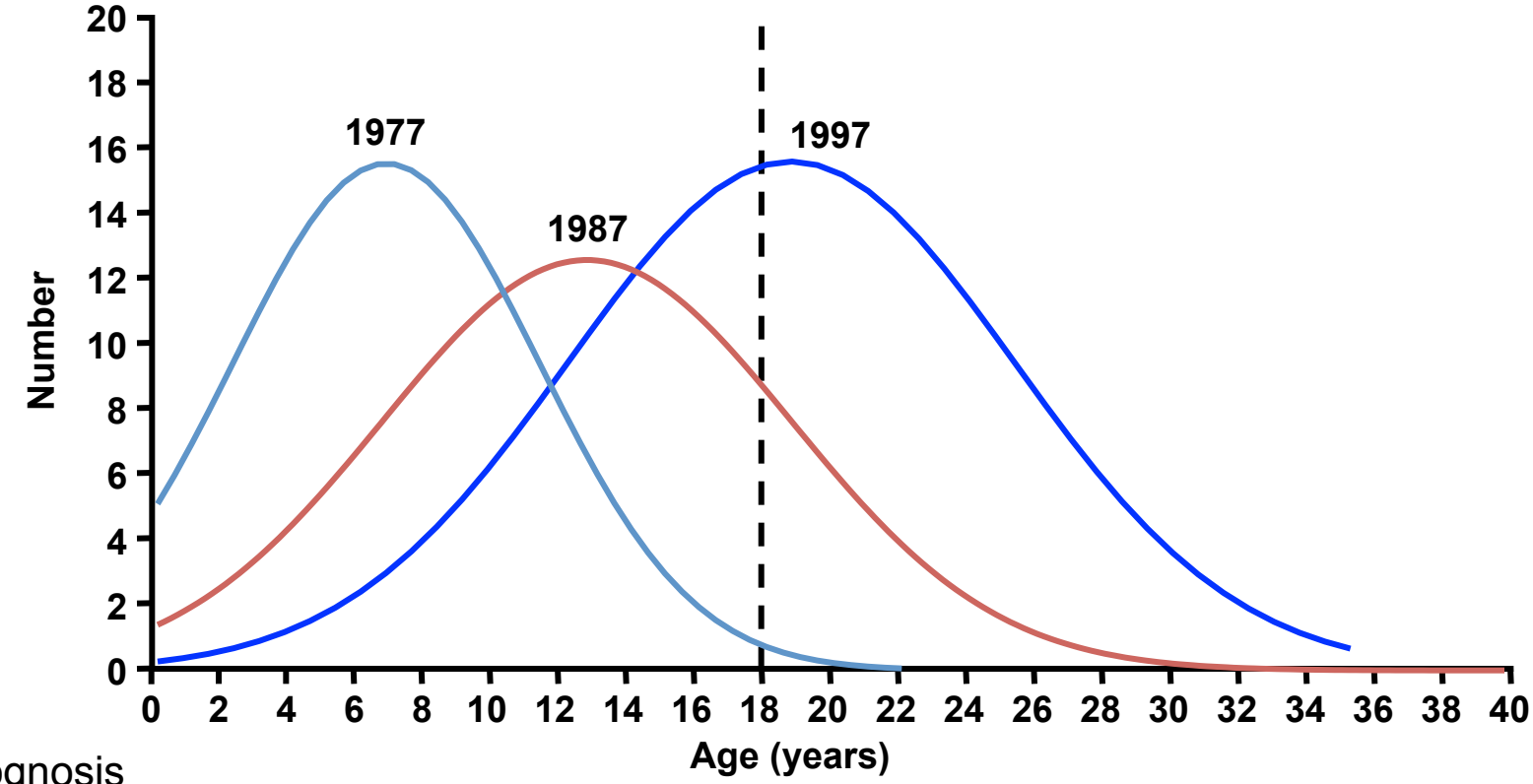
# Thalassemia major
# Improved survival over time

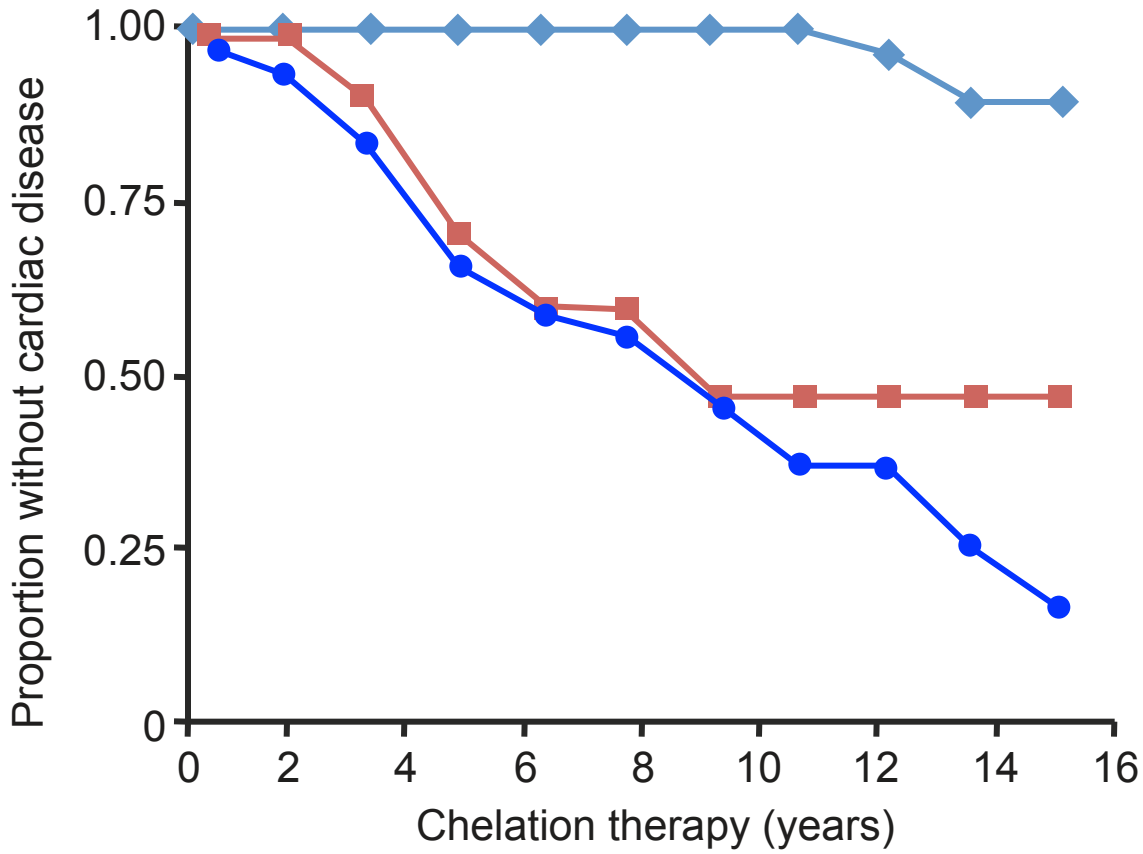



Prognosis

- Without transfusions: <5 years
- Regular transfusions with red blood cells: <20 years (CARDIAC DEATH)
- Chelation therapy in addition to transfusions: >20 years

Courtesy of Antonio Piga, MD, University of Turin, Italy

# Thalassemia major
# Impact of chelation on outcome

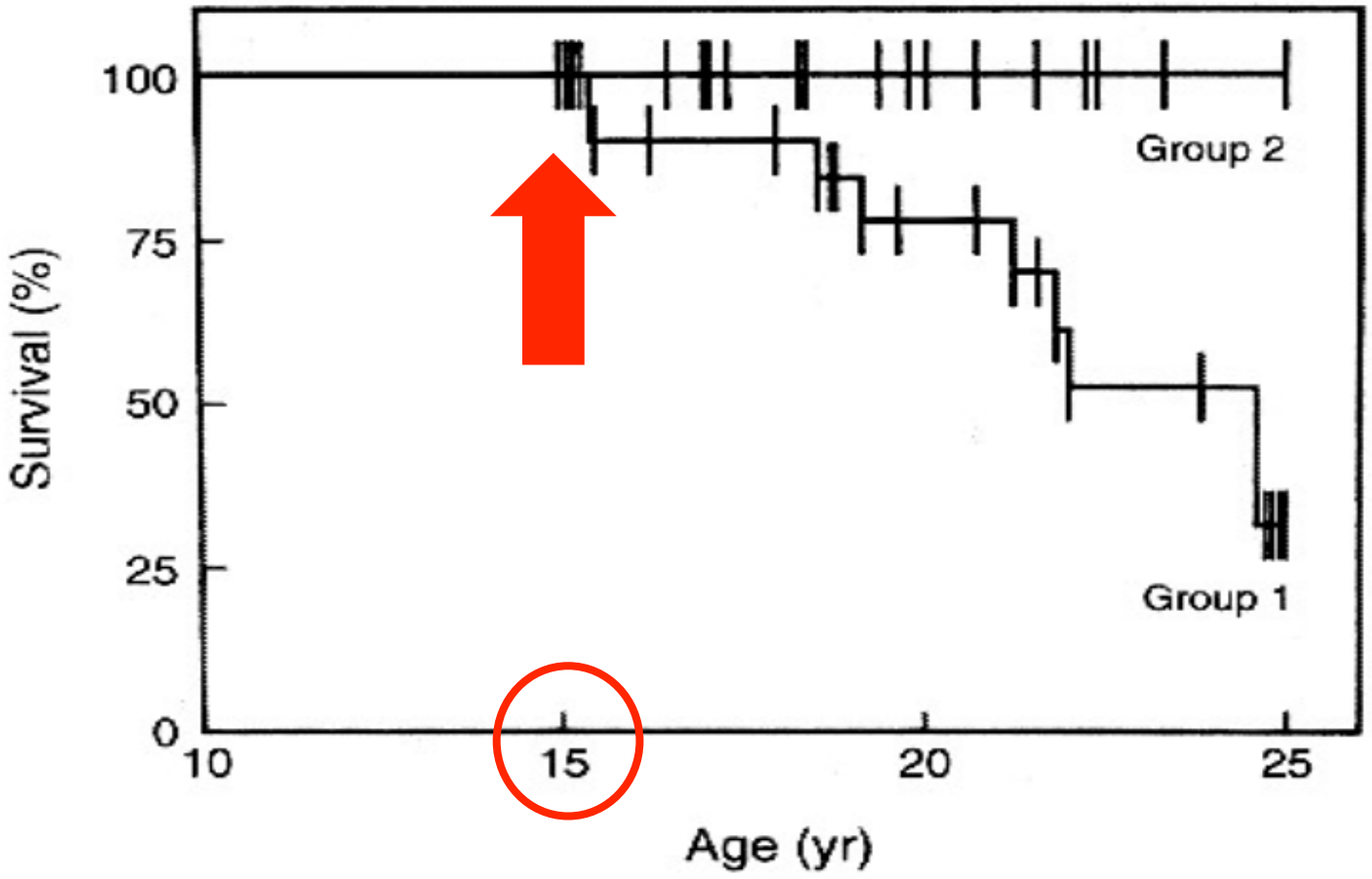



Cardiac disease-free survival in patients with:

- <33% ferritin measures >2500 ng/mL
- 33–67% ferritin measures >2500 ng/mL
- >67% ferritin measures >2500 ng/mL

Olivieri NF *et al*. *N Eng J Med* 1994;331:574–578

# Thalassemia major
# Impact of chelation on outcome

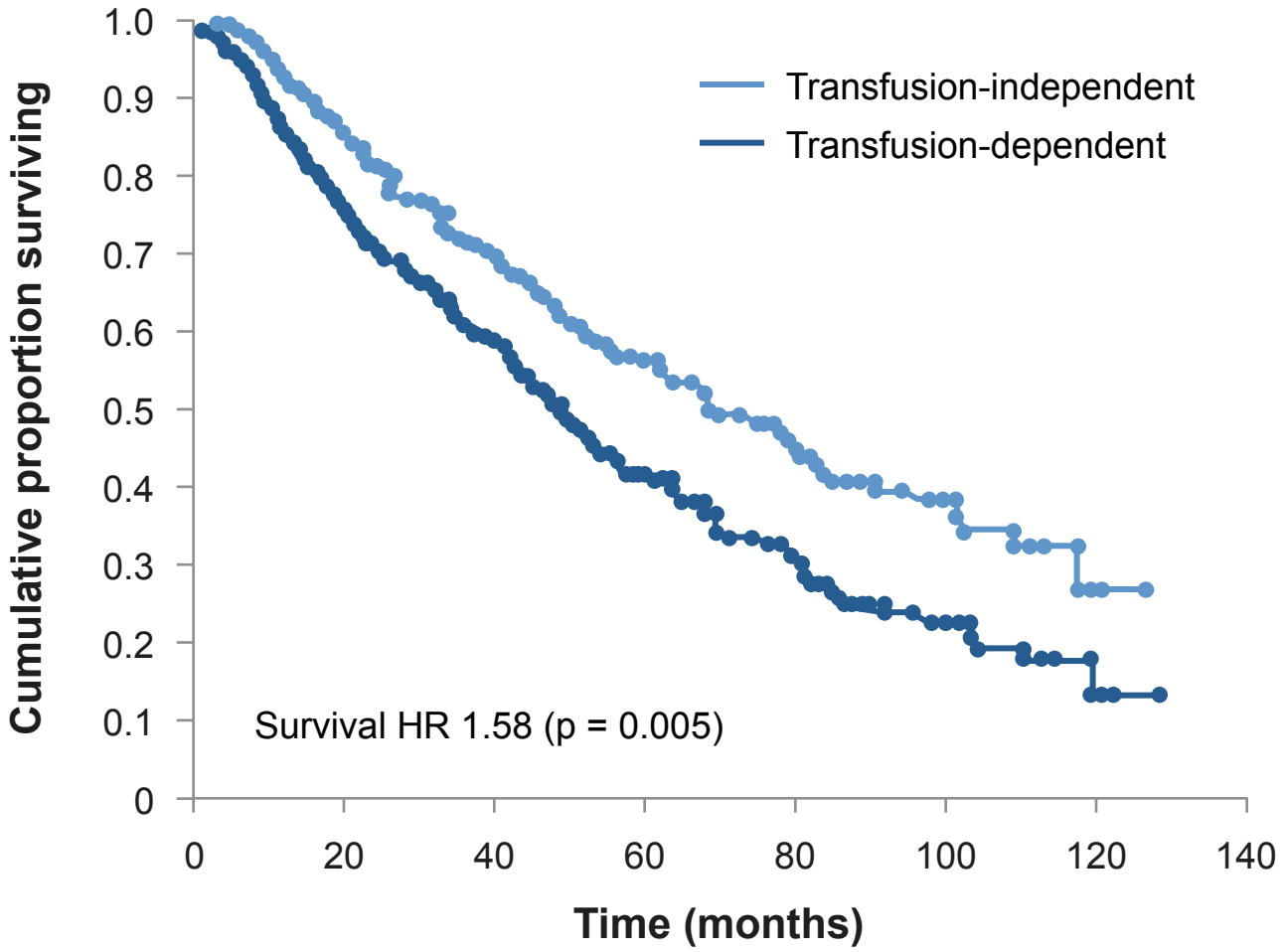



Brittenham GM, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. N Engl J Med 1994; 331: 567-73

# Clinical impact of IO in MDS

- Impact of IO on outcome more difficult to demonstrate
- Different patient population (compared to thalassemia)
  - Older age
  - Comorbidities
  - Other risk factors for mortality eg leukemic transformation, bleeding en infection complications

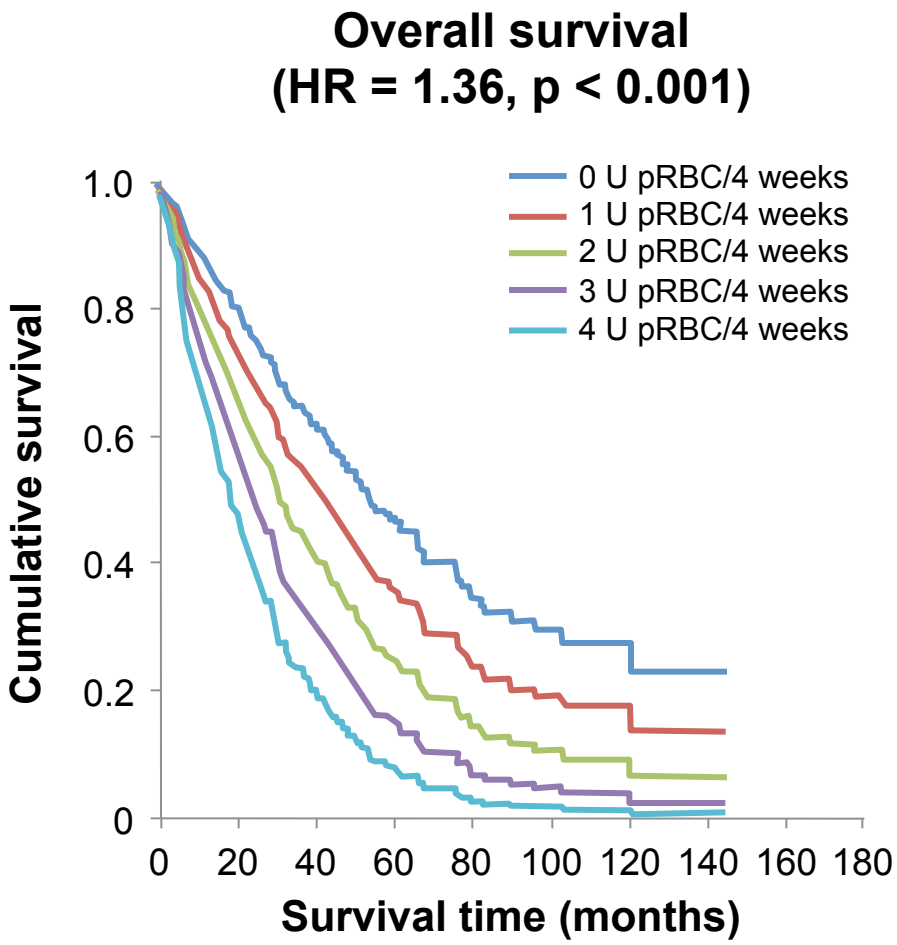
# Transfusion dependency significantly increases mortality risk in MDS

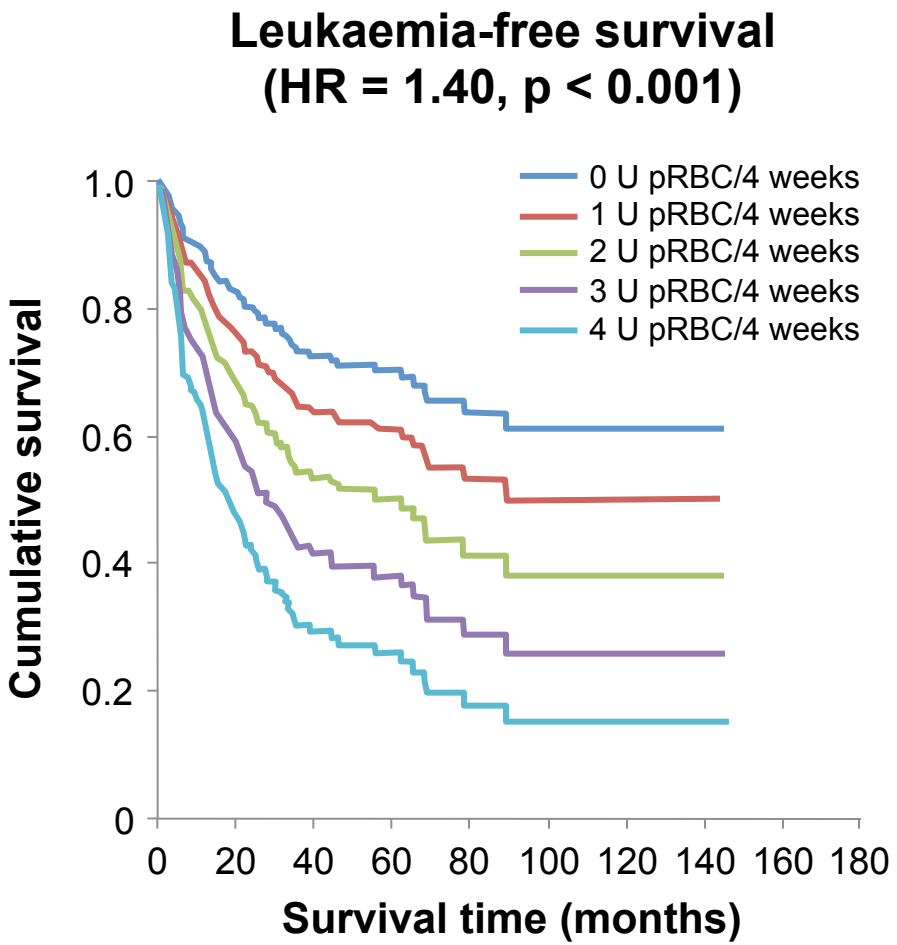



HR, hazard ratio.

Cazzola M, Malcovati L. N Engl J Med. 2005;352:536-8.

# Survival of MDS patients by severity of transfusion requirement

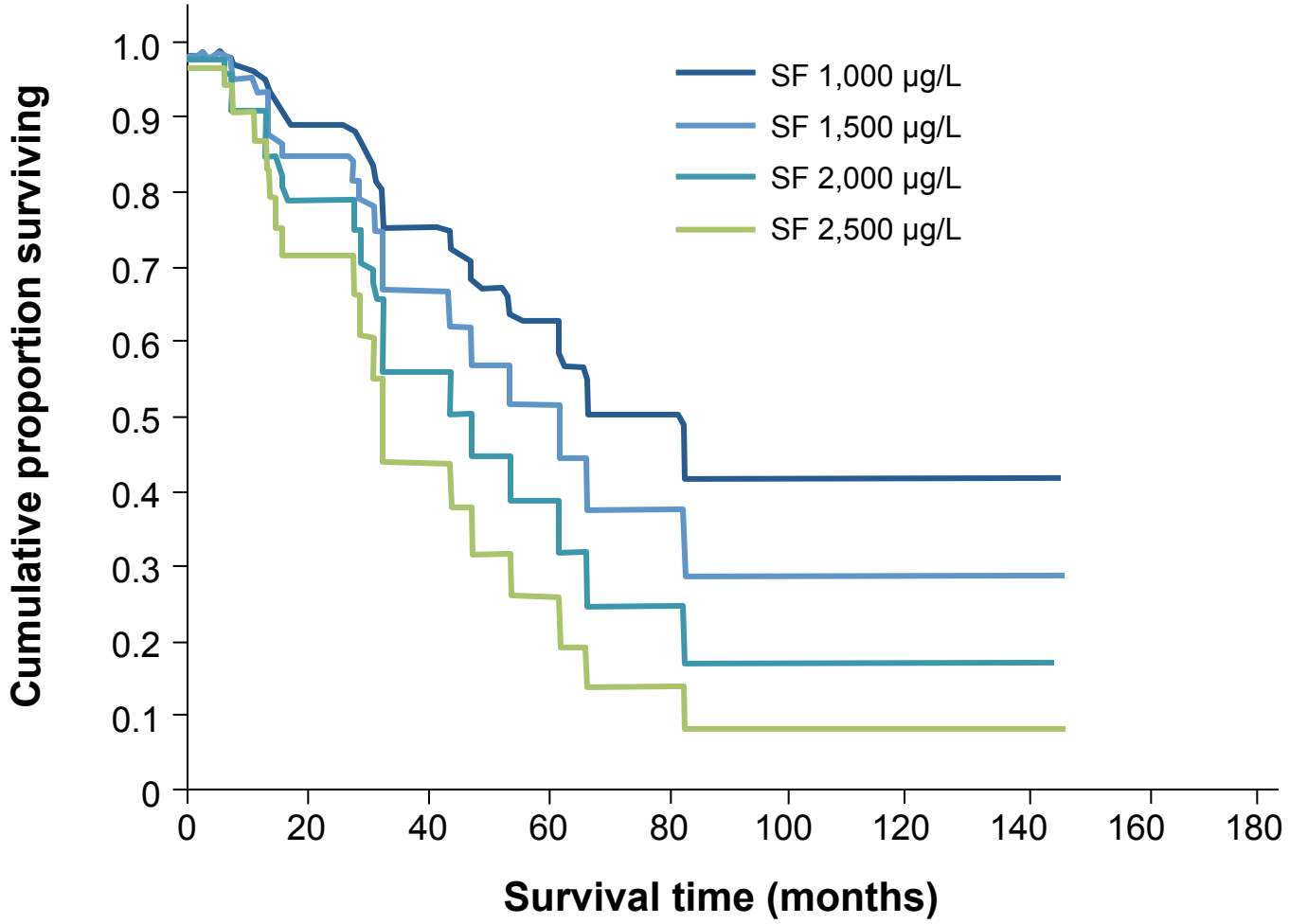



pRBC, packed red blood cells.

Malcovati L, et al. Haematologica. 2006;91:1588-90.

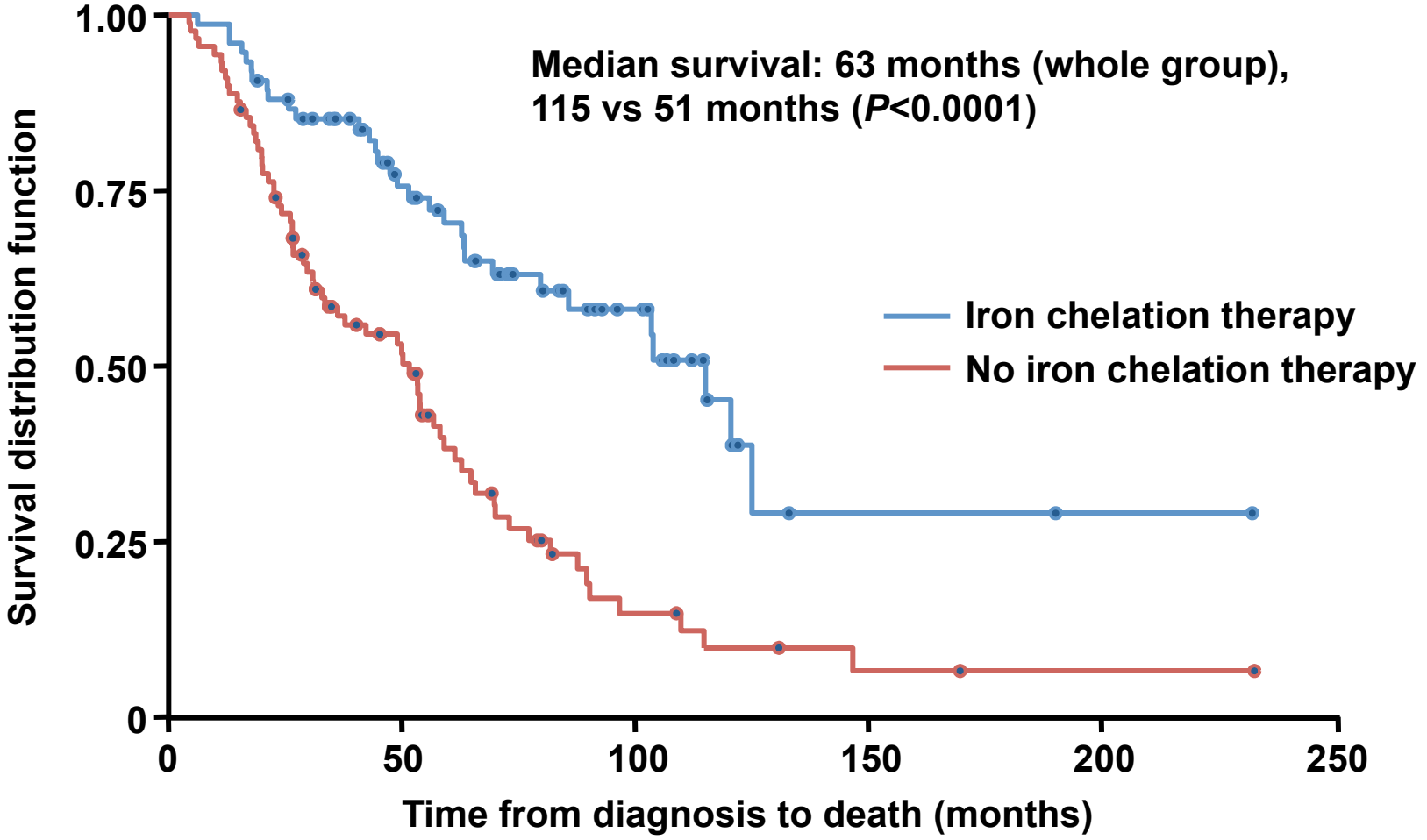
# Every 500µg/L increase in serum ferritin above 1000µg/L associated with 30% greater risk of death




SF, serum ferritin.

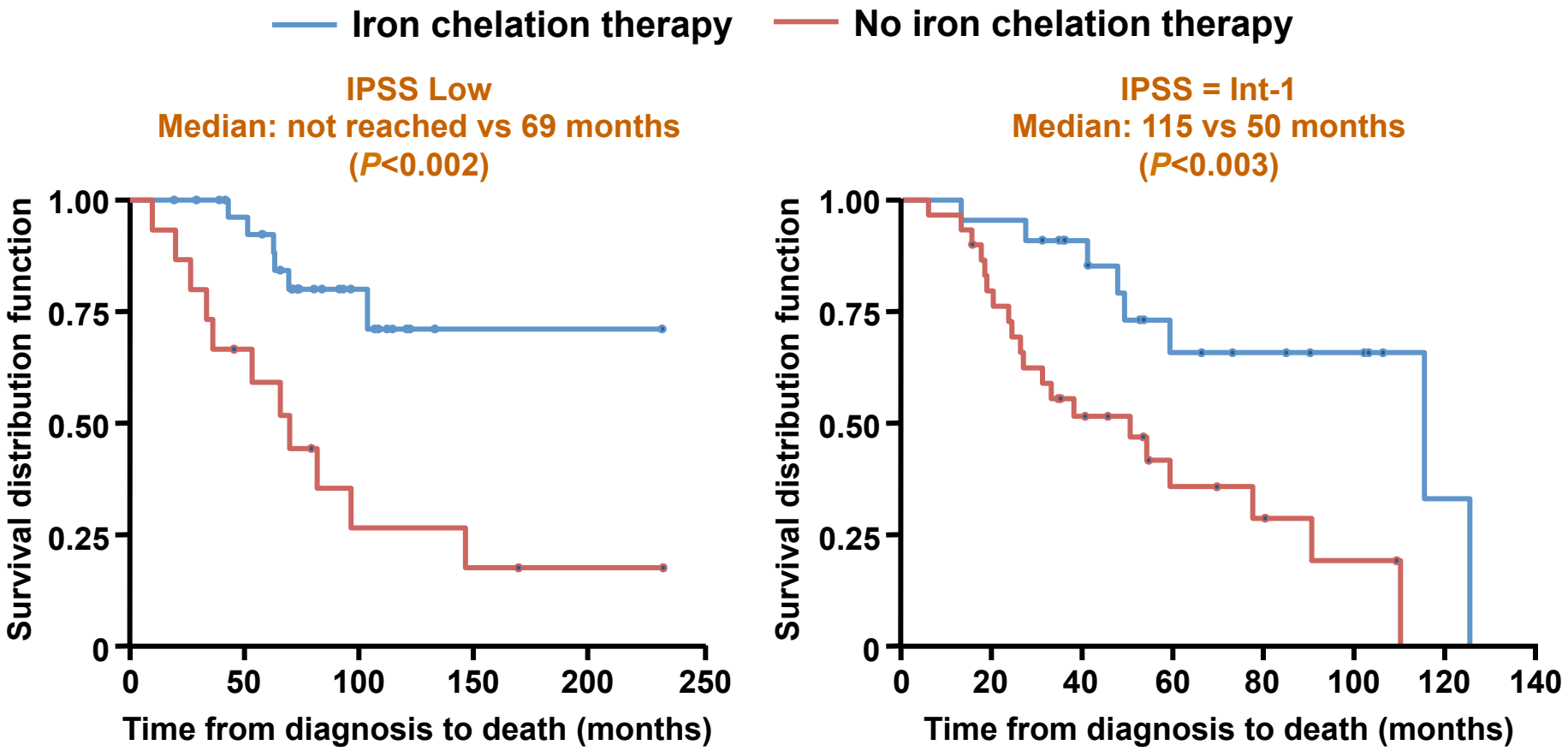
Malcovati L, et al. Haematologica. 2006;91:1588-90.

# Iron chelation therapy may improve outcome in MDS



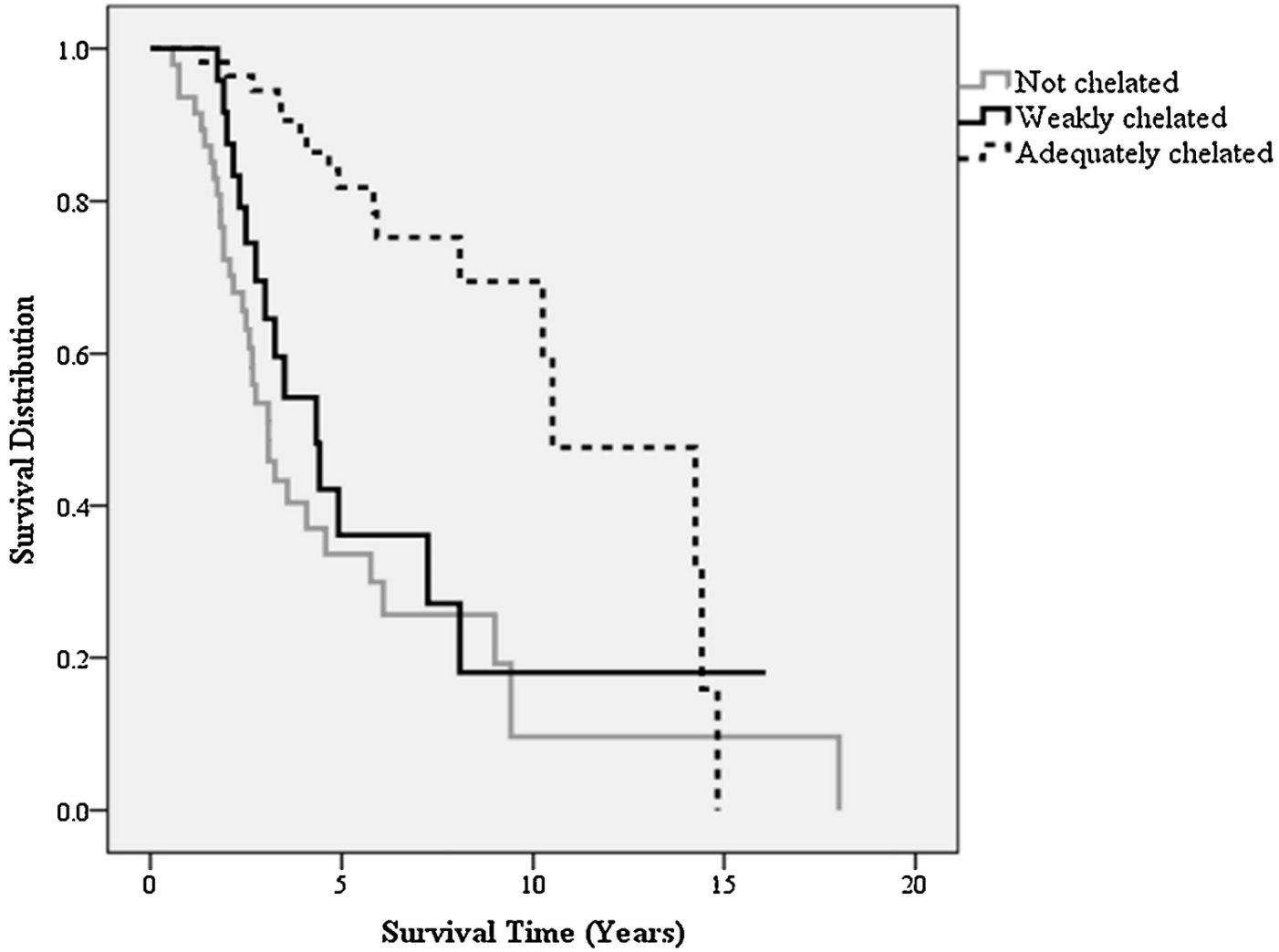

Rose C *et al.* Presented at ASH 2007 [*Blood* 2007;110(11):abst 249]

# Impact of iron chelation therapy depends on IPSS category




Rose C *et al.* Presented at ASH 2007 [*Blood* 2007;110(11):abst 249]

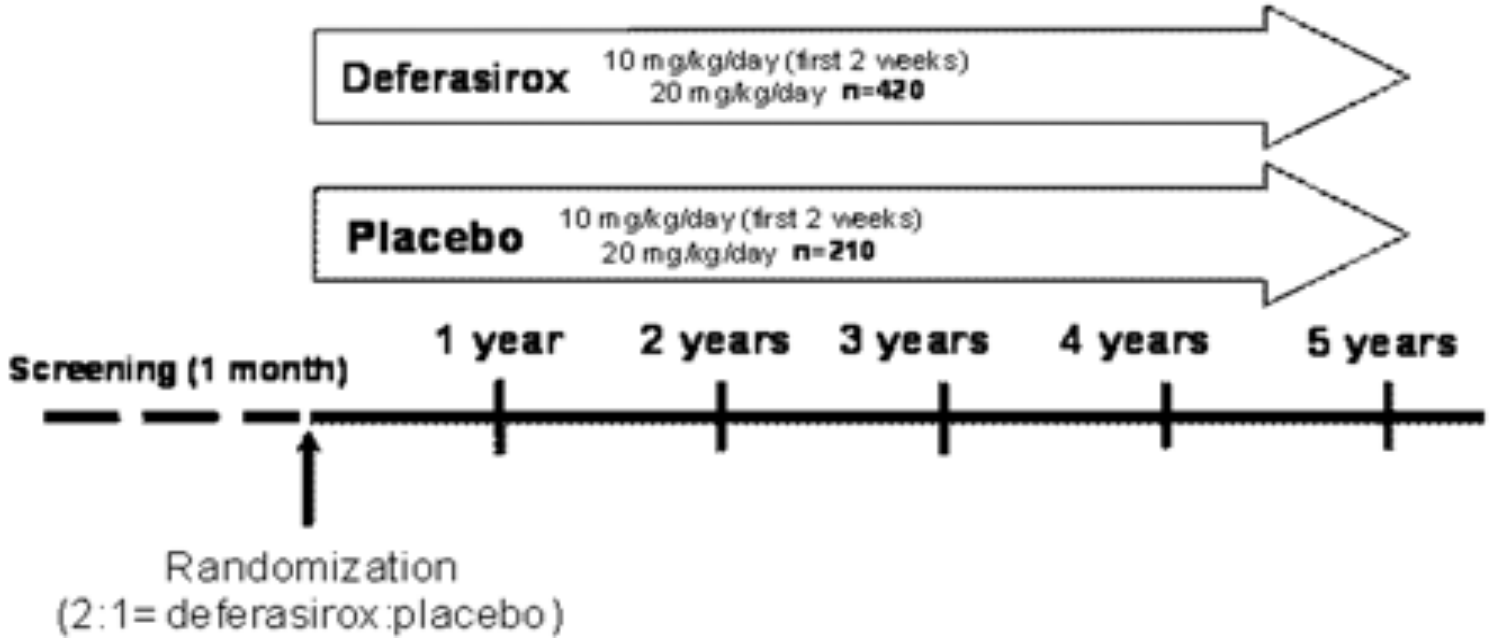
# Impact of iron chelation therapy by intensity of chelation “the Belgian experience”




Delforge M, Dominik Selleslag, Beguin Y, et al. Adequate iron chelation therapy for at least six months improves survival in transfusion dependent patients with lower risk myelodysplastic syndromes. Leuk Res 2014; 38: 557-563

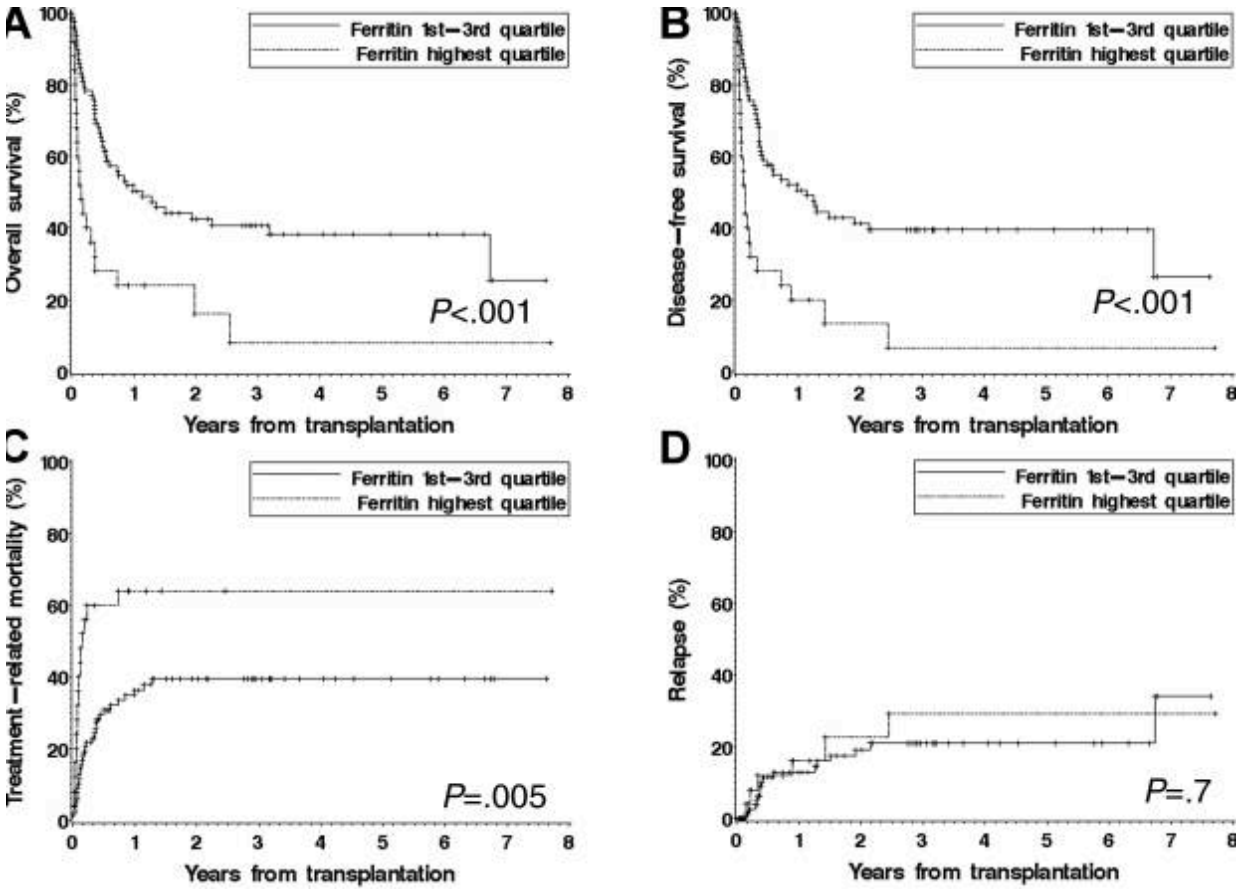
# Prospective study on survival impact of ICT TELESTO

- A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Deferasirox (Exjade®) in Patients with Low/Intermediate-1 Risk MDS and Transfusional Iron Overload.



# Prognostic impact of IO in alloSCT

- Pre-transplant ferritin
  - <230ng/ml
  - 230-930ng/ml
  - 930-2030ng/ml
  - >2030ng/ml




Armand et al. Blood 2007

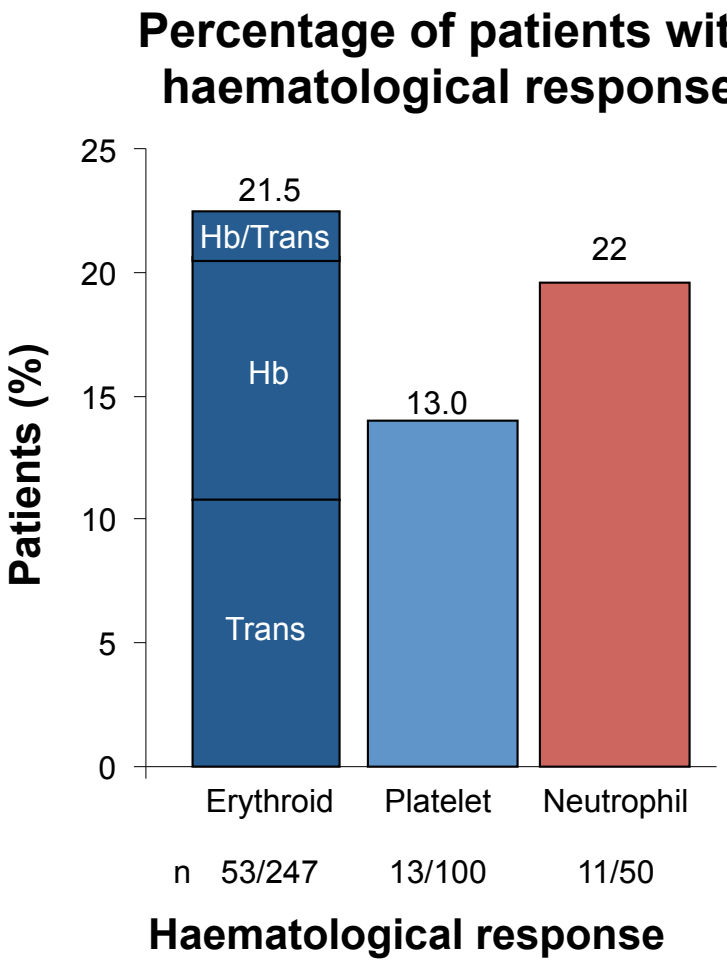
# Causes of inferior NRM and survival in alloSCT

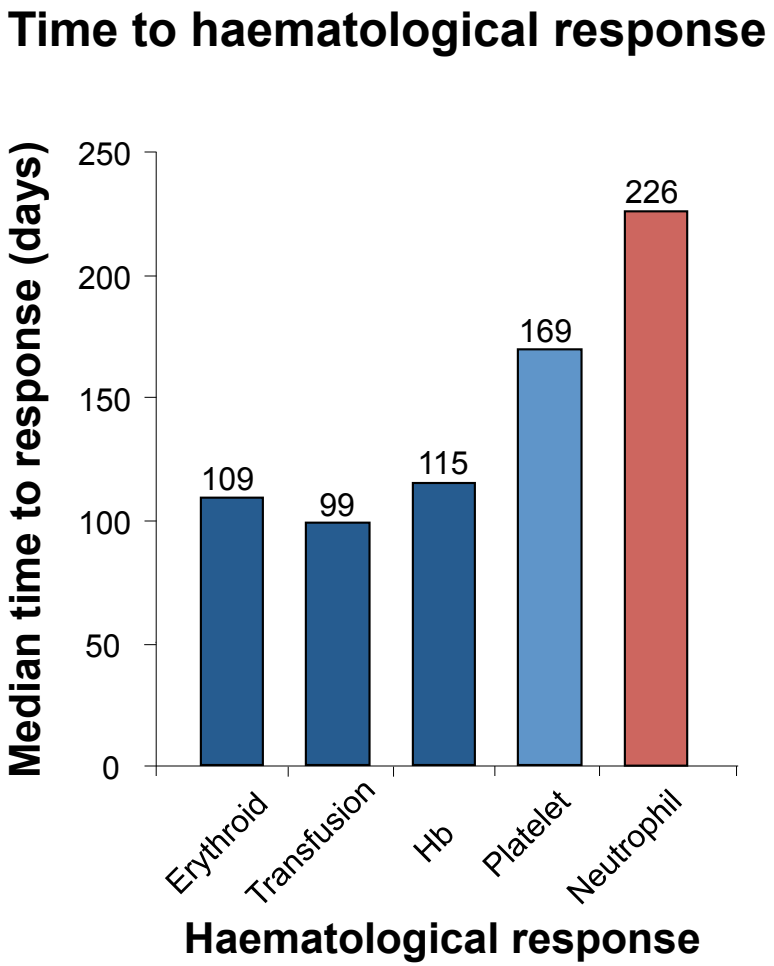
- Increased susceptibility of infections
  - Iron promotes bacterial and fungal growth in experimental studies
  - Suppression of immune system

| *Outcome* | *Ferritin (categorical)* | | | *Ferritin (continuous)* | | |
|---|---|---|---|---|---|---|
| | *OR* | *95% CI* | P | *OR* | *95% CI* | P |
| Day100 mortality | 3.82 | 1.32–11.0 | 0.013 | 1.51 | 1.07–2.14 | 0.02 |
| Overall survival | 2.28 | 1.29–4.02 | 0.004 | 1.34 | 1.09–1.65 | 0.005 |
| Acute GVHD/death | 3.11 | 1.56–6.18 | 0.001 | 1.20 | 0.987–1.46 | 0.068 |
| BSI/death | 1.99 | 1.06–3.75 | 0.032 | 1.22 | 1.01–1.48 | 0.041 |

Pullarkat et al. BMT 2008

# ICT may improve hematopoiesis

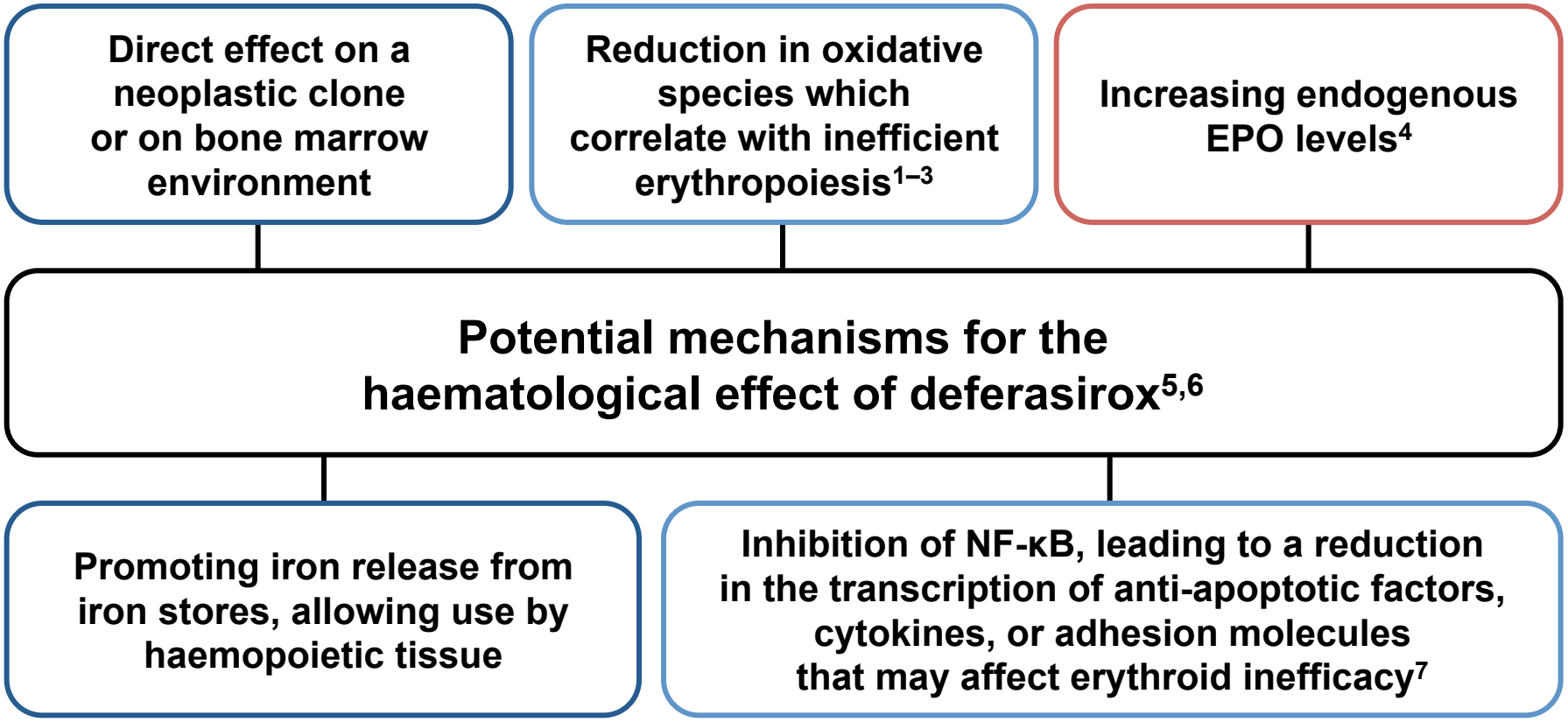



EPIC, Evaluation of Patients' Iron Chelation with Exjade study.

Gattermann N, et al. Hematologic responses with deferasirox therapy in transfusion dependent myelodysplastic syndromes patients. Haematologica. 2012;97:1364-71.

# ICT may improve hematopoiesis: how?




NF-κB, nuclear factor kappa B.

1. Ghoti H, et al. Eur J Haematol. 2007;79:463-7.
2. Hartmann J, et al. Blood. 2008;112:abstract 2694. 3. Chan LSA, et al. Blood. 2008;112:abstract 2685.
4. Ren X, et al. J Appl Physiol. 2000;89:680-6. 5. Breccia M, et al. Acta Haematol. 2010;124:46-8.
6. Guariglia R, et al. Leuk Res. 2011;35:566-70. 7. Messa E, et al. Haematologica. 2010;95:1308-16.

# Outline

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- Iron overload (IO) disorders
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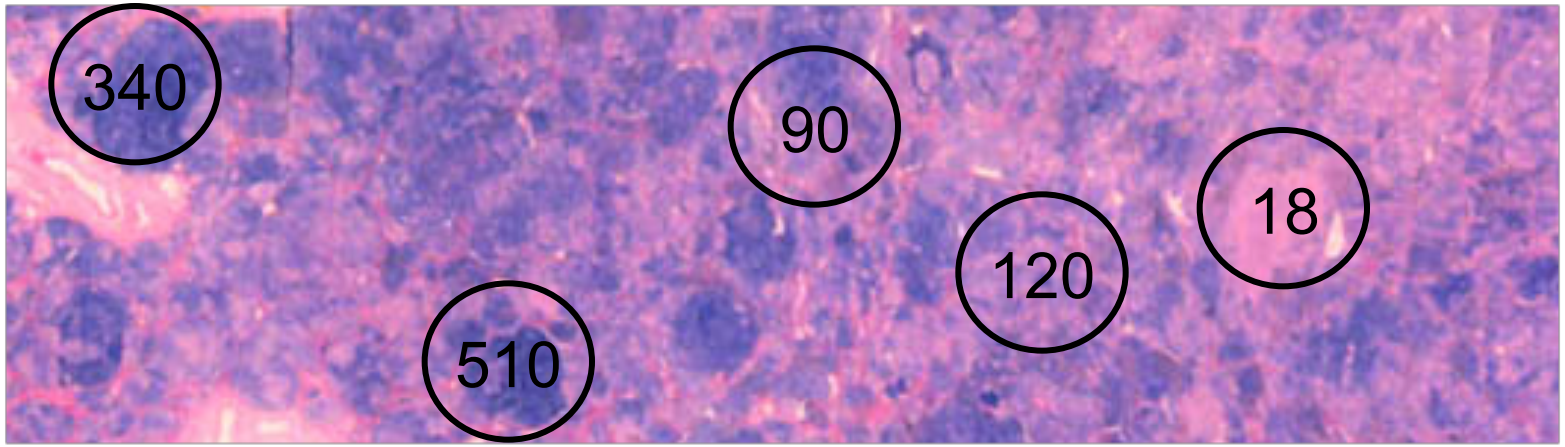
# Assessment body iron

- Liver Iron Concentration (LIC)
- Serum ferritin
- Magnetic Resonance Imaging (MRI) liver and heart

# Measuring LIC by liver biopsy

| Advantages | Disadvantages |
| --- | --- |
| • Validated reference standard<br>• Direct measurement of LIC<br>• Quantitative, specific and sensitive<br>• Provides information on liver histology/pathology | • Invasive; painful; potentially serious complications, eg bleeding<br>• Difficult to follow-up<br>• Risk of sampling error, especially in patients with cirrhosis |

# Heterogeneity of iron distribution in the cirrhotic liver



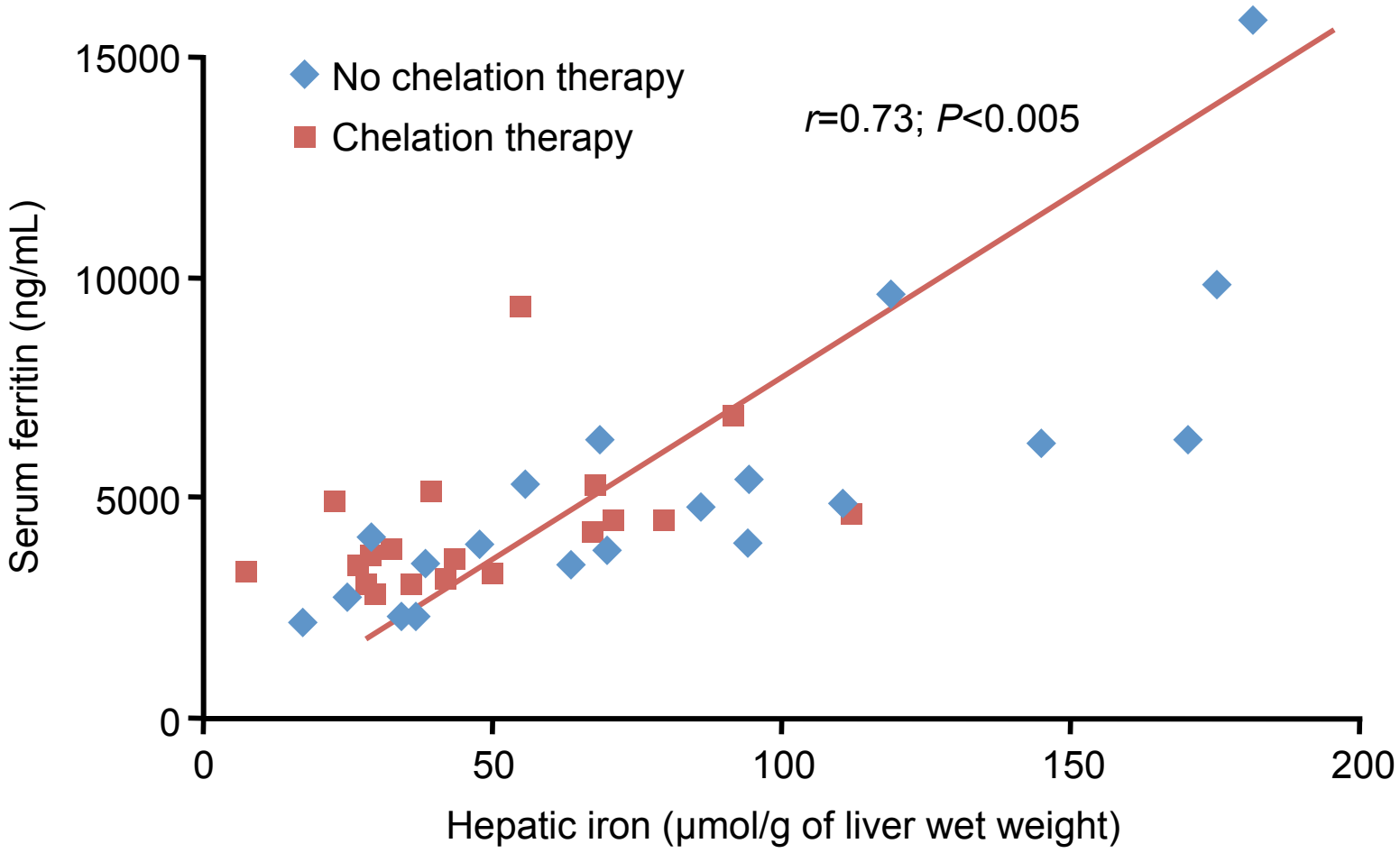

LIC (µmol/g dw)

Biopsy sampling error increases with cirrhosis

# Measuring serum ferritin

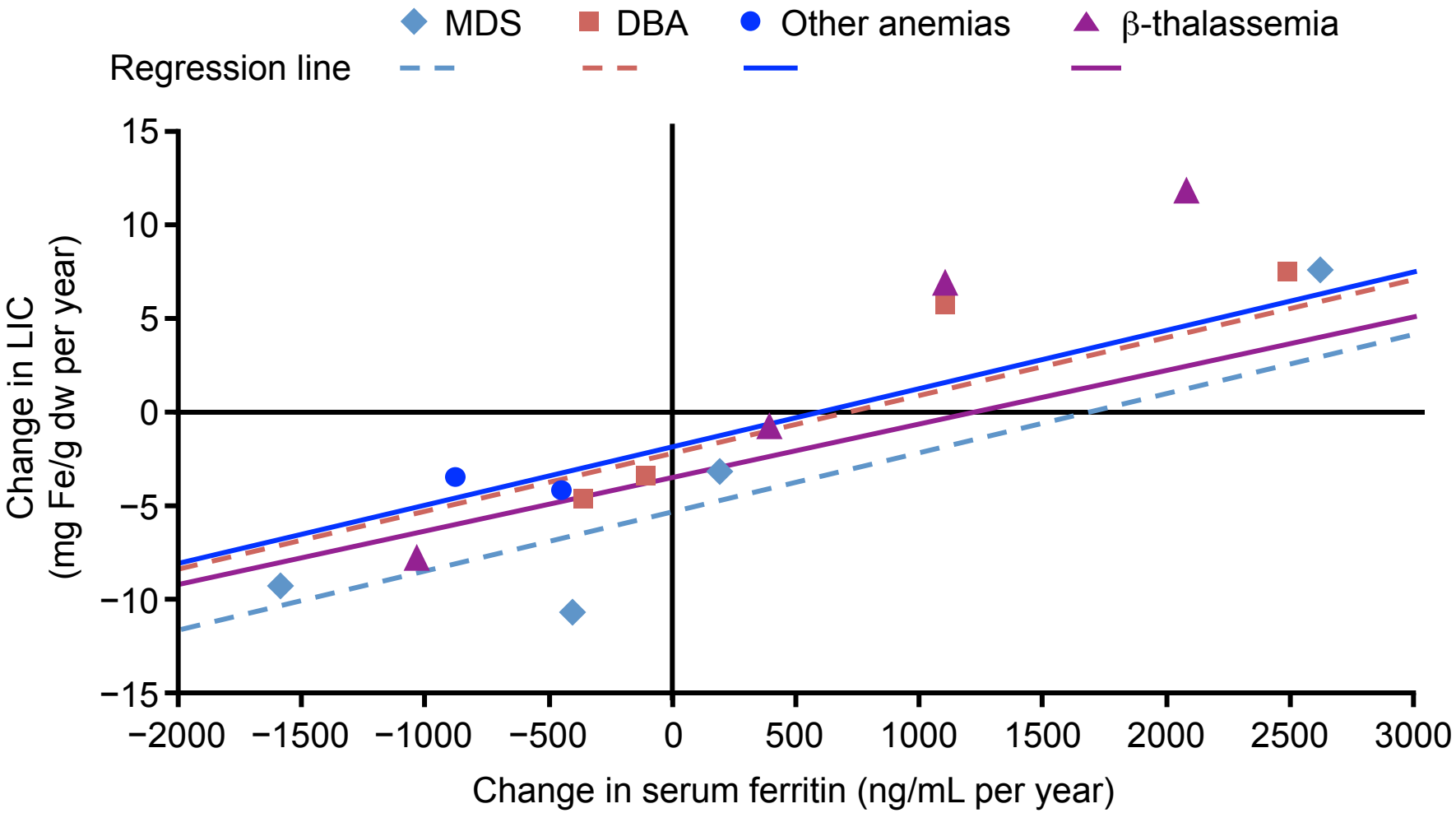
| Advantages | Disadvantages |
| --- | --- |
| • Easy to assess | • Indirect measurement of iron burden |
| • Inexpensive | • Subject to natural fluctuation |
| • Repeat serial measures are useful for monitoring chelation therapy | • Non-specific marker that may be affected by inflammation, infection, GVHD, liver damage |
| • Allows longitudinal follow-up of patients | |

# Relationship between serum ferritin and LIC in thalassemia major




Olivieri NF *et al*. *New Engl J Med* 1995;332:918–922

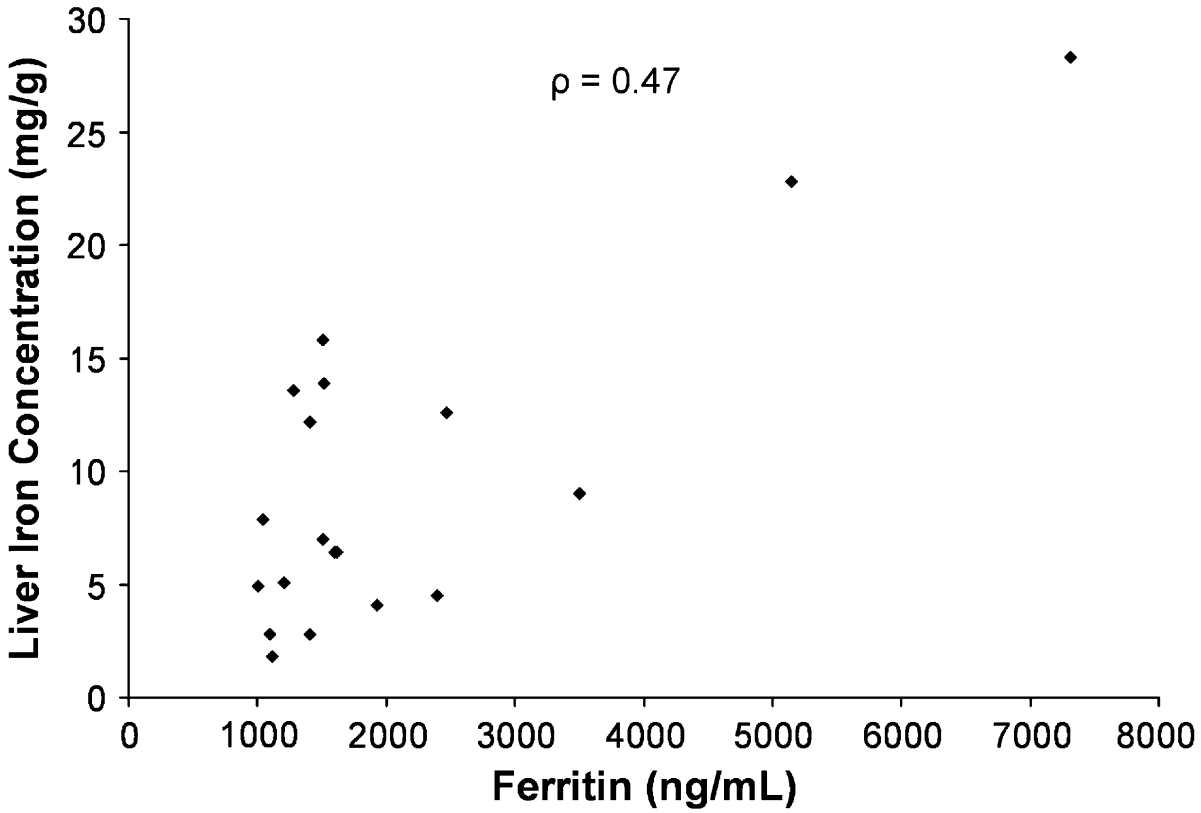
# Relationship between serum ferritin and LIC in various anemias




MDS, myelodysplastic syndromes; DBA, Diamond-Blackfan anemia

Porter J *et al*. *Eur J Hematol* 2008;80:168–176

# Weak correlation between serum ferritin and LIC in SCT recipients



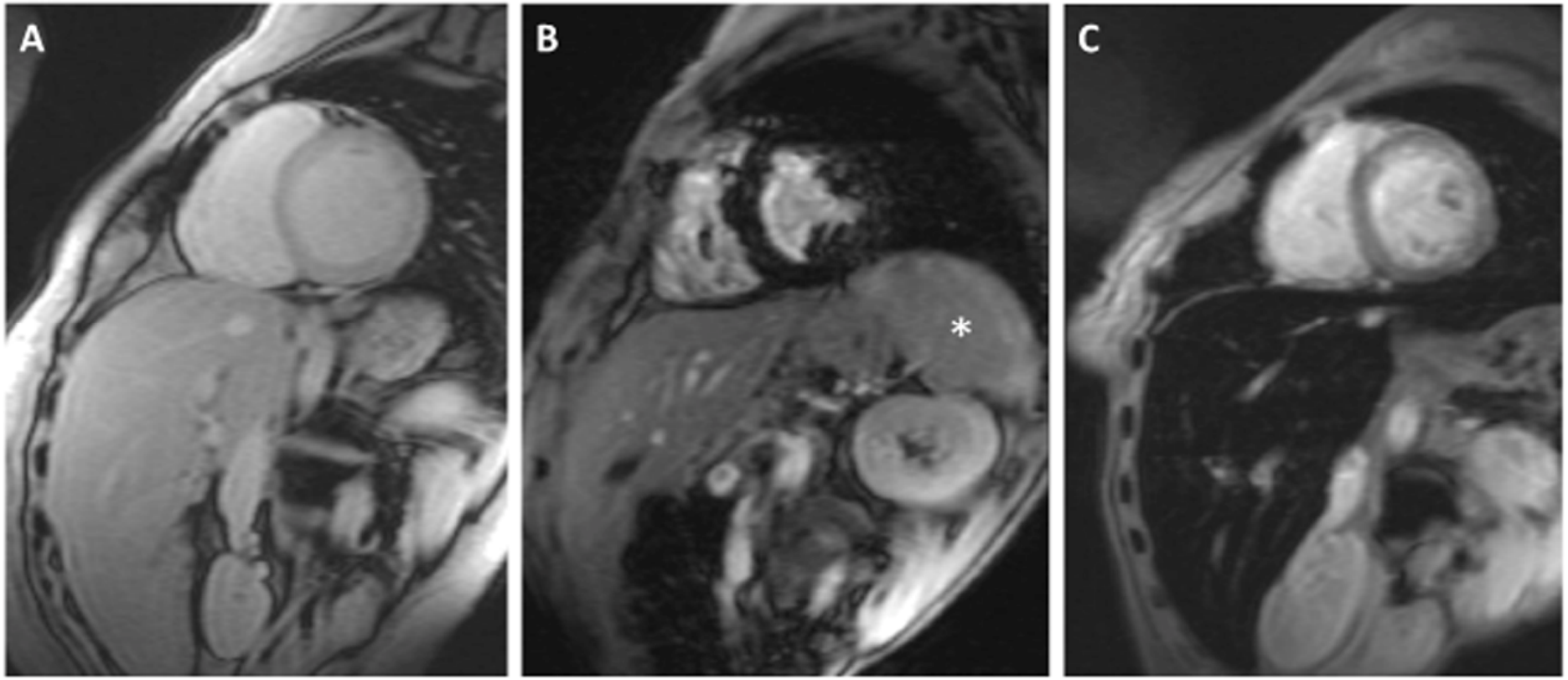

Majhail *et al*. *BBMT 2008*

# Measuring LIC with MRI

| Advantages | Disadvantages |
| --- | --- |
| • Assesses iron content throughout the liver<br>• Status of liver and heart can be assessed in parallel<br>• Allows longitudinal patient follow-up | • Indirect measurement of LIC<br>• Requires MRI imager with dedicated imaging method<br>• Cost and availability |

MRI = magnetic resonance imaging

# Iron causes the organ to darken more rapidly

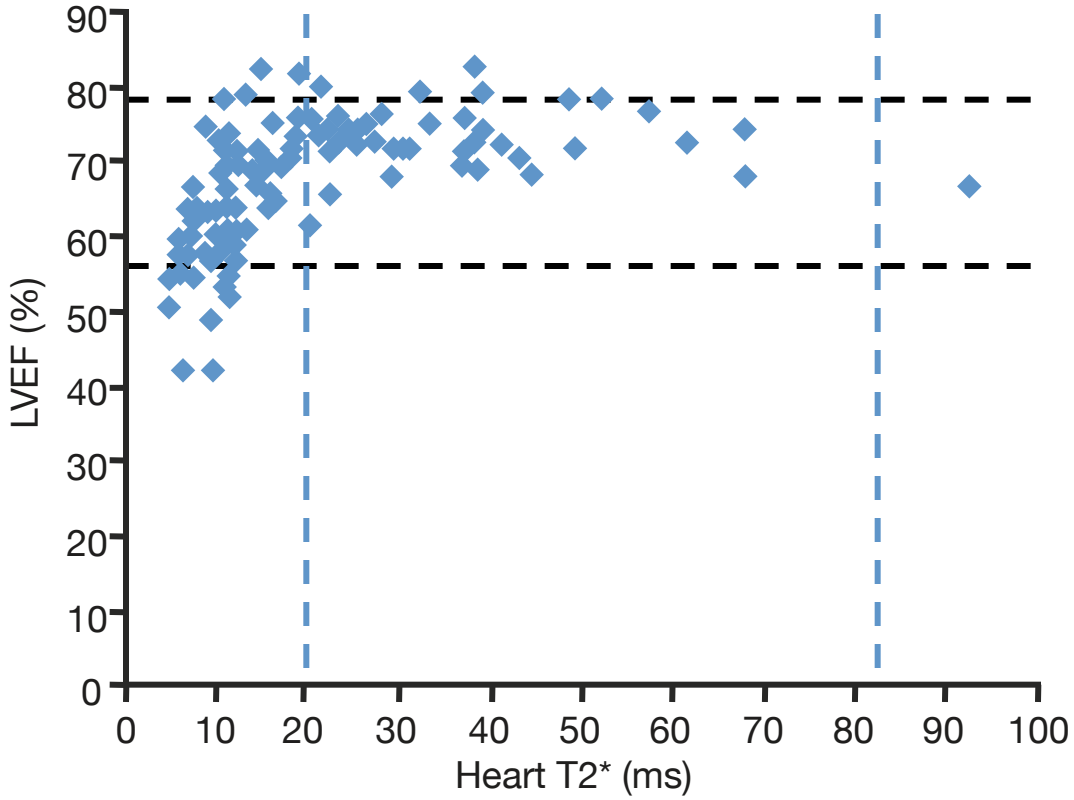


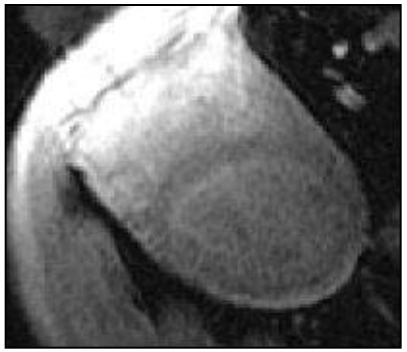

T2* MRI
T2* is the time (in msec) needed for the organ to lose 2/3 rd of its signal

# Measuring cardiac iron with MRI

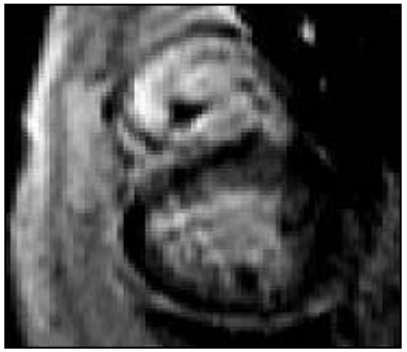
| Advantages | Disadvantages |
| --- | --- |
| • Rapidly assesses iron content in the septum of heart | • Indirect measurement of cardiac iron |
| • Functional parameters can be examined concurrently | • Requires MRI imager with dedicated imaging method |
| • Iron status of liver and heart can be assessed in parallel | • Cost and availability |
| • Allows longitudinal follow-up | |

# T2* MRI: emerging new standard for cardiac iron



Cardiac T2* value of 37 ms in a normal heart

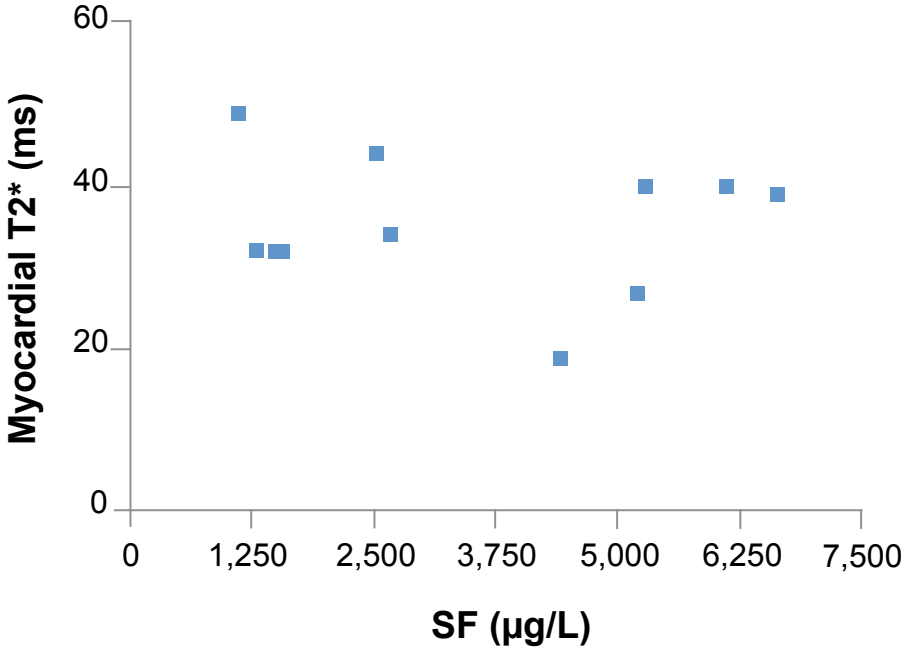


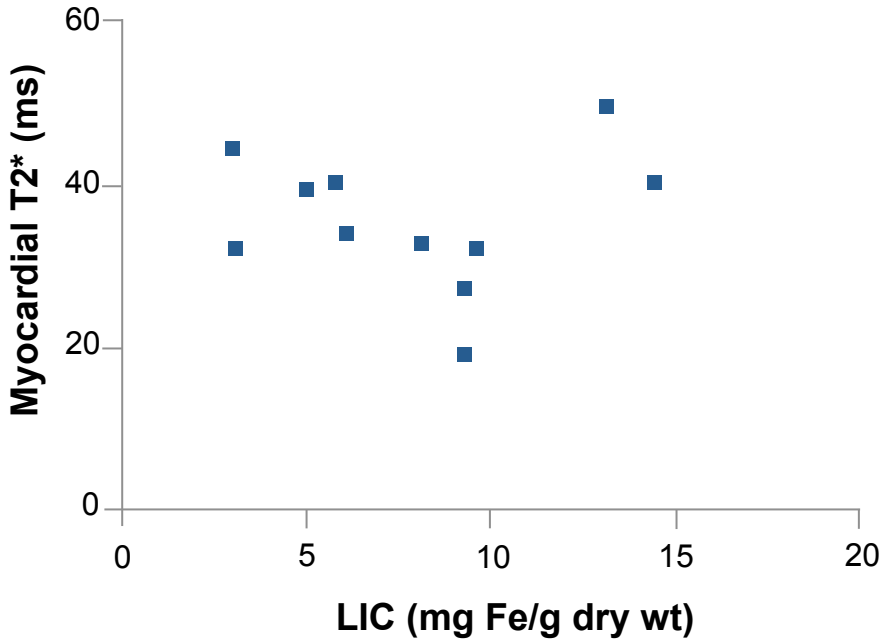
Cardiac T2* value of 4 ms in a significantly iron overloaded heart

Myocardial T2* values <20 ms are associated with progressive and significant decline in LVEF

Anderson LJ *et al*. *Eur Heart J* 2001;22:2171–2179

# SF levels and LIC correlate poorly with myocardial iron loading in patients with MDS

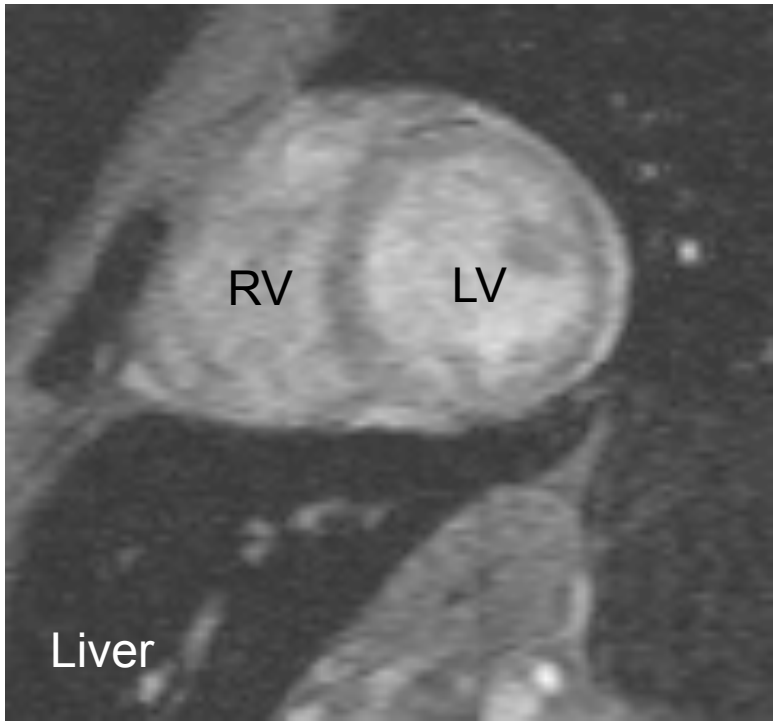


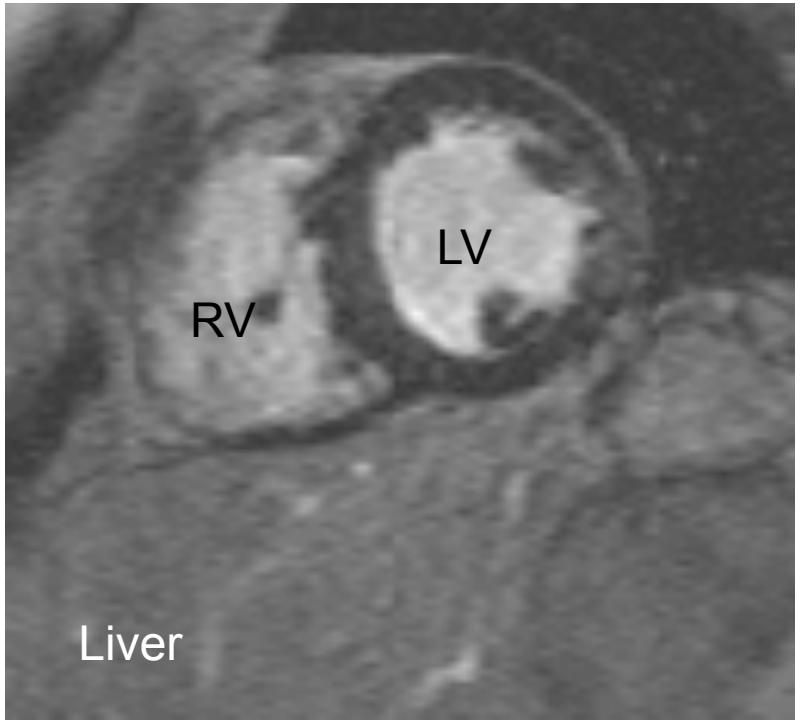

Transfusion history: 23–257 units over 1–10 years

Chacko J, et al. Br J Haematol. 2007;138:587-93.

# Discordance between liver iron and cardiac iron overload in thalassaemia major




**High liver iron**
**Minimal heart iron**




**High heart iron**
**Minimal liver iron**

LV, left ventricle; RV, right ventricle.

Anderson LJ, et al. Eur Heart J. 2001;22:2171-9.

# Key points in assessing iron overload

- Serum ferritin (SF)
  - SF levels measurements inconsistently reflect LIC and poorly predict cardiac iron concentration[1,2]
- Cardiac and liver MRI[3,4]
  - assessments of liver iron and cardiac iron by T2* and R2 are calibrated and reproducible
  - LIC may be a poor predictor of cardiac iron concentration

1. Brittenham GM, et al. N Engl J Med. 1982;307:1671-5.
2. Karam LB, et al. Pediatr Blood Cancer. 2008;50:62-5.
3. St Pierre TG, et al. Blood. 2005;105:855-61.
4. Anderson LJ, et al. Eur Heart J. 2001;22:2171-9.

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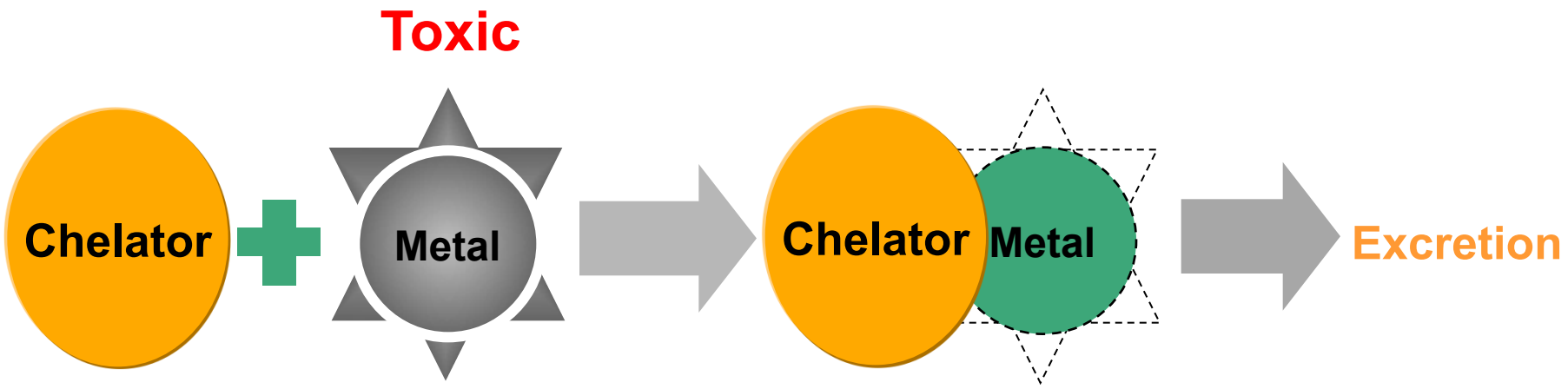
- Treatment of IO, Iron Chelation Therapy (ICT)

# Iron Chelation Therapy Concept



# Properties of an ideal chelator

## Efficacy

- Maintenance of iron balance or achievement of negative iron balance
- High and specific affinity for ferric iron ($Fe^{3+}$)
- Effective tissue and cell penetration
- High-chelating efficiency
- No iron redistribution
- Slow metabolism and elimination rate
- 24-hour chelation coverage

## Convenience

- Oral bioavailability
- Half-life compatible with once-daily dosing
- Good compliance

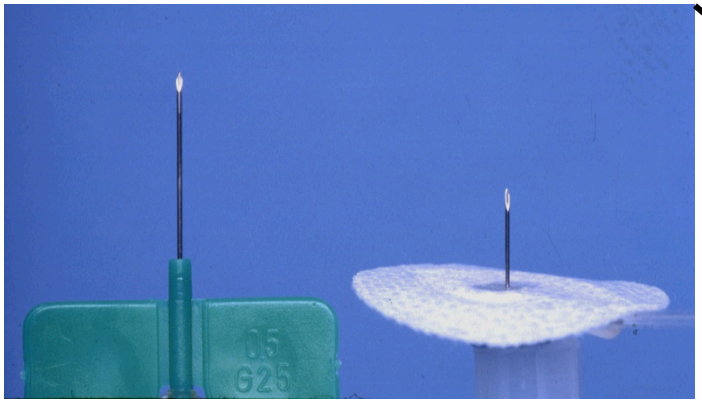
## Tolerability

- Good adverse-event profile

# Limitations of DFO therapy

**Poor oral bioavailability and a short plasma half-life**

**Slow subcutaneous infusion 3–7 times weekly**



**Inconvenient administration**

**Injection-site reactions and pain**

**Poor compliance reported to lead to increased mortality[1]**

**Equipment not widely available in many countries**

[1]Gabutti V, Piga A. *Acta Haematol* 1996;95:26–36

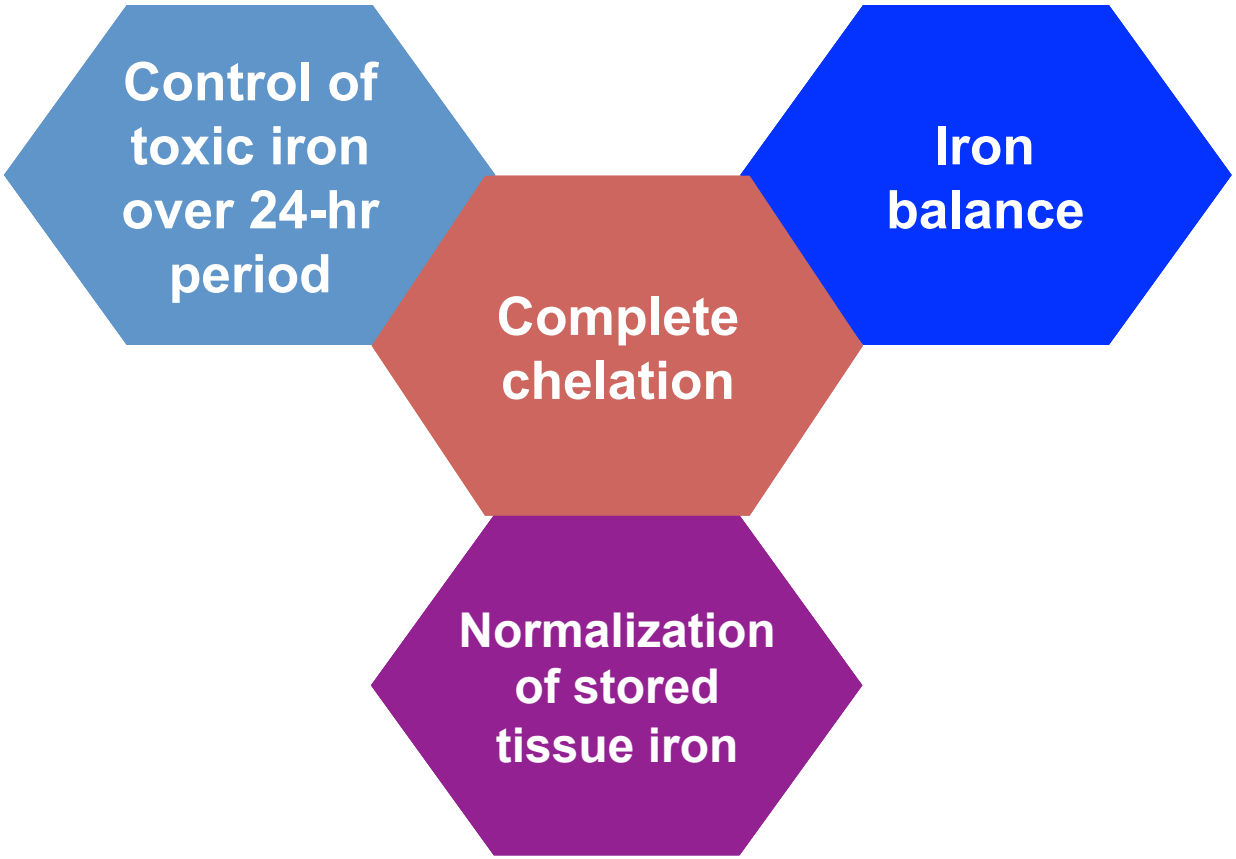
# Comparison of chelators

| Property | DFO | DFP | DFX |
|---|---|---|---|
| Usual dose (mg/kg/day) | 25–60 | 75–100 | 20–30 |
| Route | s.c., i.v. (8–12 hours, 5 days/week) | Oral 3 times daily | Oral Once daily |
| Half-life | 20–30 minutes | 3–4 hours | 8–16 hours |
| Excretion | Urinary, faecal | Urinary | Faecal |
| Main adverse effects in PI | Local reactions, ophthalmological, auditory, growth retardation, allergic | Gastrointestinal disturbances, agranulocytosis/ neutropenia, arthralgia, elevated liver enzymes | Gastrointestinal disturbances, rash, mild non-progressive creatinine increase, elevated liver enzymes, ophthalmological, auditory |

# Reimbursement iron chelators

- Deferiprone
  - thalassemia patients (<18y)
  - deferoxamine is contra-indicated
- Deferasirox
  - Thalassemia major
  - SCD en congenital anemia (DBA) if deferoxamine inadequate
  - MDS with IPSS max 1,5 or preparing for alloSCT if deferoxamine inadequate or not feasible for socio-professional reasons

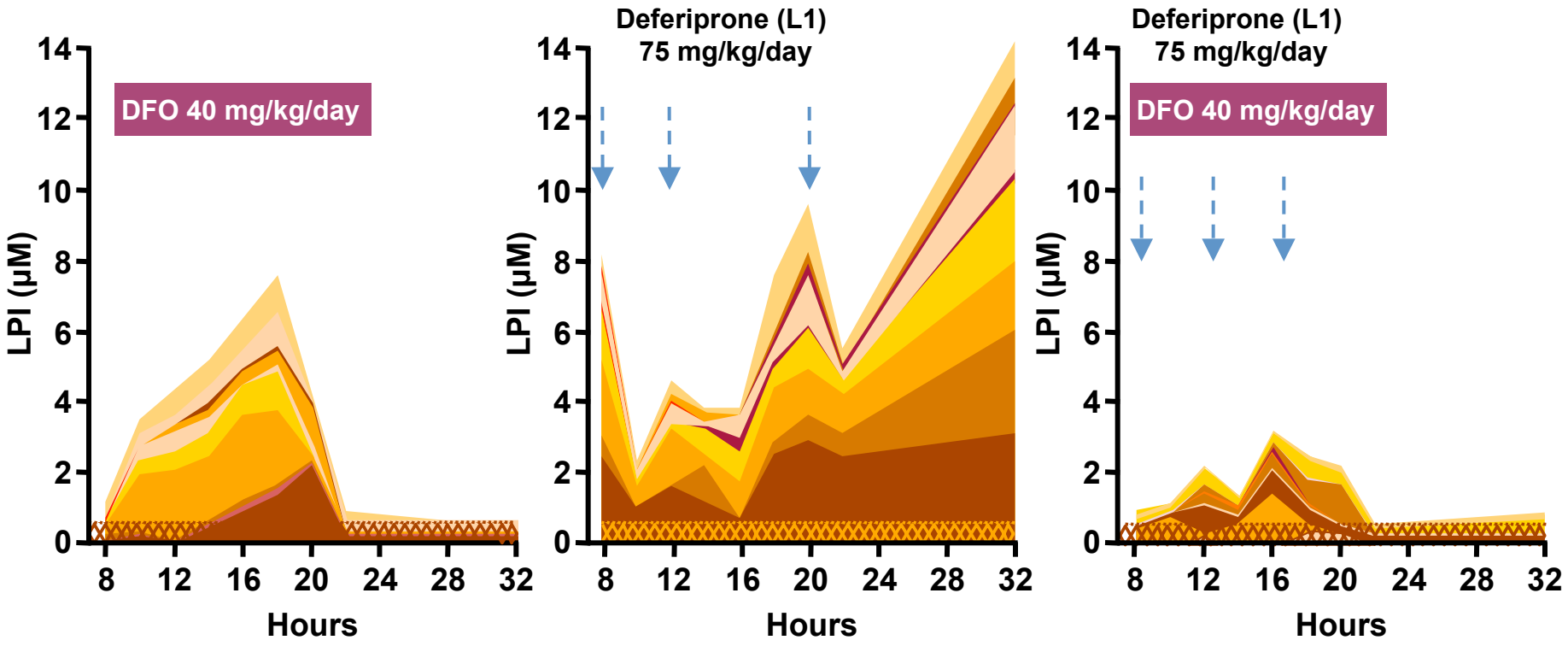
# Goals of Iron Chelation Therapy




The primary goals of iron chelation therapy are

to **remove excess iron** and **provide protection from the effects of toxic iron**

# Effect on Labile Plasma Iron




Cabantchik ZI, *et al*. *Best Pract Res Clin Hematol* 2005;18:277–287

# Effective control of iron in the blood with chelation therapy

| Maintenance or reduction of serum ferritin levels with appropriate dosing | | | |
|---|---|---|---|
| **DFO** | **Deferiprone** | **DFO:deferiprone combination** | **Deferasirox** |
| ✓ | ✓ | ✓ | ✓ |

| 24-hour control of NTBI/LPI levels | | | |
|---|---|---|---|
| **DFO** | **Deferiprone** | **DFO:deferiprone combination** | **Deferasirox** |
| **x** | **x** | ✓ | ✓ |
| **Levels rebound when infusion is stopped** | **Levels rebound between doses** | **Continuous administration required** | **24-hour chelation coverage achieved with once-daily dosing** |

**24-hour control achieved with continuous combination therapy of DFO and deferiprone or with once-daily dosing of deferasirox**

# Recommendations

| | Spanish Guidelines, 2008[1] | Italian Guidelines, 2002[2] | Japanese Guidelines, 2008[3] | MDS Foundation Guidelines, 2008[4] |
|---|---|---|---|---|
| | Recommended that chelation therapy should be considered: | | | |
| **Transfusion status** | • Transfusion dependent | • Received >50 RBC units | • Received >40 Japanese RBC units | • Received 2 RBC units/month for ≥1 year |
| **Serum ferritin level** | • >1000 ng/mL | – | • >1000 ng/mL | • >1000 ng/mL |
| **Patient profile** | • IPSS Low or Int-1<br>• Very low, Low or Int (WPSS)<br>• Low risk (Spanish prognostic index) | • Life-expectancy >6 months | • Life-expectancy >1 year | • Life-expectancy >1 year |

[1]Arrizabalaga B *et al*. *Haematologica* 2008;93(Suppl 1):3–10; [2]Alessandrino EP *et al*. *Haematologica* 2002;87:1286–1306; [3]Suzuki T *et al*. *Int J Hematol* 2008;88:30–35; [4]Bennett JM. *Am J Hematol* 2008;83:858–861