Carenza ed Eccesso di Ferro:
nuove conoscenze ed approccio terapeutico

Iron chelation

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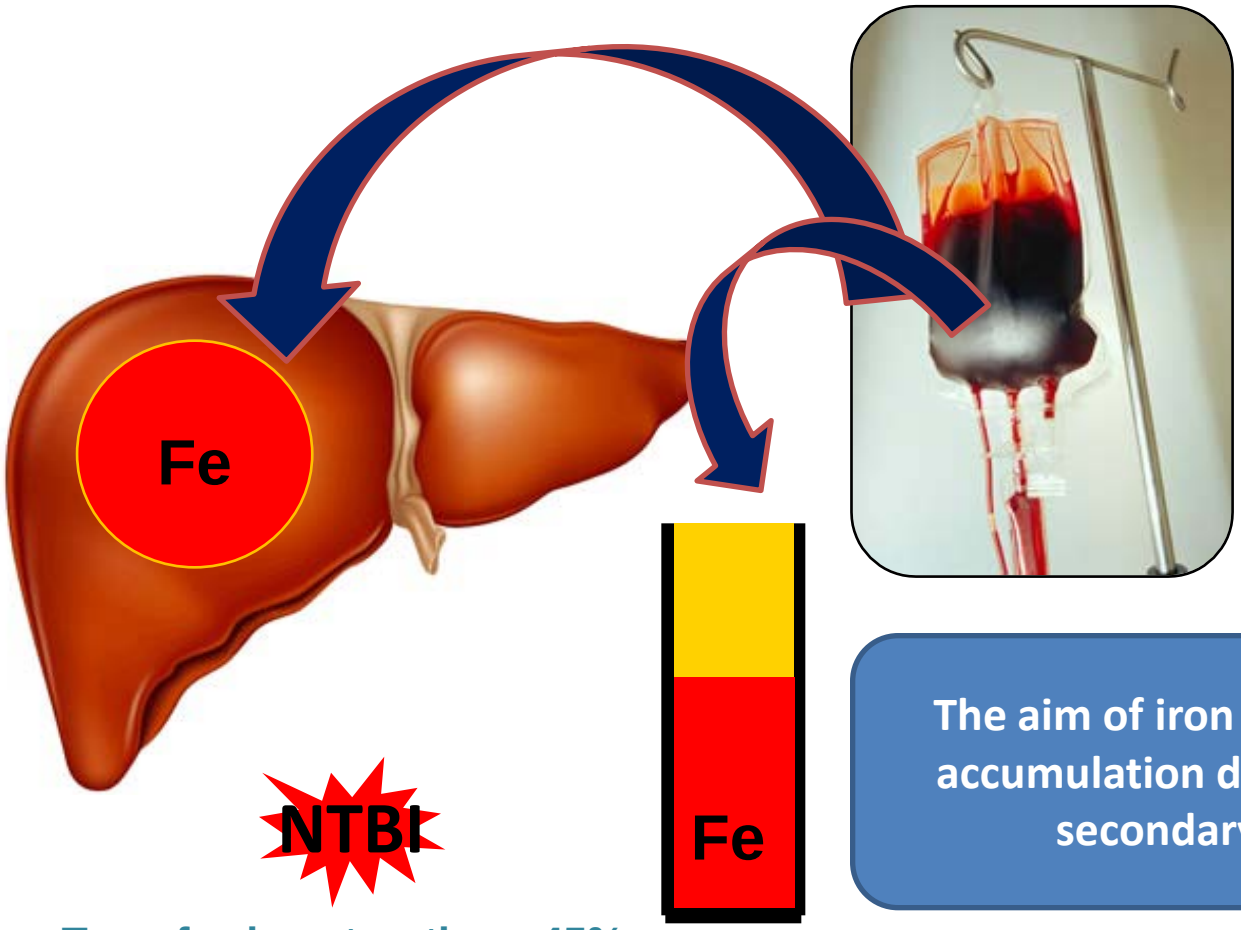
Disclosure

- Member of advisory board for:
  - Novartis
  - Sanofi Genzyme
  - Celgene

Mechanism of iron loading and toxicity

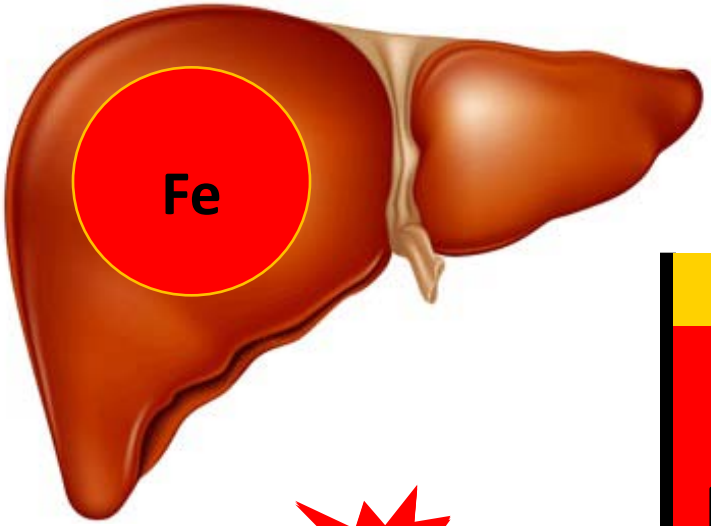


Transferrin saturation >45%

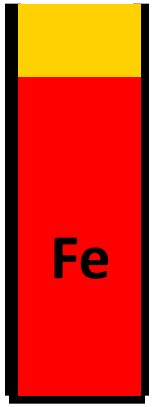
The aim of iron chelation is to control iron accumulation during iron loading to avoid secondary distribution of iron

Loréal O *et al. J Hepatol* 2000;32:727–733

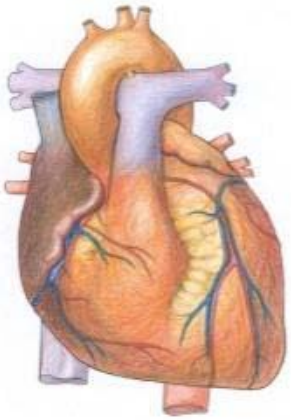
Mechanism of iron loading and toxicity

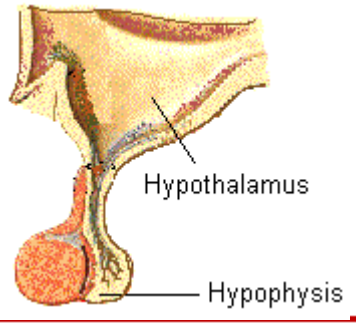


LPI



Transferrin saturation >75%





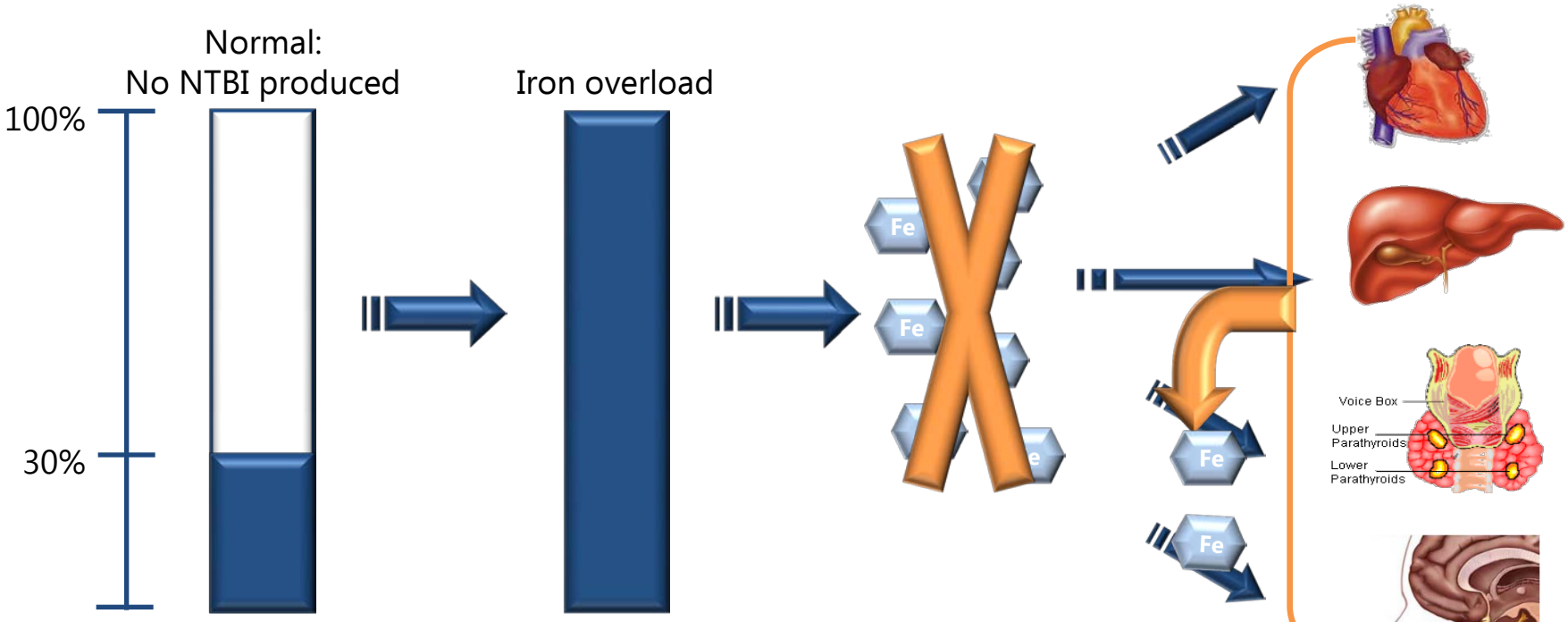
Loréal O *et al. J Hepatol* 2000;32:727–733; Hershko C. *Ann N Y Acad Sci* 2010;1202:1–9.

Preventing iron accumulation prevents organ damage

Transferrin saturation due to frequent blood transfusions

Subsequent formation of NTBI in plasma

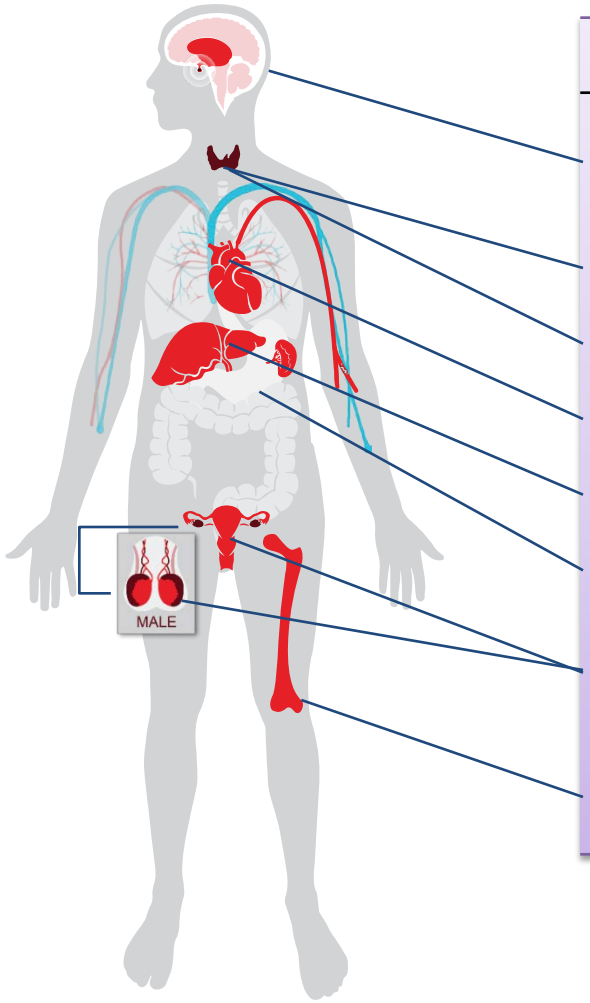
Uncontrolled iron loading of organs



Once iron overload has occurred, removal of excess storage iron is slow

1. Daar S *et al. Haematologica* 2006;91:abst 31. ESCALATOR sub-group; Cross-sectional study; n=14.
2. Cappellini MD *et al*. Blood 2006;107:3455–3462. Randomized, multinational Phase III study; n=586.
3. Cabantchik ZI *et al. Blood* 2005;106:abst 824. *In vitro* study.

Organ systems affected by transfusional iron overload



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. Review.
2. Ebrahimpour L *et al. Hematology* 2012;17:297–301 . Prospective cross-sectional study; n=80.
3. Oudit GY *et al. Nat Med* 2003;9:1187–1194. Animal study.

OUTLINE

1. Goals of iron chelation therapy
2. Achieve iron balance
3. Remove excess iron
4. Continuous protection from NTBI/LPI

Goals of chelation therapy

- ✓ **Achieve iron balance**
  - Balance iron intake and excretion
- ✓ **Remove excess iron**
  - Prevent iron overload in organs
- ✓ **Provide continuous protection from the effects of (labile) toxic iron**
  - Prevent organ damage as a result of toxic effects of labile iron

Principles of chelation therapy

- Prevention
  - Balance input and output
  - Achieve harmless levels of body iron safely
- Rescue
  - Patients with high levels of body iron
  - Patients with high levels of myocardial iron
  - Patients with heart dysfunction

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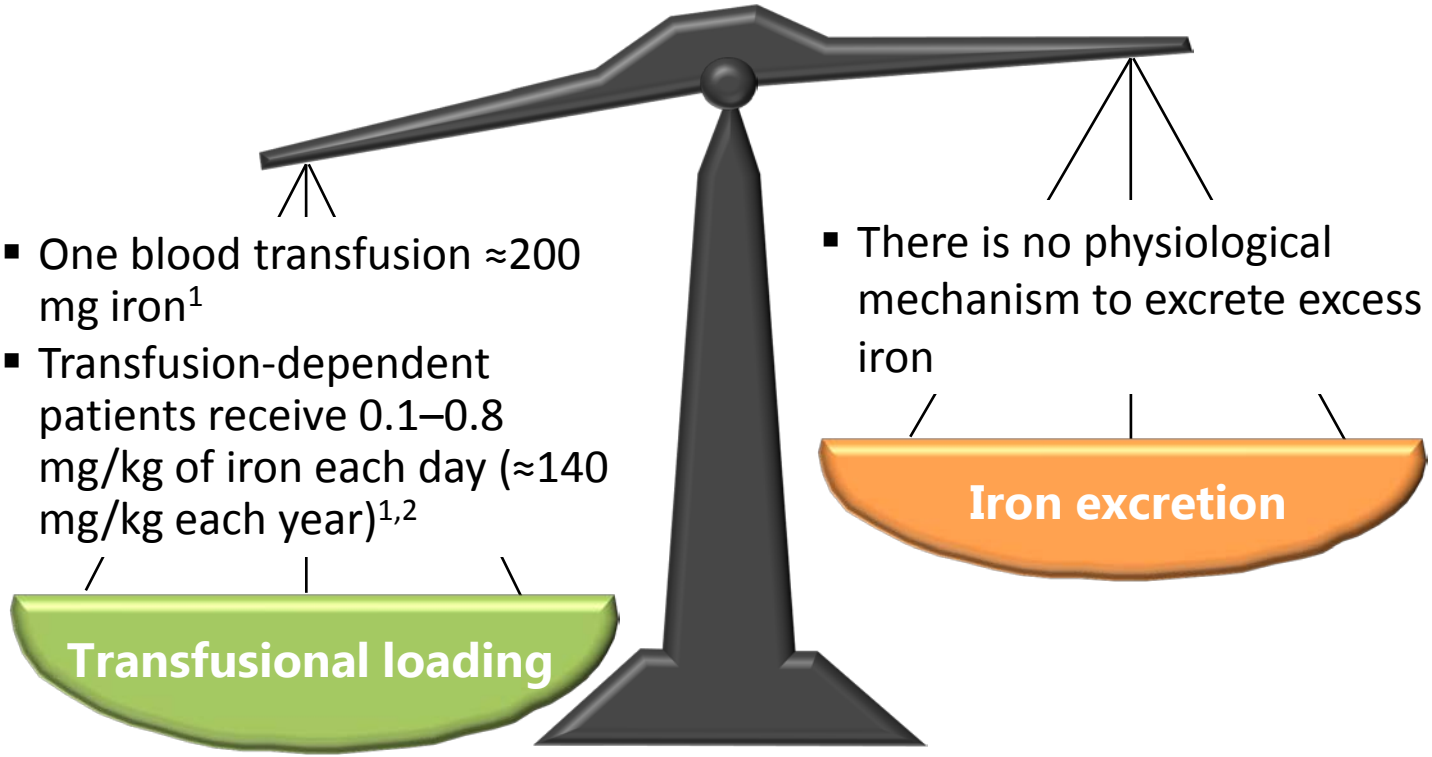
Iron balance is achieved when iron excretion equals iron accumulation



0.4–0.5 mg/kg daily iron excretion is required in order to achieve iron balance in a transfusion-dependent individual[3]

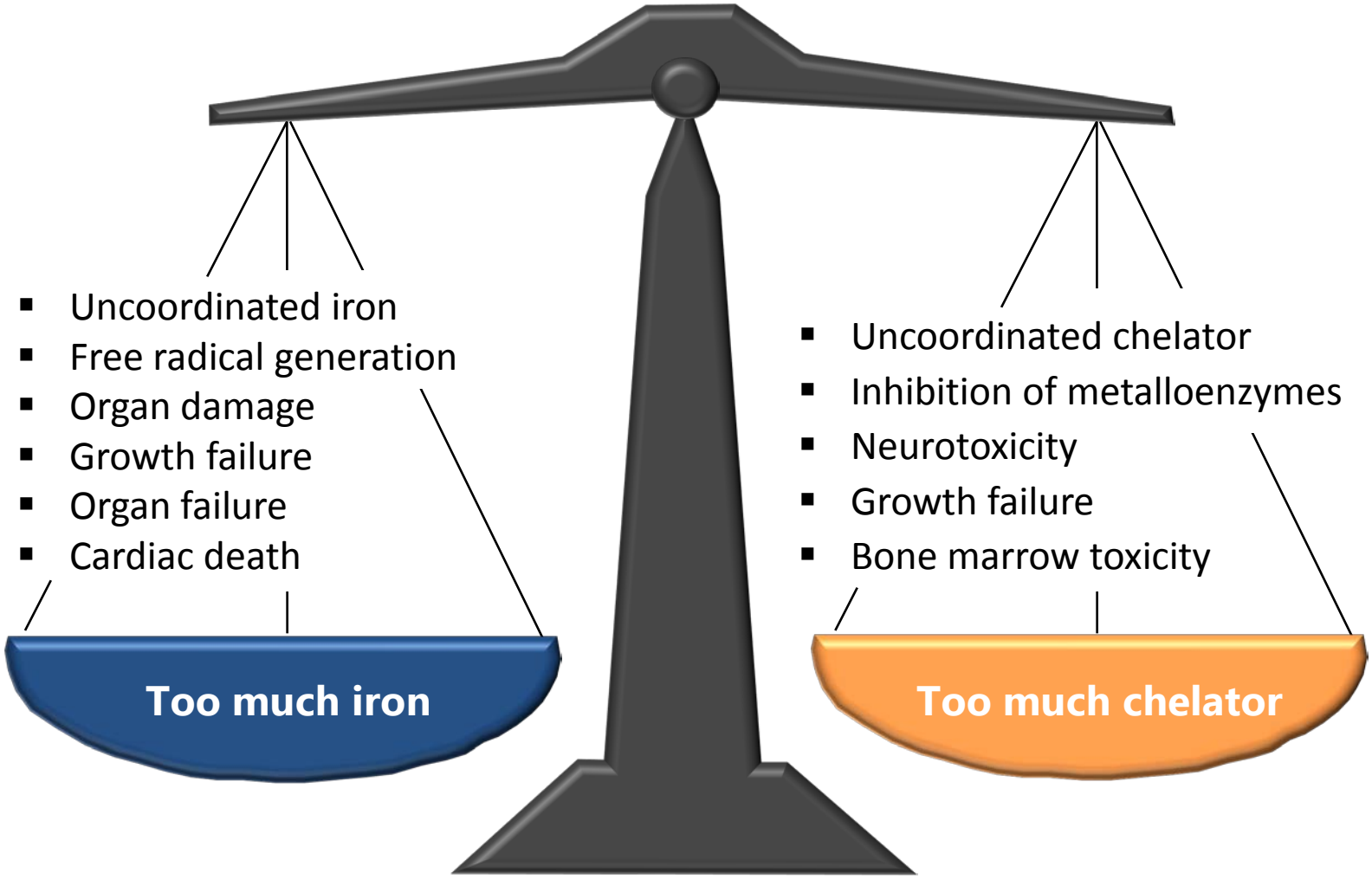
1. Porter JB. *Br J Haematol* 2001;115:239–252. Review.
2. Cohen A *et al. Blood* 2008;111:583–587. Multicenter, randomized, open-label, Phase III study; n=541.
3. Kushner JP *et al. Hematology Am Soc Hematol Educ Program* 2001;47–61. Review.

Iron balance can be achieved with chelation therapy

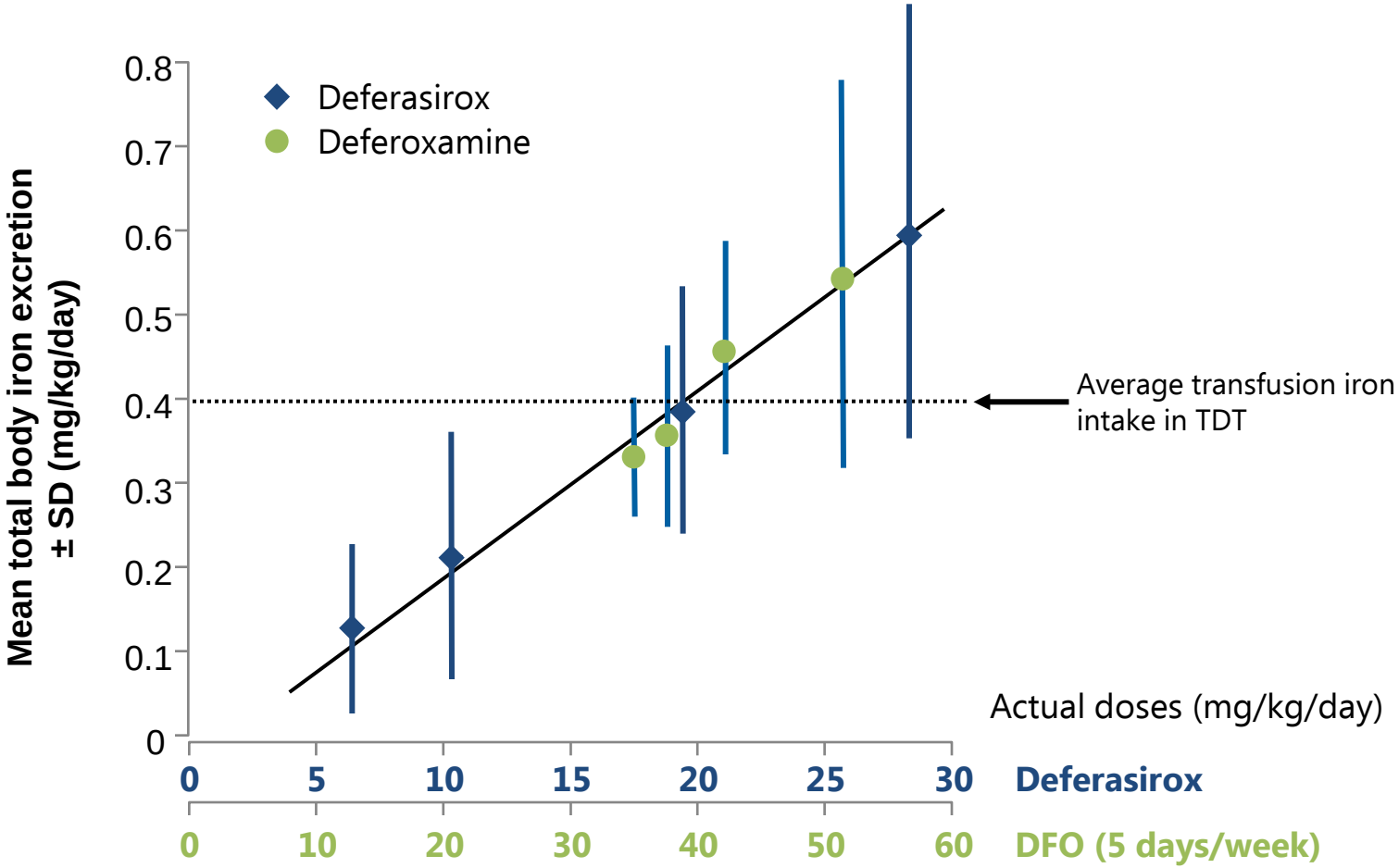
- Response to chelation therapy is affected by chelator dose and transfusional iron intake
- Iron balance can be achieved by selecting the right dose of chelator for a given transfusional iron loading rate

Cohen AR *et al*. Blood 2008;111:583–587. Multicenter, randomized, open-label, Phase III study; n=541.

The challenge of iron chelation: a question of balance



Iron balance can be achieved by adjusting chelator dose



DFO, deferoxamine; SD, standard deviation; TDT, transfusion-dependent thalassemia

Cohen AR *et al. Blood* 2008;111:583–587. Multicenter, randomized, open-label, Phase III study; n=541.

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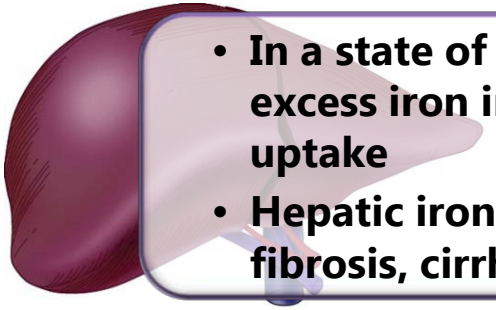
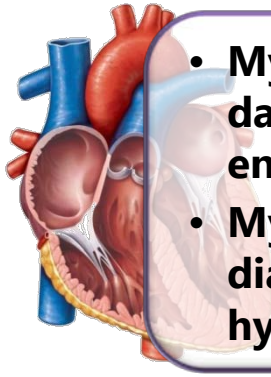
Excess iron is stored in organs and can result in serious complications



- In a state of iron overload, the liver is a major site of iron storage; excess iron initially fills the liver through transferrin-mediated uptake
- Hepatic iron overload can lead to serious complications such as fibrosis, cirrhosis and hepatocellular carcinoma

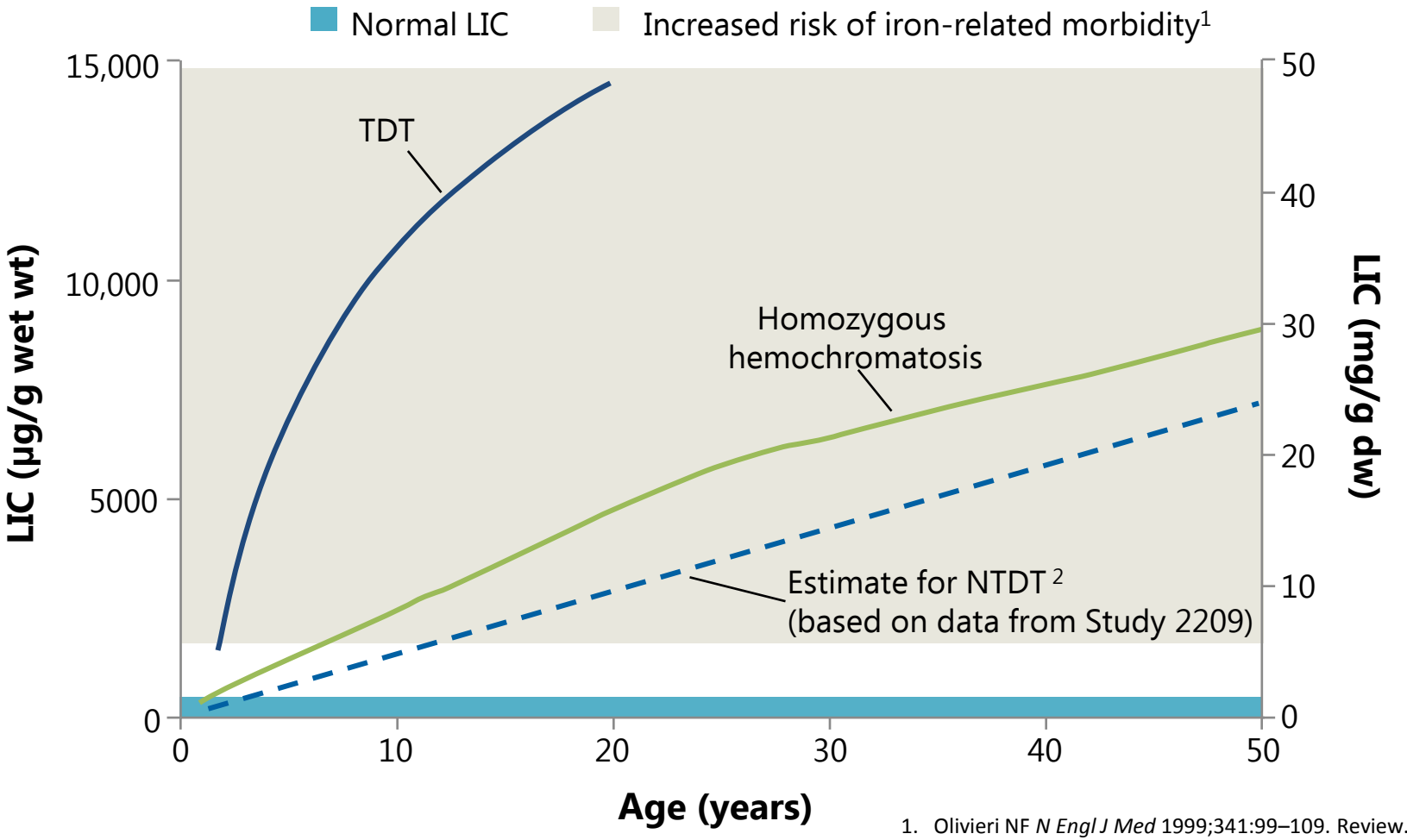
Iron loading occurs in parallel in different organ systems (including the liver, heart and endocrine glands) at different rates due to organ-specific mechanisms of iron uptake



- Myocardial iron overload can affect heart function by causing direct damage to myocytes, as well as iron-mediated effects on vascular and endocrine functions
- Myocardial iron overload can lead to left ventricular systolic and diastolic, dysfunction, pulmonary hypertension, valvulopathies, arrhythmias and pericarditis

Maakaron JE *et al. Ann Hepatol* 2013;12:142–146. Case study.
Isma'eel H *et al. Br J Cardiol* 2008;15:40–46. Review.
Noetzli LJ *et al. Blood* 2008;112:2973–2978. Longitudinal observational study; n=38.

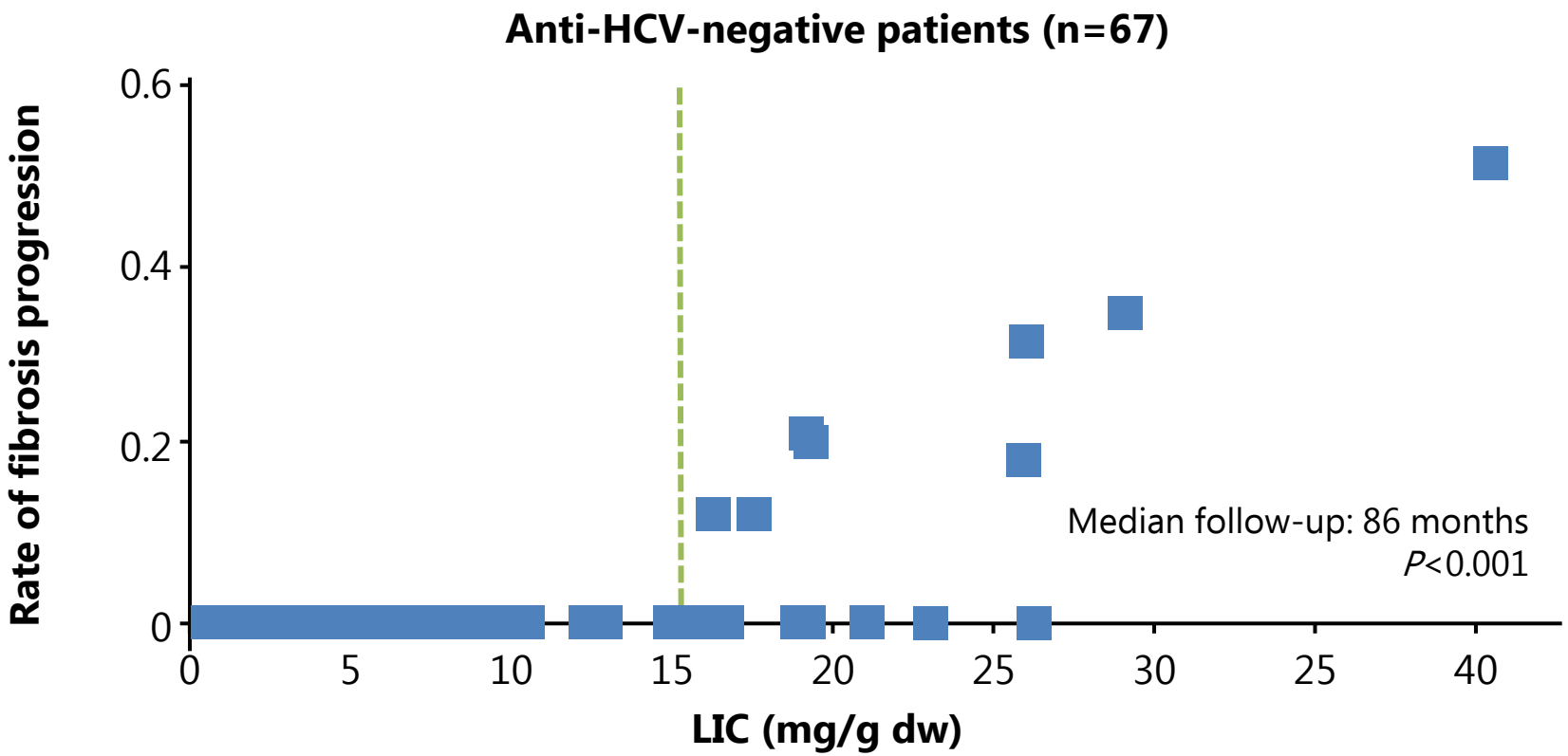
Liver iron load above 7 mg/g dw increases the risk of complications in TDT



dw, dry weight; LIC, liver iron concentration; NTDT, non-transfusion-dependent thalassemia

1. Olivieri NF *N Engl J Med* 1999;341:99–109. Review.
2. Taher AT *et al. Blood* 2012;120:970–977. THALASSA; Prospective, randomized, double-blind, placebo-controlled study; n=166.

Liver iron is an independent risk factor for liver fibrosis progression

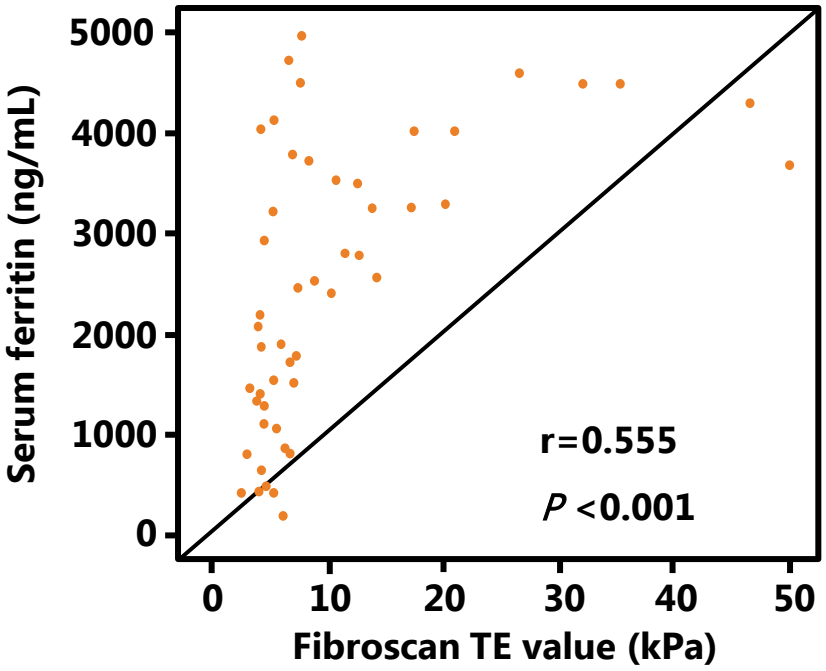


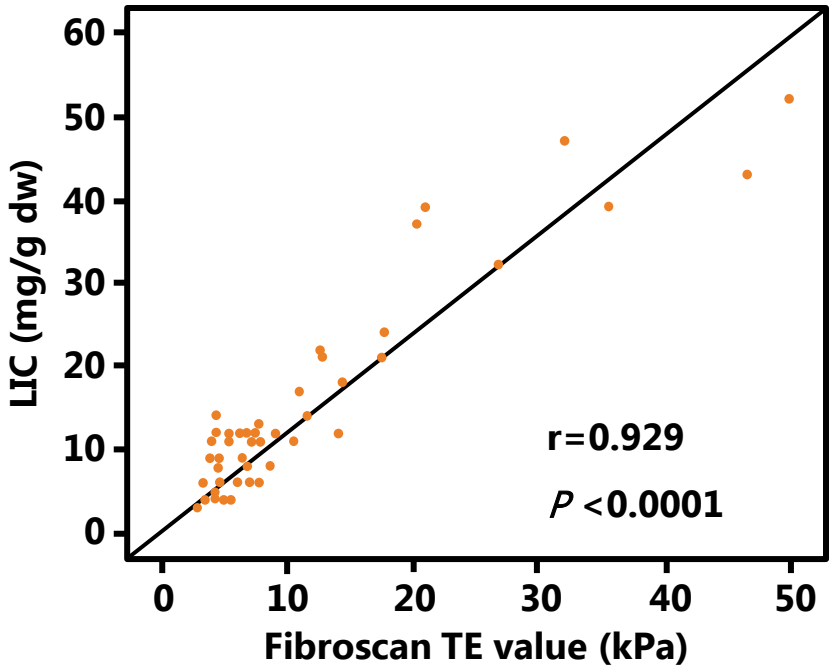
High liver iron (median [IQR], 19.2 [12.8–40.6] mg/g dw) was a significant predictor of fibrosis progression

HCV, hepatitis C virus; IQR, interquartile range

Angelucci E *et al. Blood* 2002;100:17–21. Prospective cohort study; n=233.

Liver iron load is positively correlated with cirrhosis and liver fibrosis





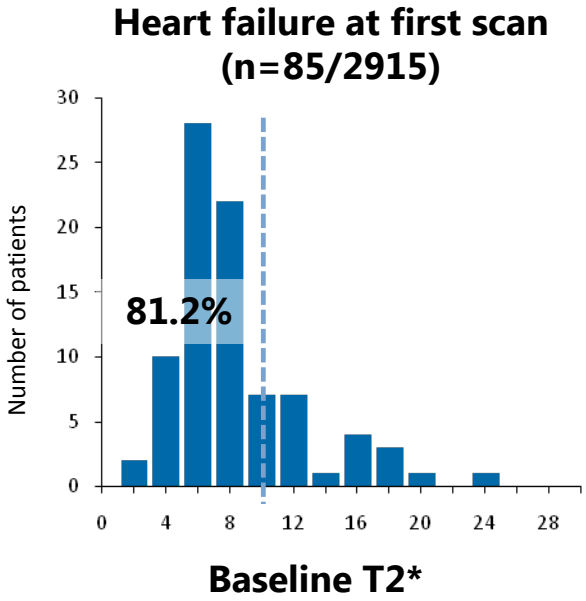
Liver fibrosis and cirrhosis were defined as Fibroscan TE value >6.0 kPa and 12.5 kPa, respectively.

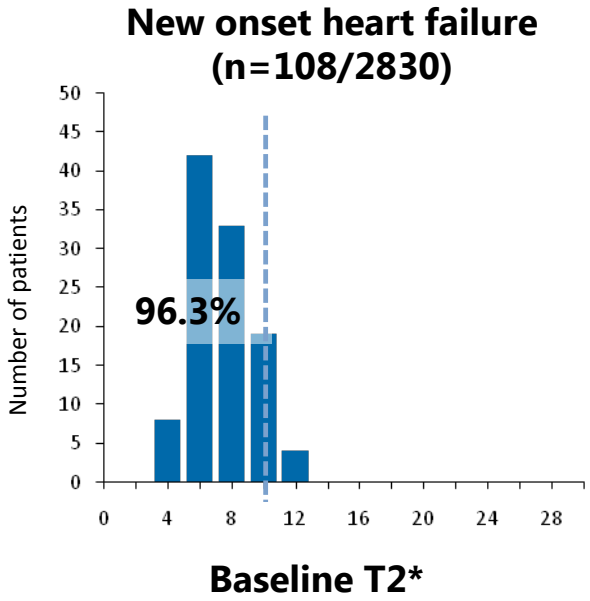
Liver cirrhosis and variable degrees of liver fibrosis are encountered in up to 35% of HCV-positive β thalassemia major patients

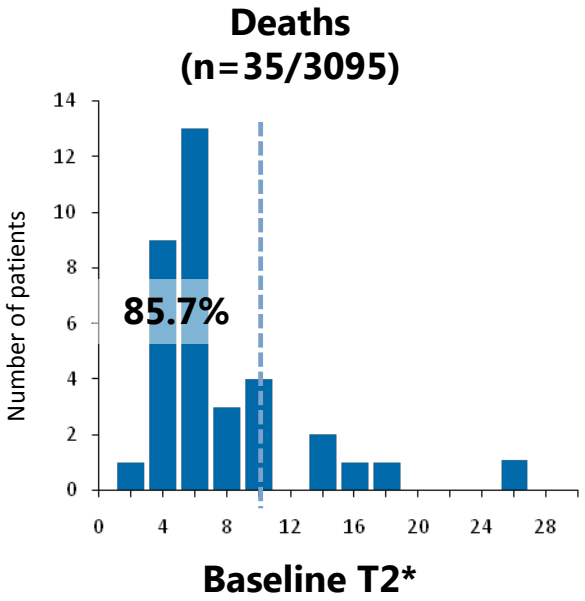
TE, transient elastography

Elalfy MS *et al. Ann Hepatol* 2013;12:54–61. Cross-sectional study; n=51.

High myocardial iron is strongly associated with heart failure and death





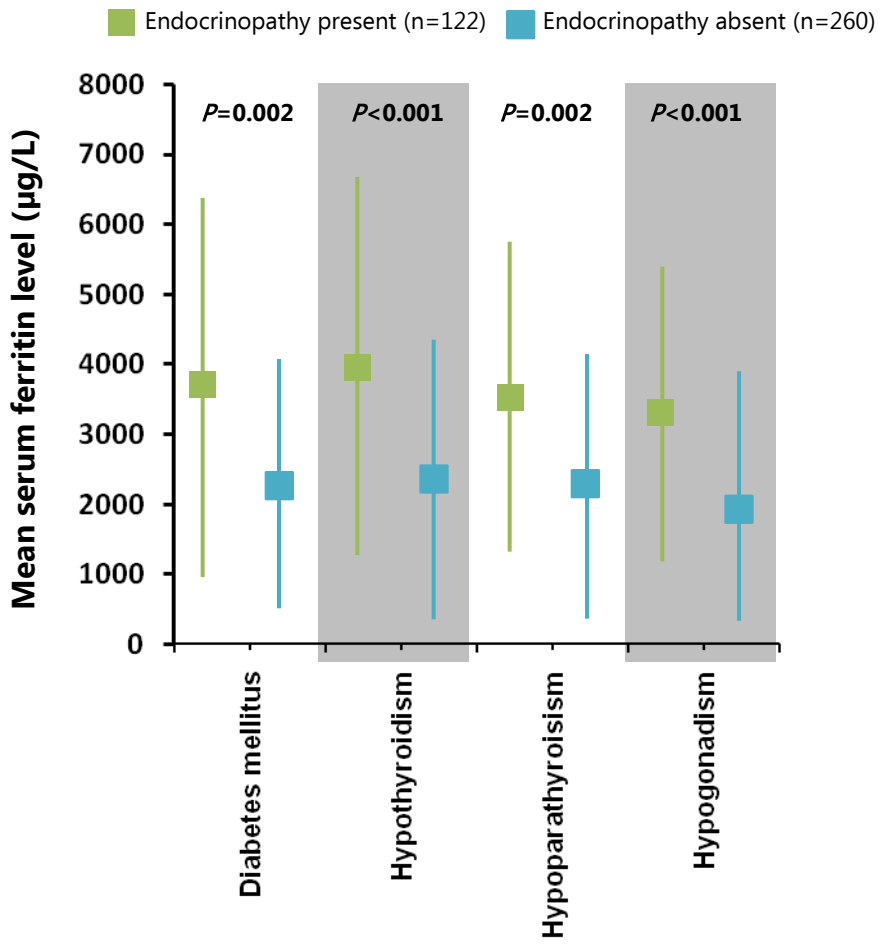


Myocardial iron loading Baseline T2* value	Severe ≤10 ms	Moderate 10 ms–≤20 ms	None >20 ms
Patients (n=3095)	20.6%	22.8%	56.6%

Over 80% of cardiac events occurred in patients with myocardial T2* <10 ms

Carpenter JP *et al. Haematologica* 2013;98:1368–1374.; MINT; Multicenter cross-sectional study; n=3095.

High serum ferritin levels are associated with endocrinopathies



Patients with serum ferritin >2500 ng/mL were:

- **3.53x more likely to have diabetes mellitus**
- **3.25x more likely to have hypothyroidism**
- **3.27x more likely to have hypoparathyroidism**
- **2.75x more likely to have hypogonadism**

…compared with patients with serum ferritin ≤1000 ng/mL

Belhoul KM *et al. Ann Hematol* 2012;91:1107–1114. Cross-sectional study; n=382.

OUTLINE

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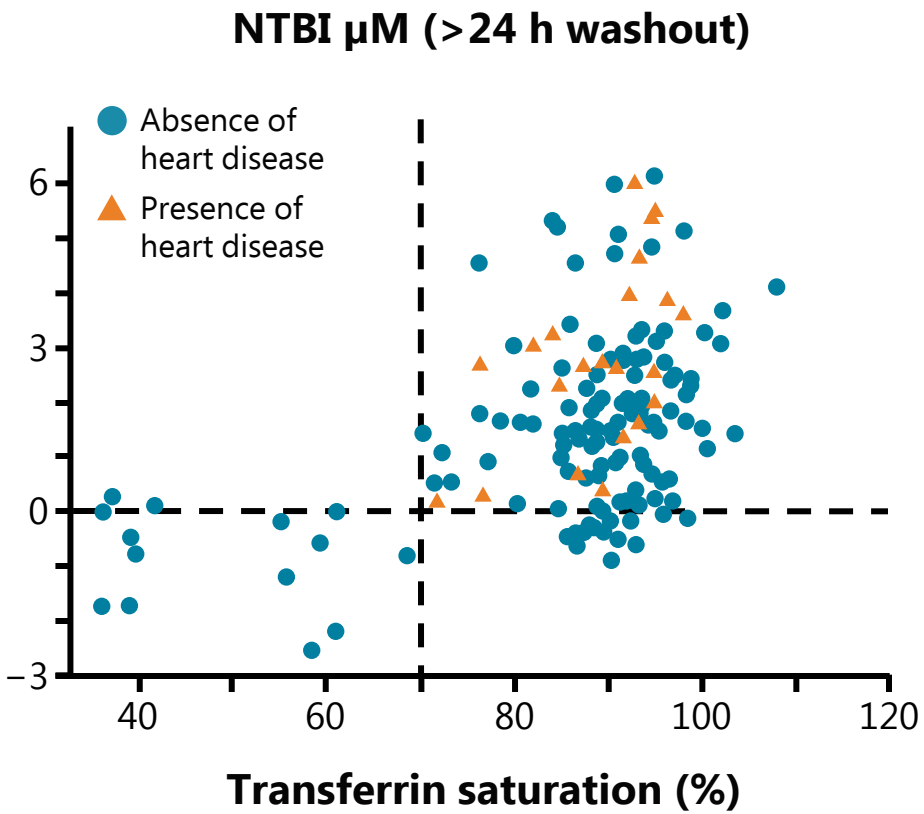
Iron overload leads to the formation of NTBI and LPI

- NTBI is found when transferrin approaches saturation[1]
- LPI is a chelatable redox-active component of NTBI[2]
- NTBI and LPI values correlate approximately with total body iron in TDT[3–6]
- LPI values may be increased by a high transfusional iron loading rate[7]

1. Hershko C and Peto TE. *Br J Haematol* 1987;66:149–151.
2. Cabantchik ZI *et al. Best Pract Res Clin Haematol*. 2005;18:277–287.
3. Porter JB *et al. Blood* 1996;88:705–714.
4. Al Refaie FN *et al. Br J Haematol* 1992;82:431–436.
5. Pootrakul P *et al. Blood* 2004;104:1504–1510.
6. Daar S *et al. Eur J Haematol*. 2009;82:454–457.
7. Porter JB *et al*. *Eur J Haematol* 2011;87:338–348.

NTBI appears when transferrin saturation exceeds 70%



All patients with iron toxicity-related cardiomyopathies have NTBI; however, the reverse is not the case

Piga A *et al*. *Am J Hematol* 2009;84:29–33. Multicenter, cross-sectional study; n=174.

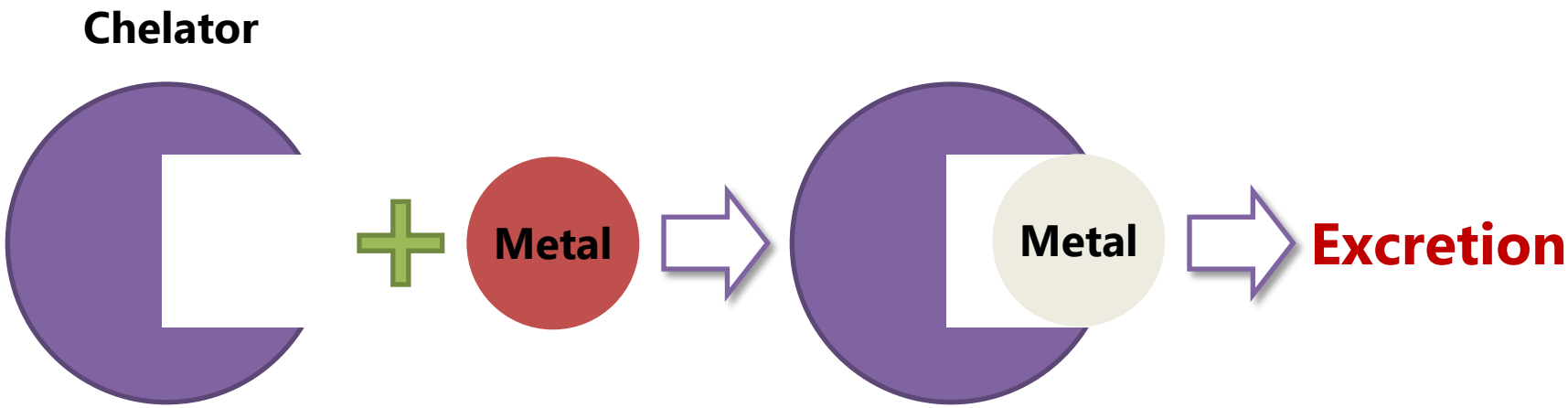
Continuous exposure to chelator protects tissue from NTBI and LPI

- Minimizes exposure to NTBI and LPI in tissues and plasma
- Continuous capture of iron released from
  - red cell catabolism in macrophages
  - ferritin catabolism (mainly in liver)
- Minimizes new cellular uptake of NTBI

Cabantchik ZI *et al. Best Pract Res Clin Haematol* 2005;18:277–287. Review.
Porter JB. *Am J Hematol* 2007;82:1136–1139. Review.

What is chelation therapy?

- Iron chelators reduce body iron by complexing and enabling excretion of **free iron**



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

Summary

- The main goal of chelation therapy is to balance iron input and output to achieve harmless levels of body iron
- Chelation therapy can prevent, and in some cases reverse, complications caused by excess iron
- Continuous exposure to iron chelator protects tissue from toxic iron