UKD Universitätsklinikum Düsseldorf

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Hämatologie heute, Ulm, 24. April 2015

# Erkrankungen mit sekundärer Eisenüberladung

Norbert Gattermann

Klinik für Hämatologie, Onkologie und Klinische Immunologie

Heinrich-Heine-Universität Düsseldorf

UTZ Universitätstumorzentrum Düsseldorf
Comprehensive Cancer Center

Als Onkologisches Spitzenzentrum gefördert durch die Deutsche Krebshilfe e.V.

# Eisenüberladung

## Hereditäre Ursachen

- Verschiedene Typen der hereditären Hämochromatose (HH)
- Gestörter Eisentransport
- Ineffektive Erythropoese („iron loading anemia“)

  → verstärkte intestinale Eisenresorption

## Erworbene Ursachen

- Ineffektive Erythropoese
- Chronische Transfusionsbehandlung

# Eisenüberladung

## Hereditäre Ursachen

- Verschiedene Typen der hereditären Hämochromatose (HH)
- Gestörter Eisentransport
- Ineffektive Erythropoese („iron loading anemia“)
  → verstärkte intestinale Eisenresorption

## Erworbene Ursachen

- Ineffektive Erythropoese
- Chronische Transfusionsbehandlung

**Sekundäre Hämochromatose**

# Eisenüberladung

## Hereditäre Ursachen

- Verschiedene Typen der hereditären Hämochromatose (HH)
- Gestörter Eisentransport
- Ineffektive Erythropoese („iron loading anemia“)
  → verstärkte intestinale Eisenresorption

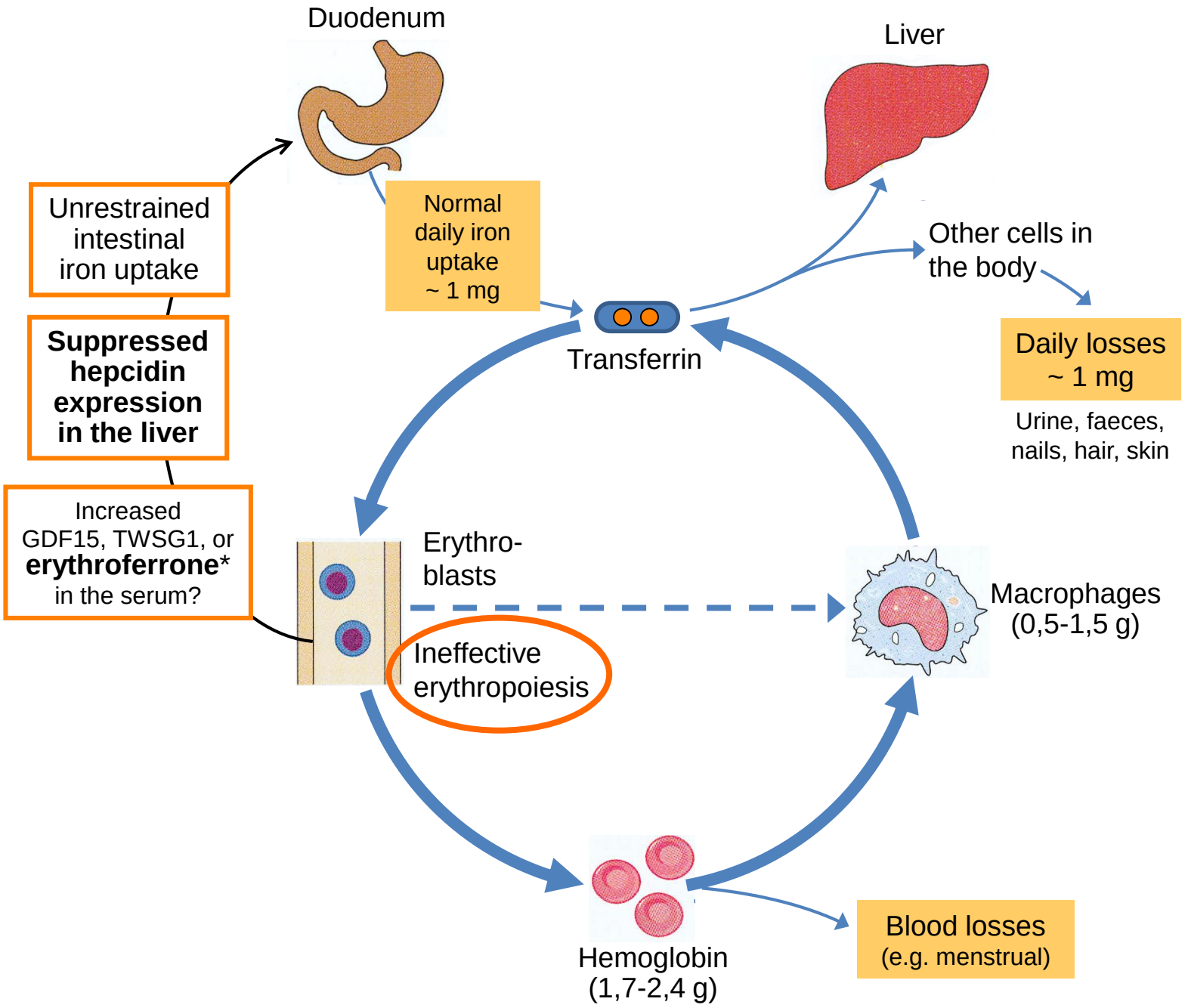
## Erworbene Ursachen

- Ineffektive Erythropoese
- Chronische Transfusionsbehandlung

Thalassämie (NTDT)
kongen. sideroblast. Anämie
kongen. dyserythropoetische A.

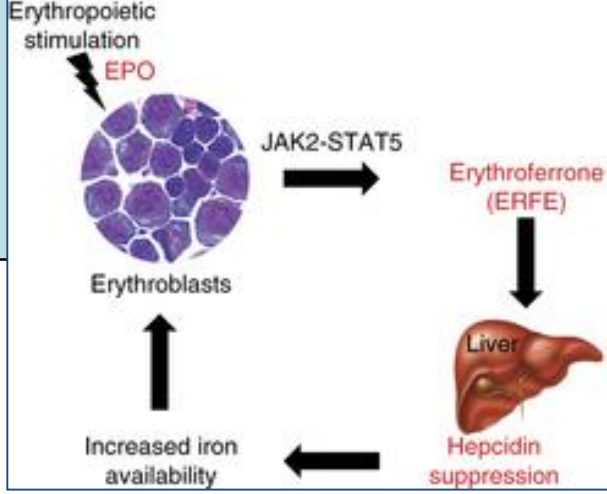
**Sekundäre Hämochromatose**

Myelodysplastische Syndrome




* Kautz et al., Nat Genetics 2014

# Erythroferrone




Nat Genet. 2014 Jul;46(7):678-84. doi: 10.1038/ng.2996. Epub 2014 Jun 1.

## Identification of erythroferrone as an erythroid regulator of iron metabolism.

Kautz L[1], Jung G[1], Valore EV[1], Rivella S[2], Nemeth E[1], Ganz T[3].

Author information

### Abstract

Recovery from blood loss requires a greatly enhanced supply of iron to support expanded erythropoiesis. After hemorrhage, suppression of the iron-regulatory hormone hepcidin allows increased iron absorption and mobilization from stores. We identified a new hormone, erythroferrone (ERFE), that mediates hepcidin suppression during stress erythropoiesis. ERFE is produced by erythroblasts in response to erythropoietin. ERFE-deficient mice fail to suppress hepcidin rapidly after hemorrhage and exhibit a delay in recovery from blood loss. ERFE expression is greatly increased in Hbb(th3/+) mice with thalassemia intermedia, where it contributes to the suppression of hepcidin and the systemic iron overload characteristic of this disease.

**Table 1. Heritable Forms of Systemic Iron Overload According to the Pathophysiological Defect.***

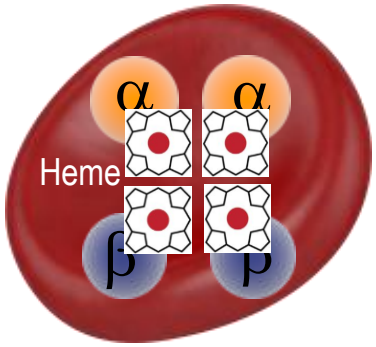
| Disorder | Gene and Inheritance | Age at Presentation | Neurologic Symptoms | Anemia | Transferrin Saturation |
|---|---|---|---|---|---|
| **Impaired hepcidin–ferroportin axis** | | | | | |
| HH type I | *HFE*, AR | Adult | No | No | High |
| HH type IIA | *HFE2*, AR | Child to young adult | No | No | High |
| HH type IIB | *HAMP*, AR | Child to young adult | No | No | High |
| HH type III | *TFR2*, AR | Young adult | No | No | High |
| HH type IVA (atypical HH) | *FP* (LOF), AD | Adult | No | Variable | Low initially |
| HH type IVB | *FP* (GOF), AD | Adult | No | No | High |
| **Impaired iron transport** | | | | | |
| Inadequate release to erythron: aceruloplasminemia | *CP*, AR | Adult | Yes | Yes | Low |
| Inadequate uptake by erythron | | | | | |
| DMT1 mutations | *DMT1*, AR | Child | No | Yes | High |
| Hypotransferrinemia | *TF*, AR | Variable | No | Yes | High |
| **Ineffective erythropoiesis** | | | | | |
| Thalassemia | *Globin*, AR | Child | No | Yes | High |
| Congenital sideroblastic anemia | *ALAS2*, XL; *SLC25A38*, AR; *GLRX5*, AR; *ABCB7*, XL | Variable | *ALAS2* and *SLC25A38*: no; *GLRX5* and *ABCB7*: yes | Yes | High |
| Congenital dyserythropoietic anemia | | | | | |
| Type I | *DAN1*, AR | Child | No | Yes | High |
| Type II | *SEC23B*, AR | Child | No | Yes | High |
| Type III | Unknown, AD | Child | No | Yes | High |

* AD denotes autosomal dominant, AR autosomal recessive, GOF gain of function, HH hereditary hemochromatosis, LOF loss of function, and XL X-linked.

Fleming & Ponka, NEJM 2012

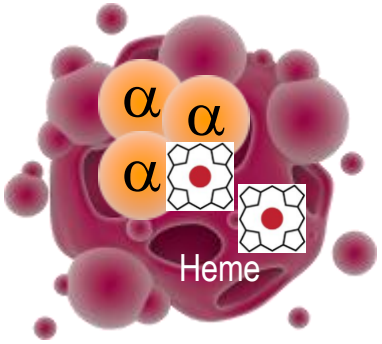
# β-thalassemia

**Adult Hb**




**Mutations that reduce β-globin synthesis**

**Hemichromes and ROS**




In β-thalassaemia, a relative excess of α-globin synthesis leads to formation of hemichromes (α-globin/heme aggregates).

Hemichromes are the primary cause of cellular toxicity in β-thalassemia because they precipitate and lodge on erythrocyte membranes, altering their structure.

Furthermore, excess heme leads to the formation of reactive oxygen species (ROSs), which induce oxidative stress and cellular damage.

In turn, this leads to IE by increasing apoptosis of erythroid precursors and reducing the number of erythrocytes produced as well as their survival in circulation.

Modified from: Ginzburg Y, Rivella S. Blood. 2011;118:4321-30.

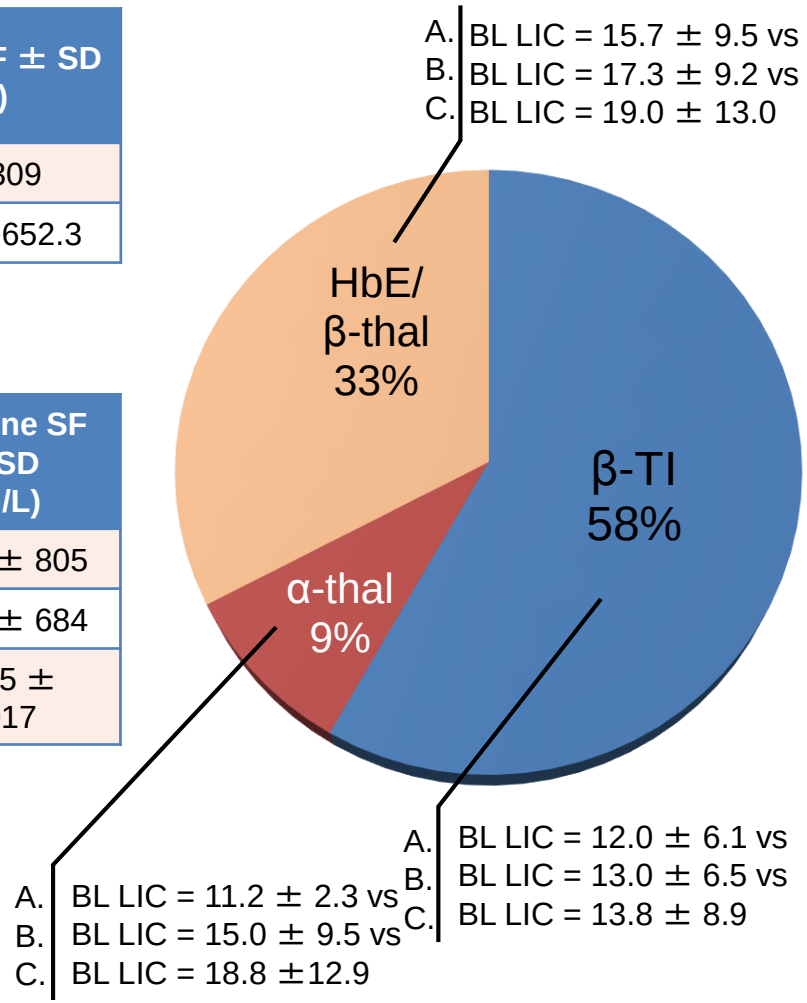
# IOL is more prevalent in NTDT than expected

| Study | Population (n) | Baseline LIC ± SD (mg Fe/g dry wt) | Baseline SF ± SD (µg/L) |
|---|---|---|---|
| Origa et al. 2007[1] | 22 | 11.3 ± 6 | 627 ± 309 |
| Taher et al. 2010[2] | 19 | 15.0 ± 7.4 | 1,316.8 ± 652.3 |

Taher et al. 2012[3] – THALASSA (n = 166)

| Group | Treatment | Population (n) | Baseline LIC ± SD (mg Fe/g dry wt) | Baseline SF ± SD (µg/L) |
|---|---|---|---|---|
| A. | DFX 5[a] | 55 | 13.11 ± 7.29 | 1,141 ± 805 |
| B. | DFX 10[a] | 55 | 14.56 ± 7.92 | 1,174 ± 684 |
| C. | Placebo[a] | 56 | 15.94 ± 10.85 | 1,305 ± 1,017 |

**THALASSA population[4]**



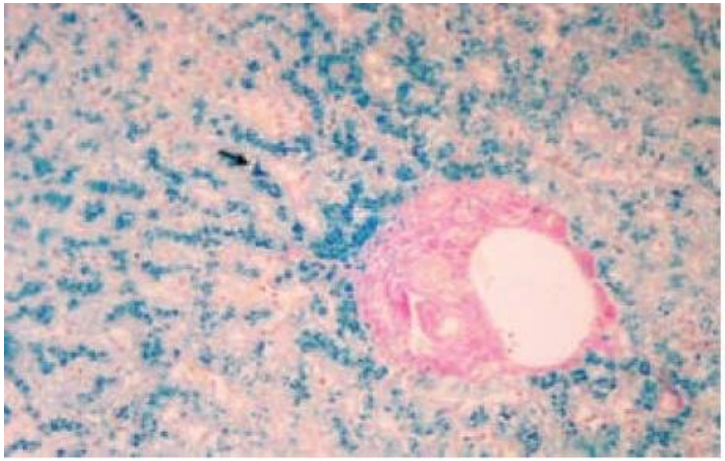


1. Origa R, et al. Haematologica. 2007;92:583-8.
2. Taher A, et al. Am J Hematol. 2010;85:288-90
3. Taher A, et al. Blood. 2012;120:970-7.
4. Taher A, et al. Am J Hematol. 2013;88:503-6

# Liver histology in NTDT and TDT demonstrates different origin and distribution of iron

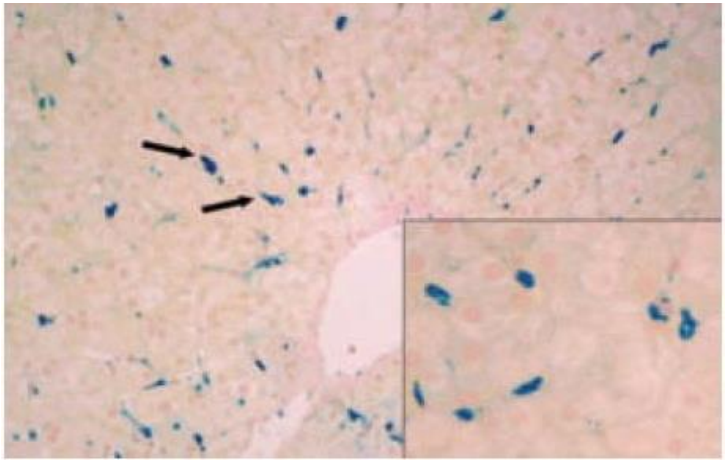
- Hepcidin deficiency allows high iron egress from macrophages
- Also, increased GI iron absorption, oversaturation of transferrin, and accumulation of NTBI lead to predominantly parenchymal IOL

**NTDT**



Preferential periportal and hepatocyte iron loading
(with rare Kupffer cells – arrow)
Low hepcidin → iron release from macrophages

**TDT**



RES distribution
(mainly in Kupffer cells – arrows)


- Origa R, et al. Haematologica. 2007;92:583-8.
- Taher AT, et al. Br J Haematol. 2011;152:512-23.

# Eisenüberladung

## Hereditäre Ursachen

- Verschiedene Typen der hereditären Hämochromatose (HH)
- Gestörter Eisentransport
- Ineffektive Erythropoese („iron loading anemia“)
  → verstärkte intestinale Eisenresorption

## Erworbene Ursachen

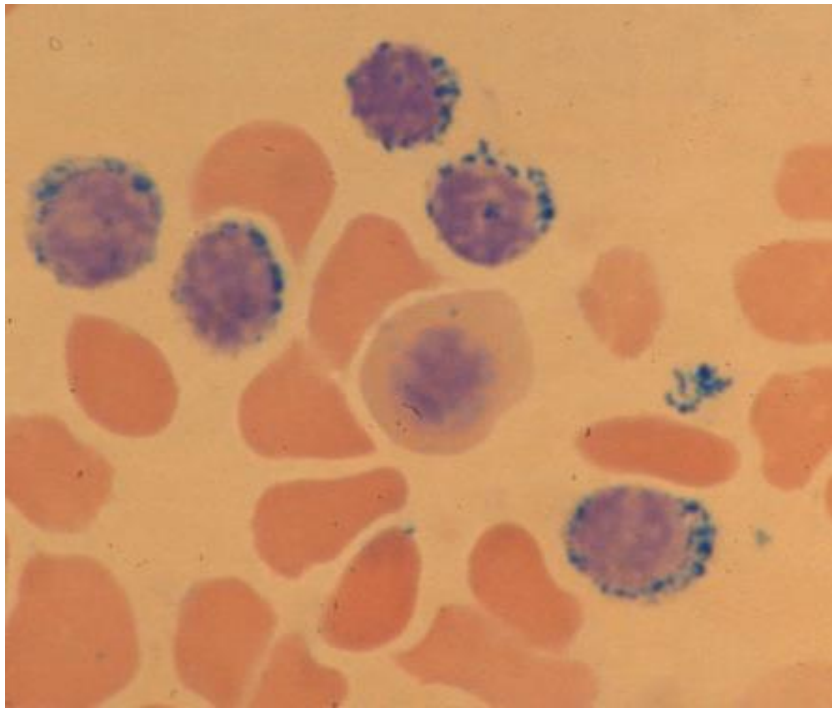
- Ineffektive Erythropoese
- Chronische Transfusionsbehandlung

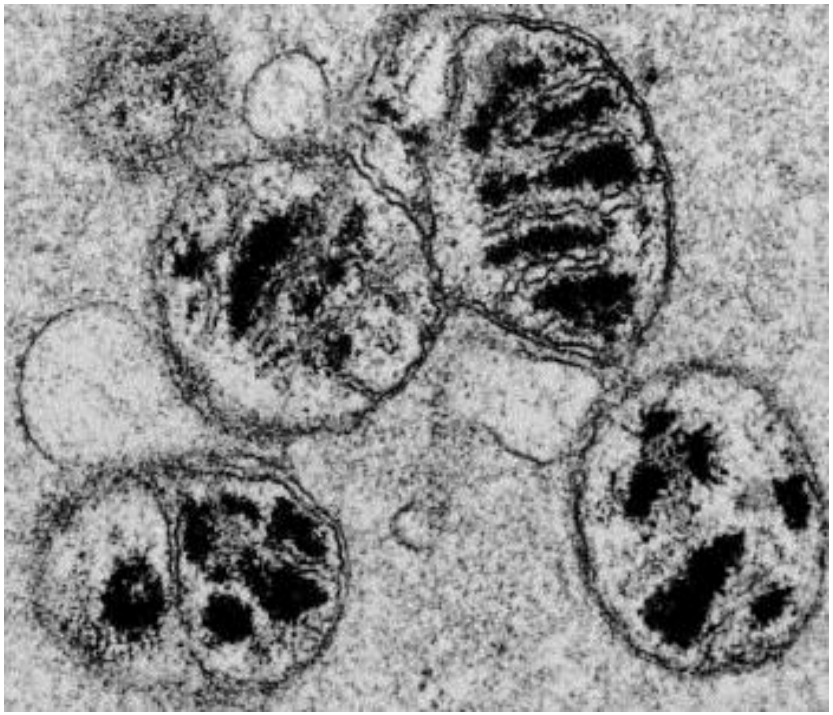
Thalassämie (NTDT)
kongen. sideroblast. Anämie
kongen. dyserythropoetische A.

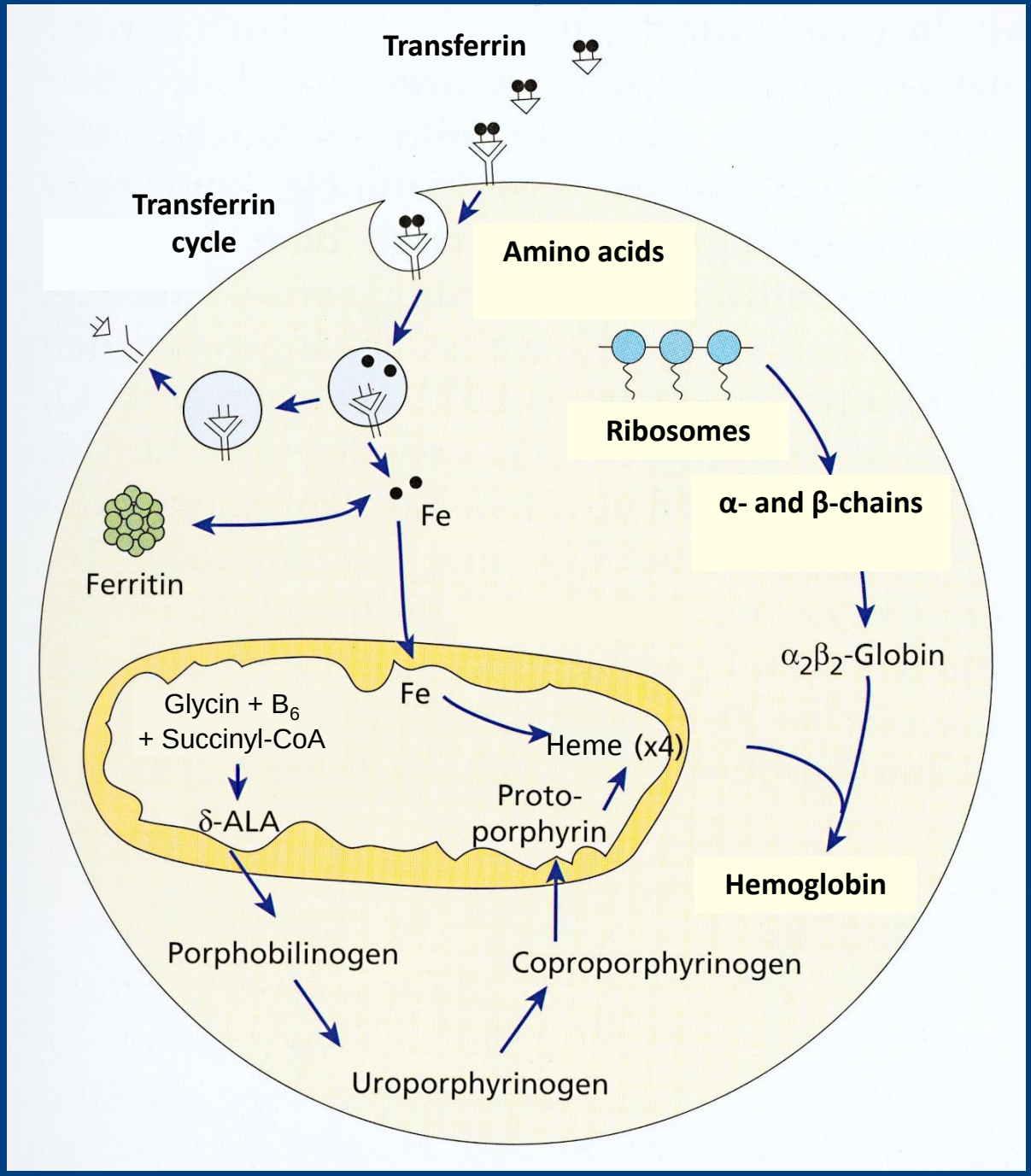
**Sekundäre Hämochromatose**

Myelodysplastische Syndrome

# The hallmark of sideroblastic anemia: Erythroblasts with mitochondrial iron overload



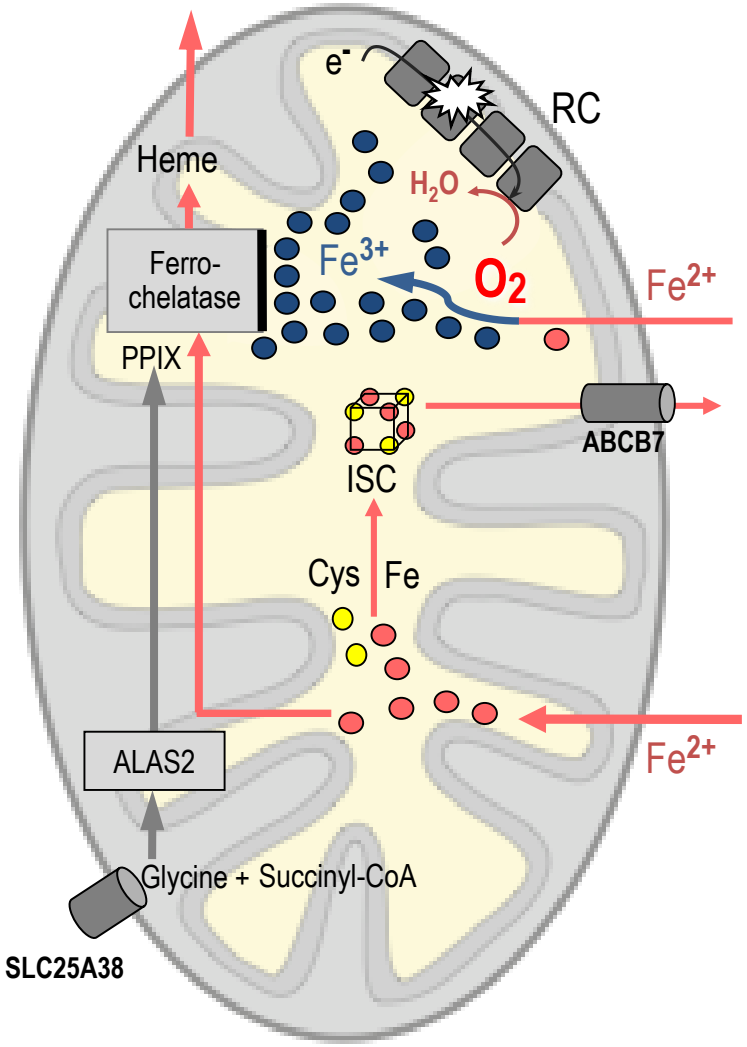



Transferrin
Transferrin cycle
Amino acids
Ribosomes
α- and β-chains
Fe
Ferritin
$\alpha_2\beta_2$-Globin
Glycin + $B_6$ + Succinyl-CoA
Fe
Heme (x4)
δ-ALA
Proto-porphyrin
Hemoglobin
Porphobilinogen
Coproporphyrinogen
Uroporphyrinogen

| Condition | Molecular basis | Clinical features |
|---|---|---|
| **Non-syndromic congenital sideroblastic anemias** | | |
| X-linked sideroblastic anemia (XLSA) (MIM ID # 300751) | Germline mutation in the erythroid-specific ALA synthase gene (*ALAS2*, chromosome Xp11.21) | Hemizygous males have hypochromic microcytic anemia due to ineffective erythropoiesis and secondary iron overload (iron-loading anemia). Heterozygous females may have minor red cell abnormalities (in particular, increased red cell distribution width). Most patients are responsive to pyridoxine. |
| Autosomal recessive pyridoxine-refractory sideroblastic anemia (MIM ID #205950) | Germline mutations in the *SLC25A38* gene (chromosome 3p22.1) | Homozygous males and females have severe microcytic anemia that almost inevitably becomes transfusion-dependent. Heterozygous individuals have no hematologic phenotype. Conservative therapy includes regular red cell transfusion and iron chelation. Allogeneic stem cell transplantation represents the only curative treatment at present. |
| | Homozygous mutation in the *GLRX5* gene (chromosome 14q32) | The reported case regards a middle-aged male affected with pyridoxine-refractory sideroblastic anemia and iron overload. |
| **Hereditary syndromic conditions** | | |
| X-linked sideroblastic anemia and spinocerebellar ataxia (XLSA/A, MIM ID #301310) | Germline mutation in the *ABCB7* gene (chromosome Xq13.1-q13.3) | Hemizygous males have moderate hypochromic microcytic anemia and tend to develop non-progressive ataxia and incoordination early in life. |
| Myopathy, lactic acidosis and sideroblastic anemia (MLASA1, MIM ID #600462) | Homozygous germline mutation in the *PUS1* gene (chromosome 12q24.33) | Myopathy, lactic acidosis, and anemia (progressive exercise intolerance during childhood). |
| Myopathy, lactic acidosis and sideroblastic anemia (MLASA2, MIM ID #613561) | Homozygous germline mutation in the *YARS2* gene (chromosome 12p.11.21) | Myopathy, lactic acidosis, and anemia (progressive exercise intolerance during childhood). |
| Thiamine-responsive megaloblastic anemia (TRMA, MIM ID #249270) | Germline mutations in the *SLC19A2* gene encoding a thiamine transporter protein (chromosome 1q23.3) | Thiamine-responsive macrocytic anemia, diabetes mellitus, and sensorineural deafness. |
| Pearson marrow-pancreas syndrome (MIM ID #557000) | Mitochondrial DNA deletion | Refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction. |

Cazzola & Invernizzi, Haematologica 2011

# Pathophysiology of sideroblastic anemias

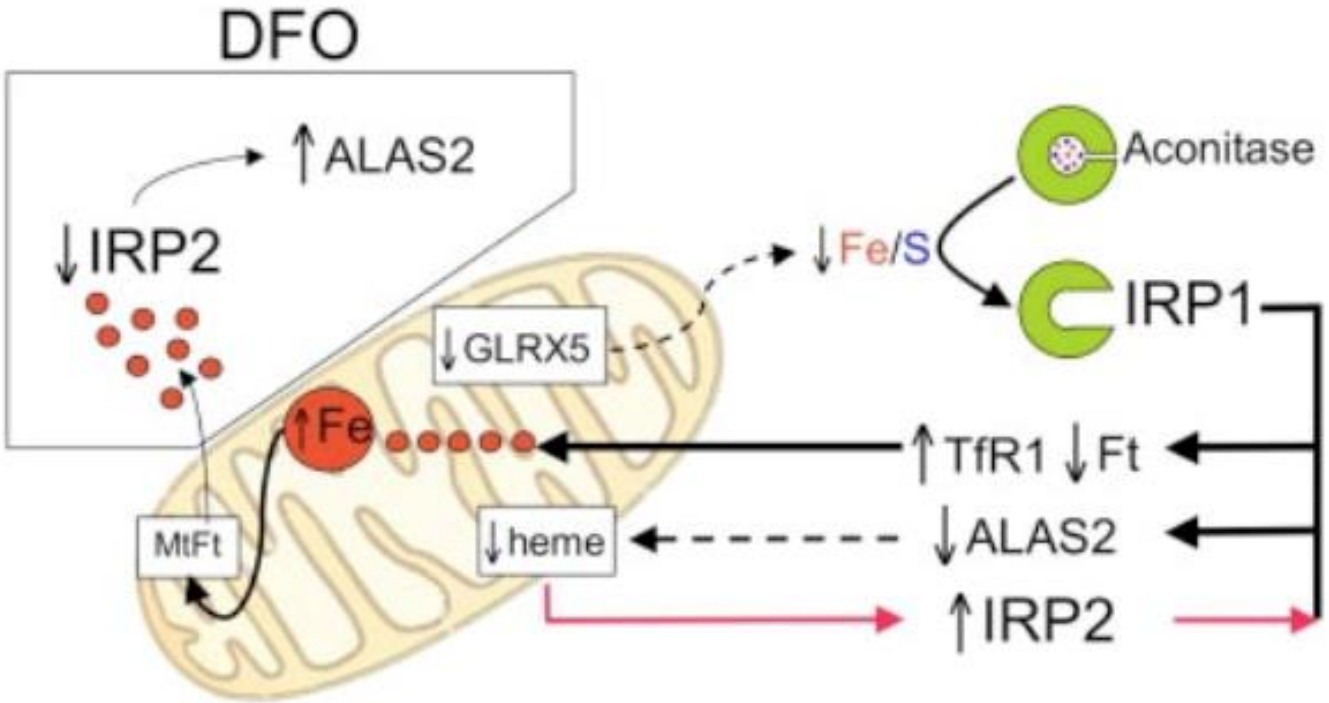


# The human counterpart of zebrafish *shiraz* shows sideroblastic-like microcytic anemia and iron overload

Clara Camaschella,[1,2] Alessandro Campanella,[1] Luigia De Falco,[4] Loredana Boschetto,[4] Roberta Merlini,[5] Laura Silvestri,[2] Sonia Levi,[1,2] and Achille Iolascon[3,4]

[1]Vita-Salute University and [2]Instituto di Ricerca e Cura a Carattere Scientifico (IRCCS) San Raffaele, Milan; [3]Department of Biochemistry and Medical Biotechnologies, University Federico II, Naples; [4]Centre of Genetics Engineering (CEINGE) Advanced Biotechnologies, Naples; [5]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

**Inherited microcytic-hypochromic anemias in rodents and zebrafish suggest the existence of corresponding human disorders. The zebrafish mutant s*hiraz* has severe anemia and is embryonically lethal because of glutaredoxin 5 (*GRLX5*) deletion, insufficient biogenesis of mitochondrial iron-sulfur (Fe/S) clusters, and deregulated iron-regulatory protein 1 (IRP1) activity. This leads to stabilization of transferrin receptor 1 (*TfR*) RNA, repression of ferritin, and ALA-synthase 2 (*ALAS2*) translation with impaired heme synthesis. We report the first case of GLRX5 deficiency in a middle-aged anemic male with iron overload and a low number of ringed sideroblasts. Anemia was worsened by blood transfusions but partially reversed by iron chelation. The patient had a homozygous (c.294A>G) mutation that interferes with intron 1 splicing and drastically reduces *GLRX5* RNA. As in *shiraz,* aconitase and H-ferritin levels were low and TfR level was high in the patient's cells, compatible with increased IRP1 binding. Based on the biochemical and clinical phenotype, we hypothesize that IRP2, less degraded by low heme, contributes to the repression of the erythroblasts ferritin and ALAS2, increasing mitochondrial iron. Iron chelation, redistributing iron to the cytosol, might relieve IRP2 excess, improving heme synthesis and anemia. GLRX5 function is highly conserved, but at variance with zebrafish, its defect in humans leads to anemia and iron overload. (Blood. 2007;110:1353-1358)**

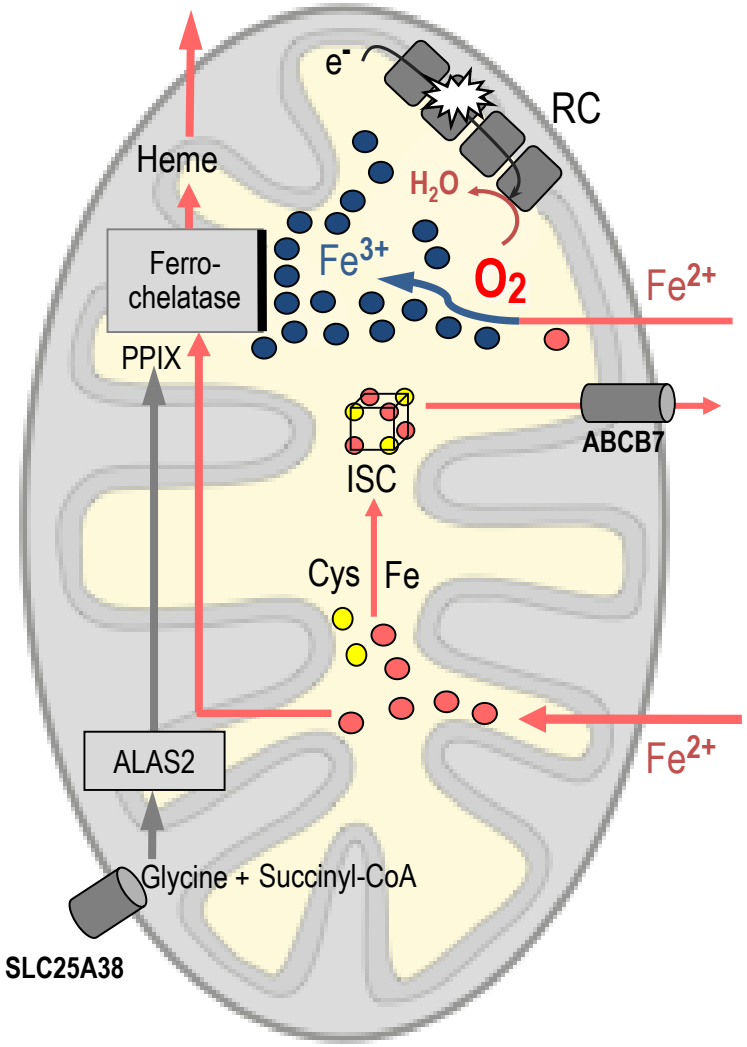



Camaschella et al., Blood 2007

| Condition | Molecular basis | Clinical features |
|---|---|---|
| **Non-syndromic congenital sideroblastic anemias** | | |
| X-linked sideroblastic anemia (XLSA) (MIM ID # 300751) | Germline mutation in the erythroid-specific ALA synthase gene (*ALAS2*, chromosome Xp11.21) | Hemizygous males have hypochromic microcytic anemia due to ineffective erythropoiesis and secondary iron overload (iron-loading anemia). Heterozygous females may have minor red cell abnormalities (in particular, increased red cell distribution width). Most patients are responsive to pyridoxine. |
| Autosomal recessive pyridoxine-refractory sideroblastic anemia (MIM ID #205950) | Germline mutations in the *SLC25A38* gene (chromosome 3p22.1) | Homozygous males and females have severe microcytic anemia that almost inevitably becomes transfusion-dependent. Heterozygous individuals have no hematologic phenotype. Conservative therapy includes regular red cell transfusion and iron chelation. Allogeneic stem cell transplantation represents the only curative treatment at present. |
| | Homozygous mutation in the *GLRX5* gene (chromosome 14q32) | The reported case regards a middle-aged male affected with pyridoxine-refractory sideroblastic anemia and iron overload. |
| **Hereditary syndromic conditions** | | |
| X-linked sideroblastic anemia and spinocerebellar ataxia (XLSA/A, MIM ID #301310) | Germline mutation in the *ABCB7* gene (chromosome Xq13.1-q13.3) | Hemizygous males have moderate hypochromic microcytic anemia and tend to develop non-progressive ataxia and incoordination early in life. |
| Myopathy, lactic acidosis and sideroblastic anemia (MLASA1, MIM ID #600462) | Homozygous germline mutation in the *PUS1* gene (chromosome 12q24.33) | Myopathy, lactic acidosis, and anemia (progressive exercise intolerance during childhood). |
| Myopathy, lactic acidosis and sideroblastic anemia (MLASA2, MIM ID #613561) | Homozygous germline mutation in the *YARS2* gene (chromosome 12p.11.21) | Myopathy, lactic acidosis, and anemia (progressive exercise intolerance during childhood). |
| Thiamine-responsive megaloblastic anemia (TRMA, MIM ID #249270) | Germline mutations in the *SLC19A2* gene encoding a thiamine transporter protein (chromosome 1q23.3) | Thiamine-responsive macrocytic anemia, diabetes mellitus, and sensorineural deafness. |
| Pearson marrow-pancreas syndrome (MIM ID #557000) | Mitochondrial DNA deletion | Refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction. |

Cazzola & Invernizzi, Haematologica 2011

# Pathophysiology of sideroblastic anemias



# Eisenüberladung

## Hereditäre Ursachen

- Verschiedene Typen der hereditären Hämochromatose (HH)
- Gestörter Eisentransport
- Ineffektive Erythropoese („iron loading anemia“)
  → verstärkte intestinale Eisenresorption

## Erworbene Ursachen

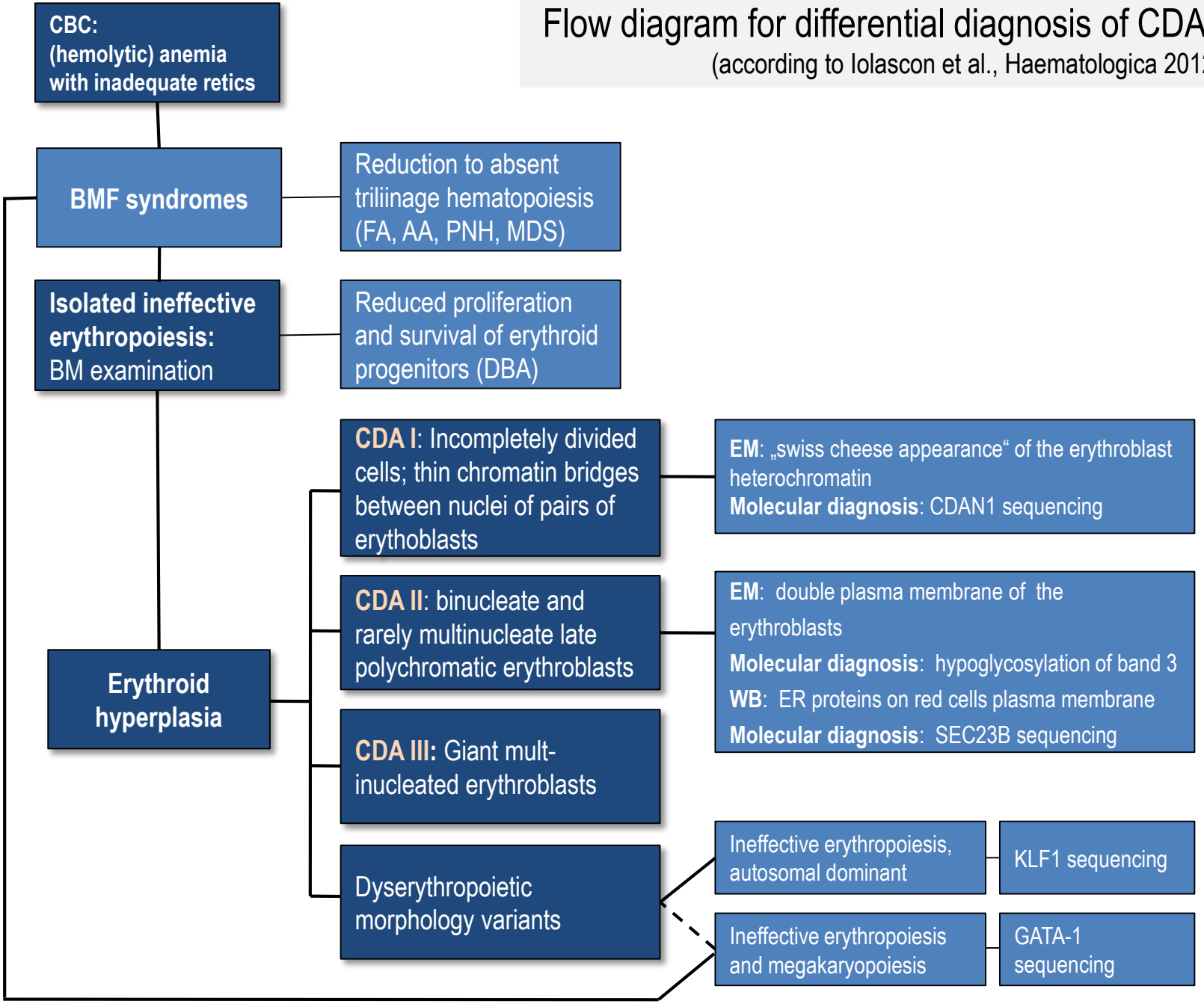
- Ineffektive Erythropoese
- Chronische Transfusionsbehandlung

**Sekundäre Hämochromatose**

- Thalassämie (NTDT)
- kongen. sideroblast. Anämie
- kongen. dyserythropoetische A.
- Myelodysplastische Syndrome

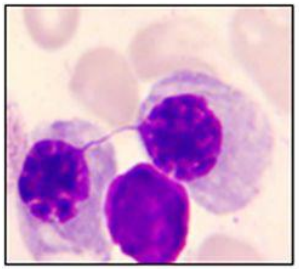
# Flow diagram for differential diagnosis of CDAs

(according to Iolascon et al., Haematologica 2012)

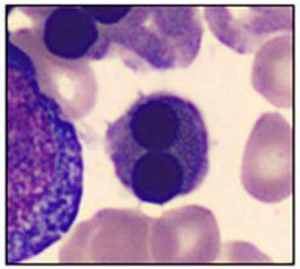


# Characteristic features of different types of congenital dyserythropoietic anemias

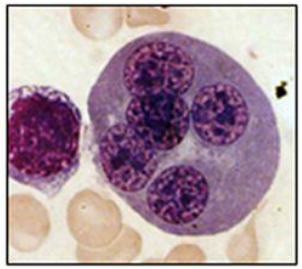
| CDA type | I | II | III Familial | III Sporadic | Variants |
|---|---|---|---|---|---|
| Inheritance | Autosomal recessive | Autosomal recessive | Dominant | Variable | Autosomal dominant or X linked or recessive |
| Cases reported | >300 | >450 | 2 families | <20 | ~70 |
| BM morphology (light microscopy) | Abnormal chromatin structure, chromatin bridges | Binuclearity, multinuclearity of mature erythroblasts | Giant multinucleated erythroblasts | Giant multinucleated erythroblasts | CDA I–like, CDA II–like, others |
| BM EM findings | "Spongy" heterochromatin, invagination of cytoplasm into the nucleus | Peripheral cysternae beneath the plasma membrane | Clefts in heterochromatin, autophagic vacuoles, intranuclear cisternae | Various | Various |
| Mutated gene | *CDAN1*, *C15ORF41* | *SEC23B* | *KIF23* | Unknown | *KLF1*, *GATA-1*, unknown |
| Associated dysmorphology/organ involvement | Skeleton | Variable, rare | Monoclonal gammopathy, myeloma, angioid streaks | Variable | CNS, others |



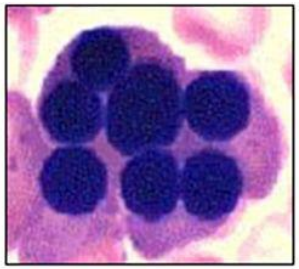
**CDA type I**



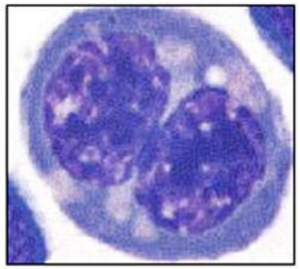
**CDA type II**



**CDA type III familial**



**CDA type III sporadic**



**CDA variants**

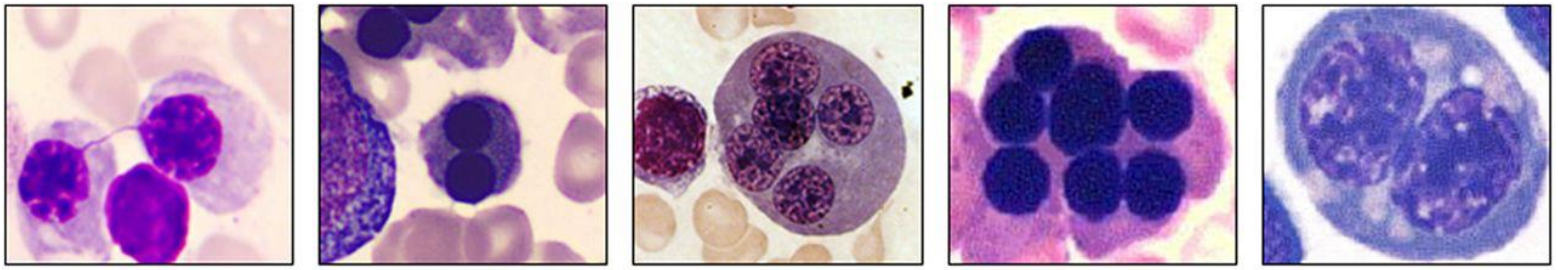
Iolascon et al. Blood 2013

# Congenital dyserythropoietic anemias: Molecular insights

**CDA I:** **Codanin-1** is a ubiquitous protein that may facilitate **histone assembly** into chromatin during cell cycle. The primary defect in CDA I seems to be in DNA replication and chromatin assembly and may involve disruption of the intrinsic connection between cell cycle dynamics and terminal erythroid differentiation.

**CDA II:** **SEC23B** encodes the cytoplasmic COPII (coat protein) component SEC23B, which is involved in the **secretory pathway of eukaryotic cells**. This multisubunit complex mediates accumulation of secretory cargo, deformation of the membrane, and anterograde transport of correctly folded cargo for budding from the endoplasmic reticulum toward the Golgi apparatus.

**CDA III**: **KIF23** encodes a kinesin-superfamily molecule, mitotic kinesin-like protein 1 (MKLP1), a mitotic protein **essential for cytokinesis**, suggesting a mechanism behind multinucleated erythroblasts.

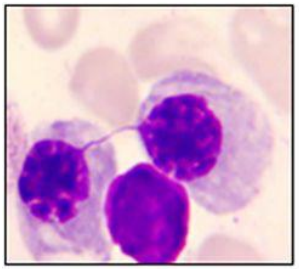


CDA type I | CDA type II | CDA type III familial | CDA type III sporadic | CDA variants

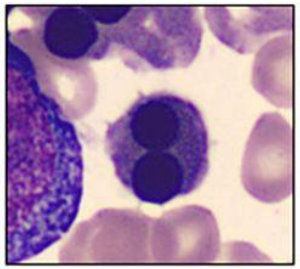
Iolascon et al. Blood 2013

# Congenital dyserythropoietic anemias: Conclusions

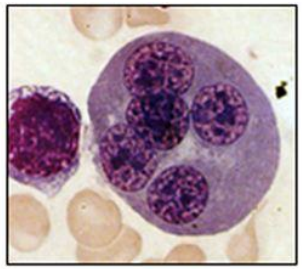
- The identification of several CDA genes has improved the diagnostic aspect of this disease
- No comprehensive explanation for the mechanism of erythropoietic disruption has been disclosed
- The fact that the proteins encoded by the CDA I, II, and III genes are ubiquitously expressed while the disease manifestations are mainly erythroid restricted remains a quandary.
- The hallmark of the CDAs is failure of terminal erythropoiesis, which can cause secondary hemochromatosis



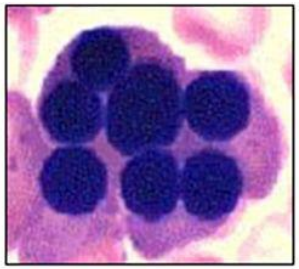
CDA type I



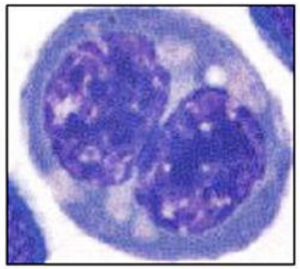
CDA type II



CDA type III familial



CDA type III sporadic



CDA variants

Iolascon et al. Blood 2013

# Eisenüberladung

## Hereditäre Ursachen

- Verschiedene Typen der hereditären Hämochromatose (HH)
- Gestörter Eisentransport
- Ineffektive Erythropoese („iron loading anemia“)
  → verstärkte intestinale Eisenresorption

## Erworbene Ursachen

- Ineffektive Erythropoese
- Chronische Transfusionsbehandlung

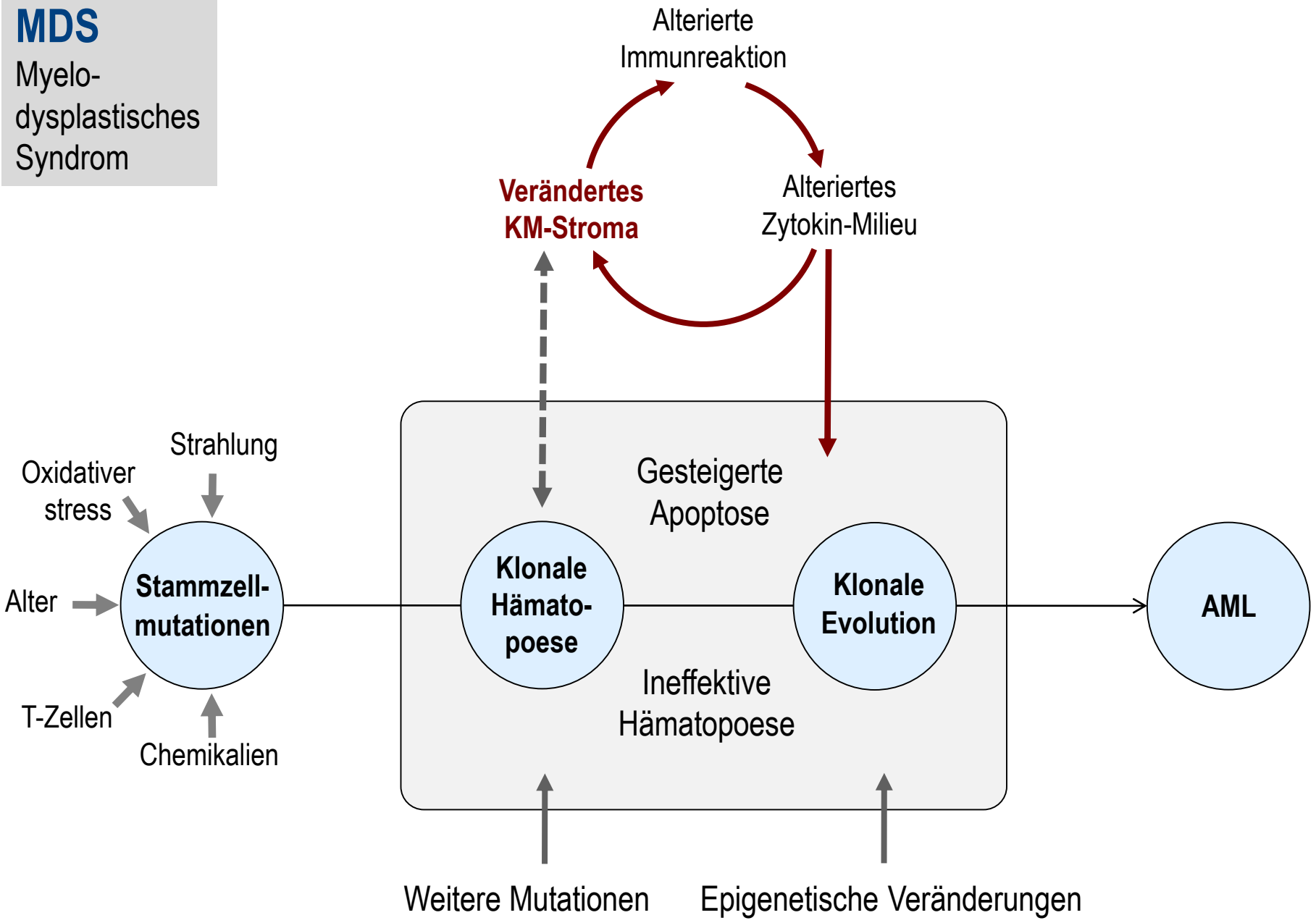
Thalassämie (NTDT)
kongen. sideroblast. Anämie
kongen. dyserythropoetische A.

**Sekundäre Hämochromatose**

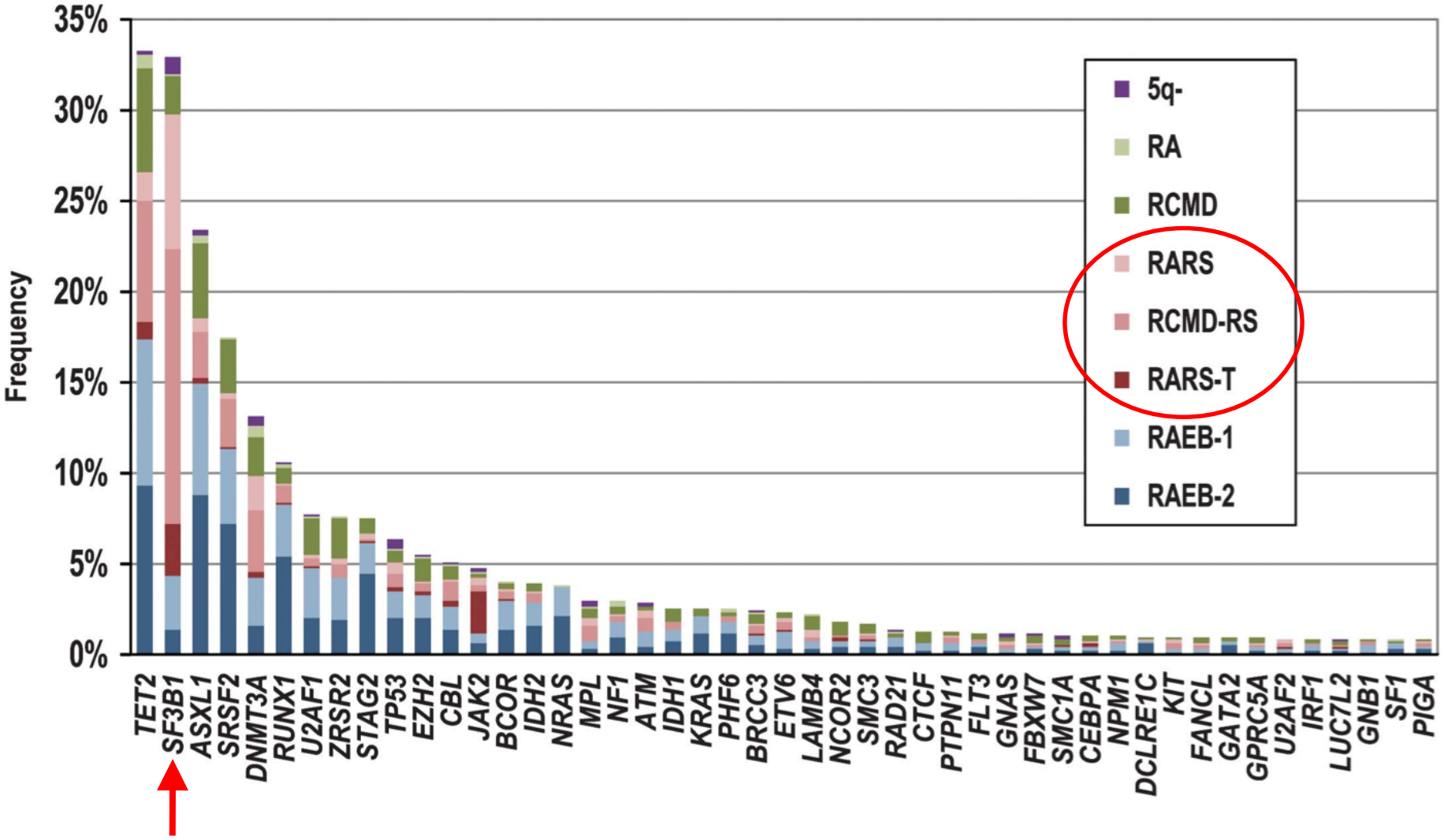
- Myelodysplastische Syndrome

# MDS

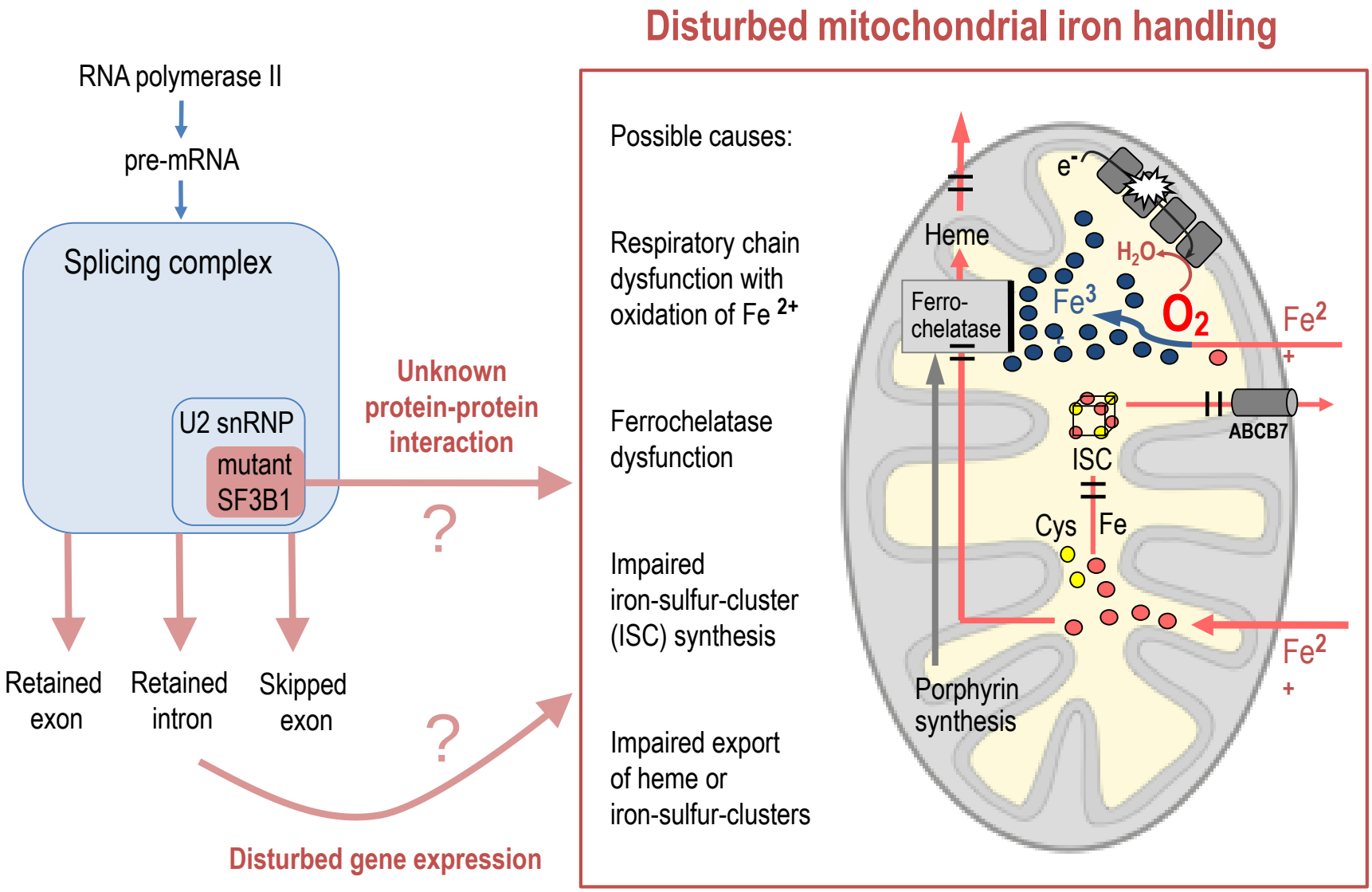
Myelo-dysplastisches Syndrom



# **MDS**: Frequency of mutations in 47 significantly mutated genes in 944 cases with different WHO subtypes, which are shown in indicated colors

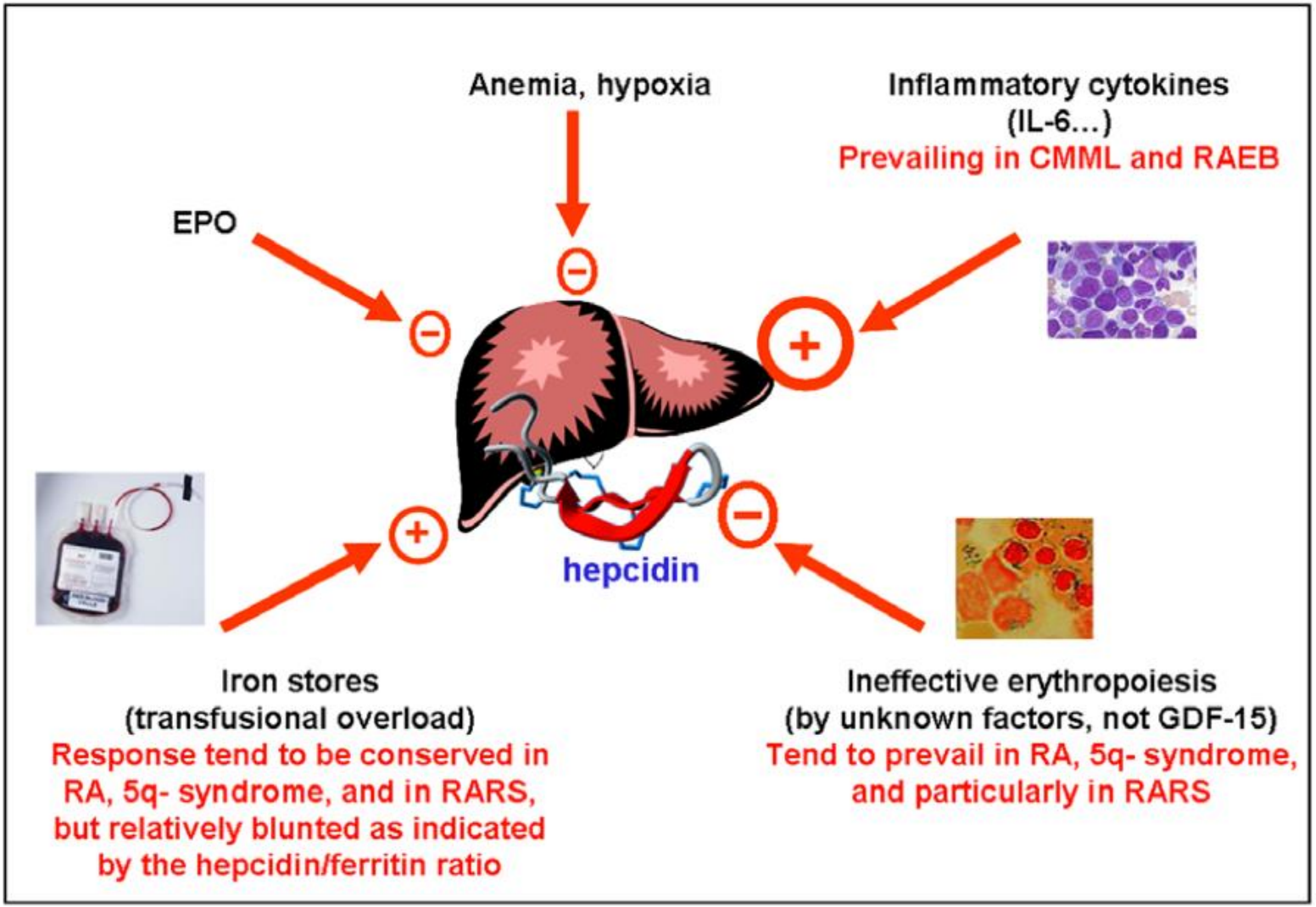



Haferlach T et al., Leukemia 2014



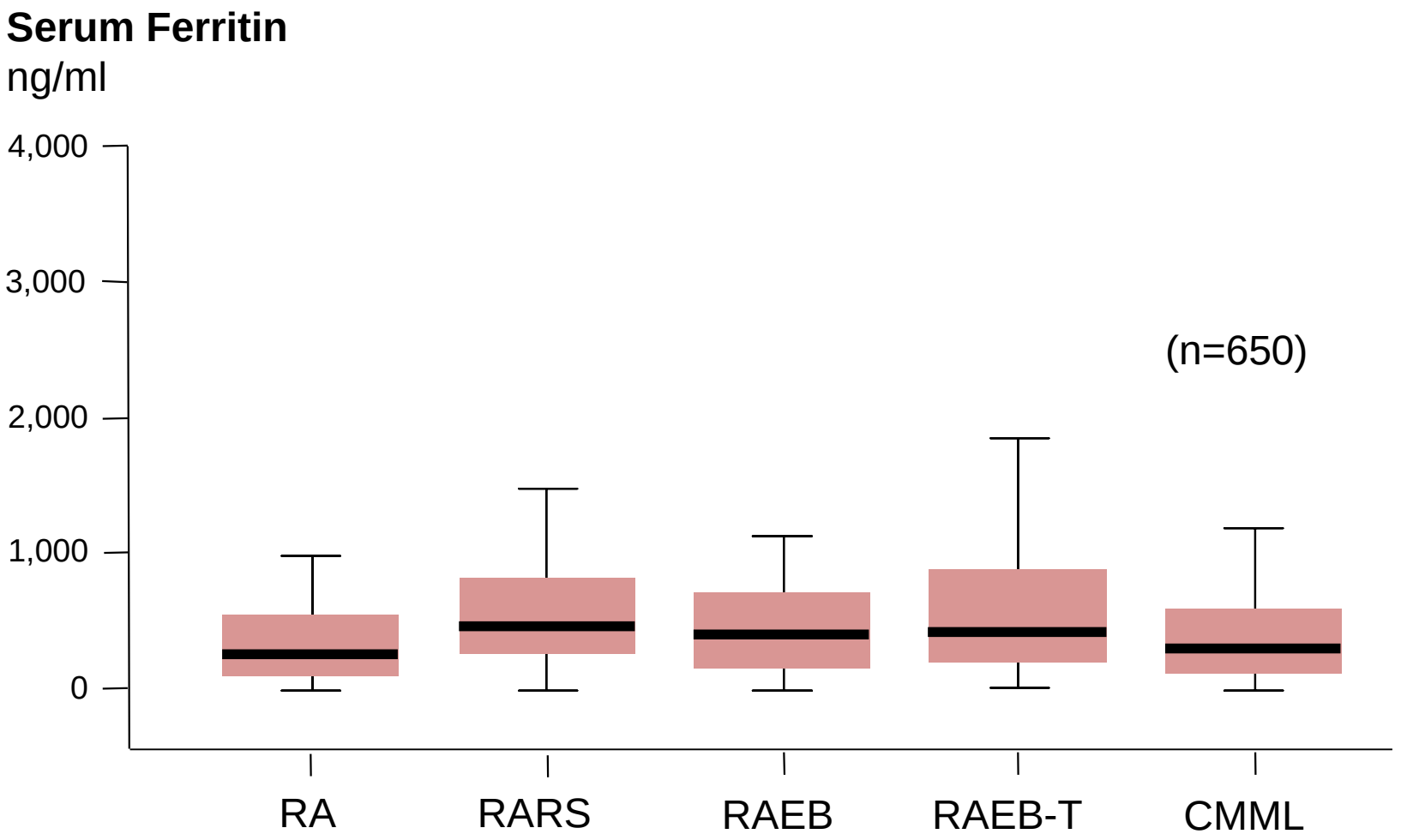

N. Gattermann. SF3B1 and the riddle of the ring sideroblast. Blood 2012;120:3167-8

# Proposed mechanisms controlling hepcidin production in different MDS types




Santini et al. (2011) PLoS ONE 6(8): e23109. doi:10.1371

# MDS: Serum ferritin at diagnosis




Düsseldorf MDS Registry

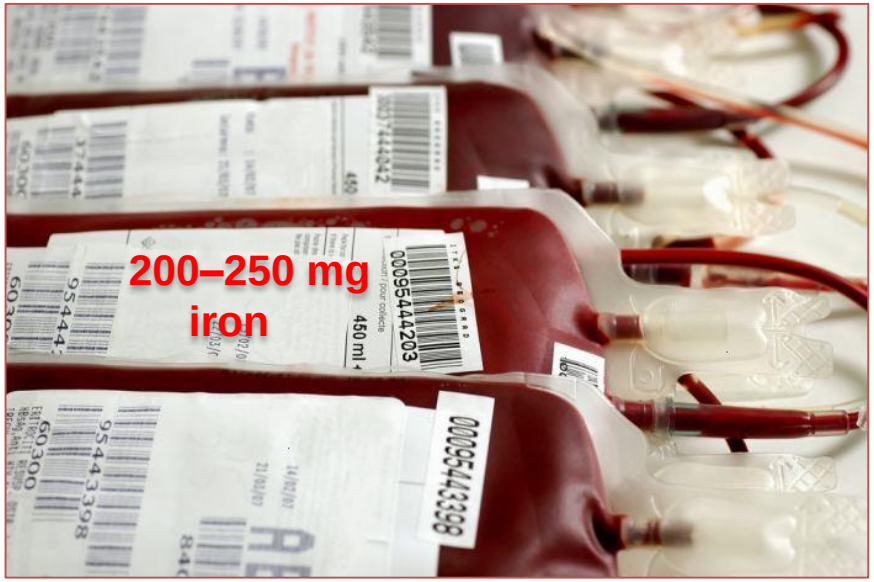
# The most important cause of iron overload in bone marrow disease: Chronic transfusion therapy

**Moderate transfusion requirement:**

- 2 RBC units per month
- 24 RBC units per year
- ~ 100 RBC units / **4** years

**High transfusion requirement:**

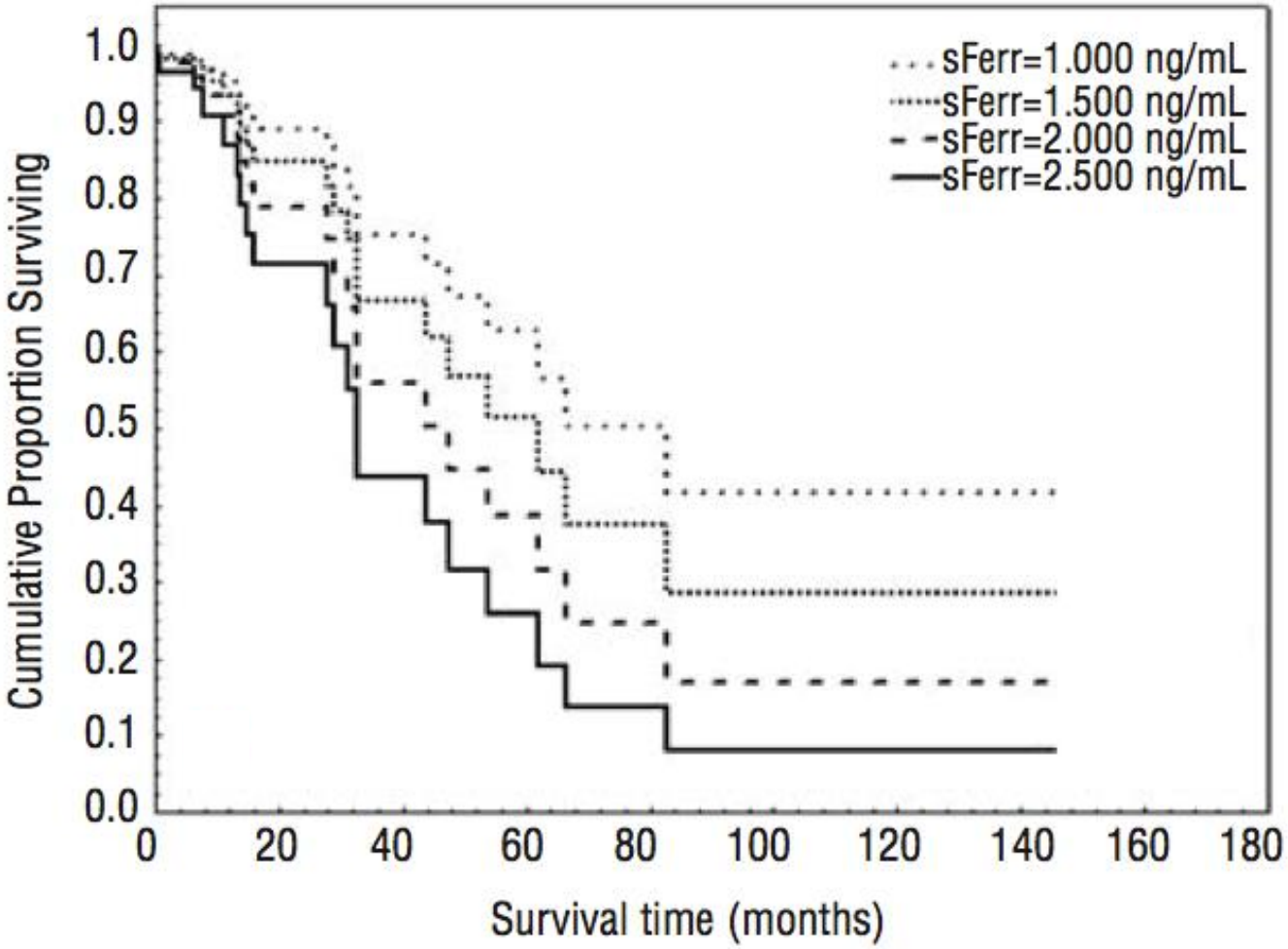
- 4 RBC units per month
- 48 RBC units per year
- ~ 100 RBC units / **2** years




**100 RBC units: ≥ 20 g Iron**

Normal total body iron: **3-4 g**

# Survival of patients according to serum ferritin level

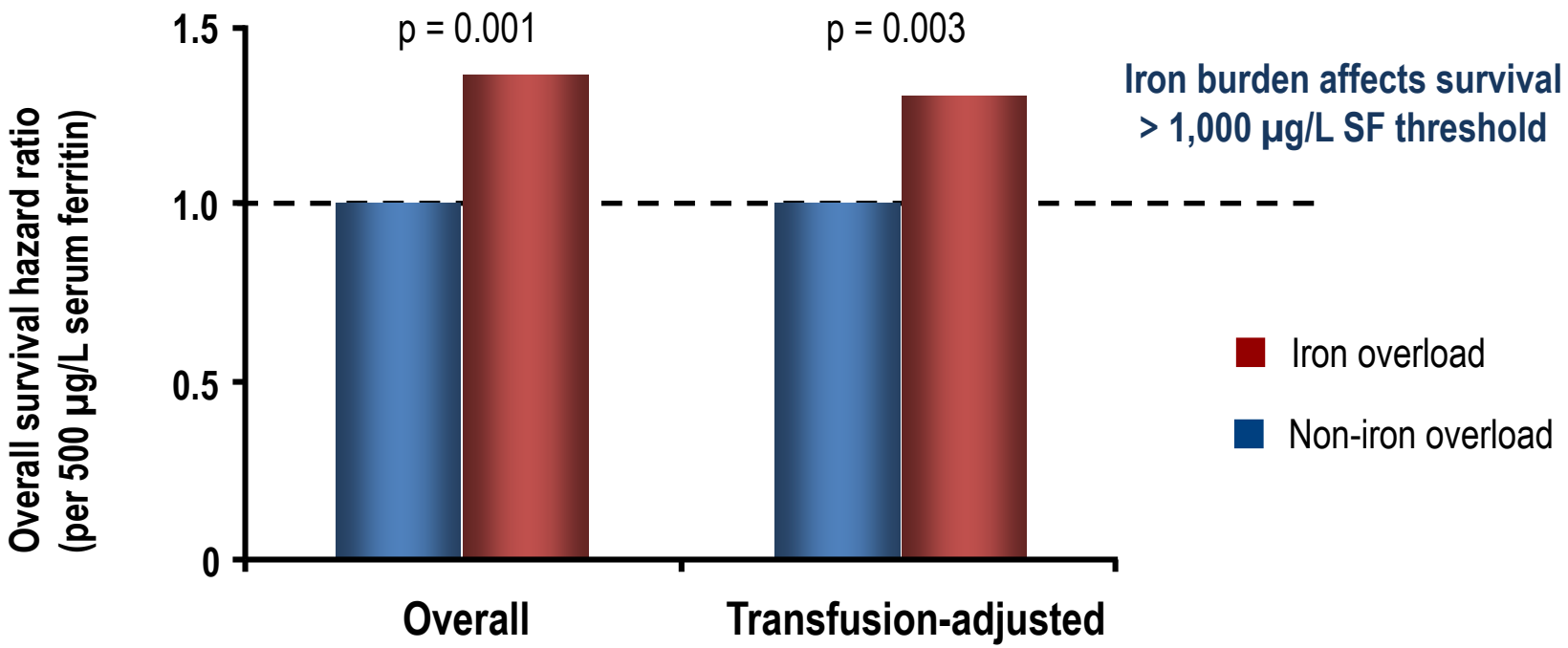



Patients with RA/RARS/5q− (HR = 1.42; p<0.001)

HR = hazard ratio; RA = refractory anemia; RARS = RA with ring sideroblasts.

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

# Serum ferritin is an independent prognostic factor in MDS

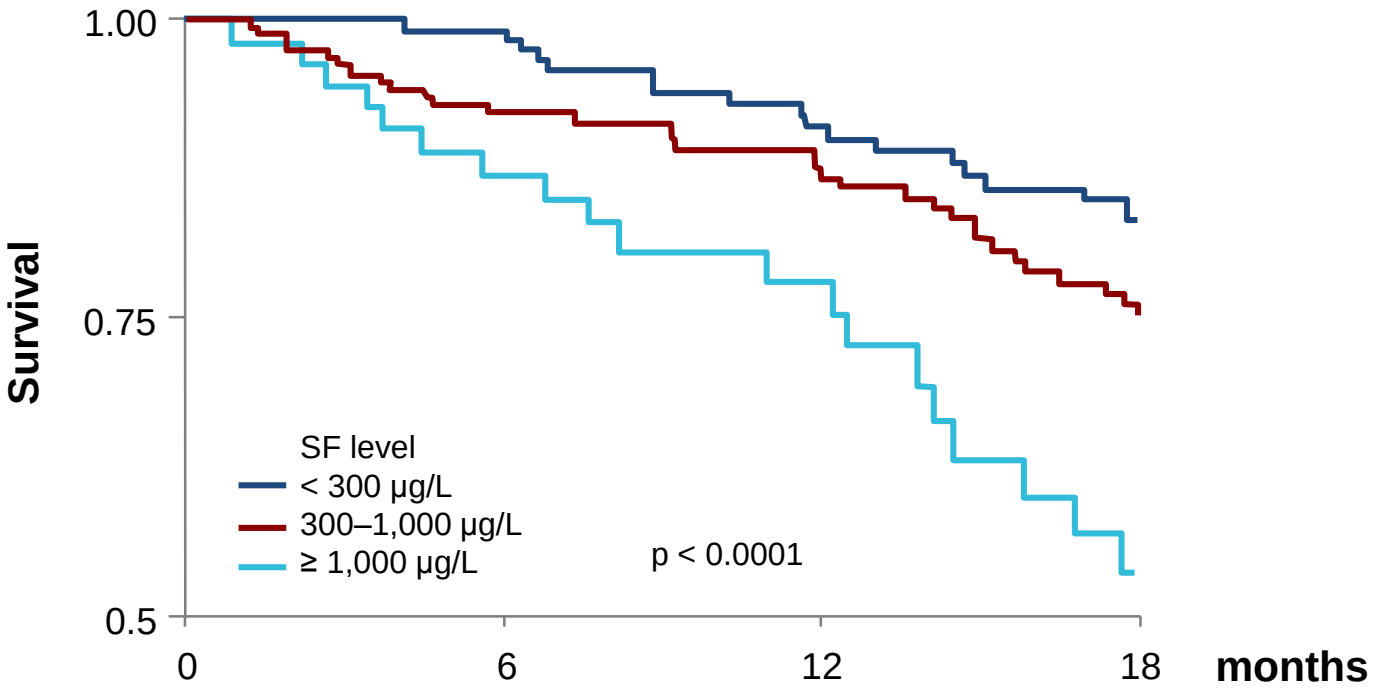



**A 30% greater risk of death was evident for every 500 µg/L increase in SF above the 1,000 µg/L threshold**

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

# LeukemiaNet prospective registry: Independent survival impact of SF

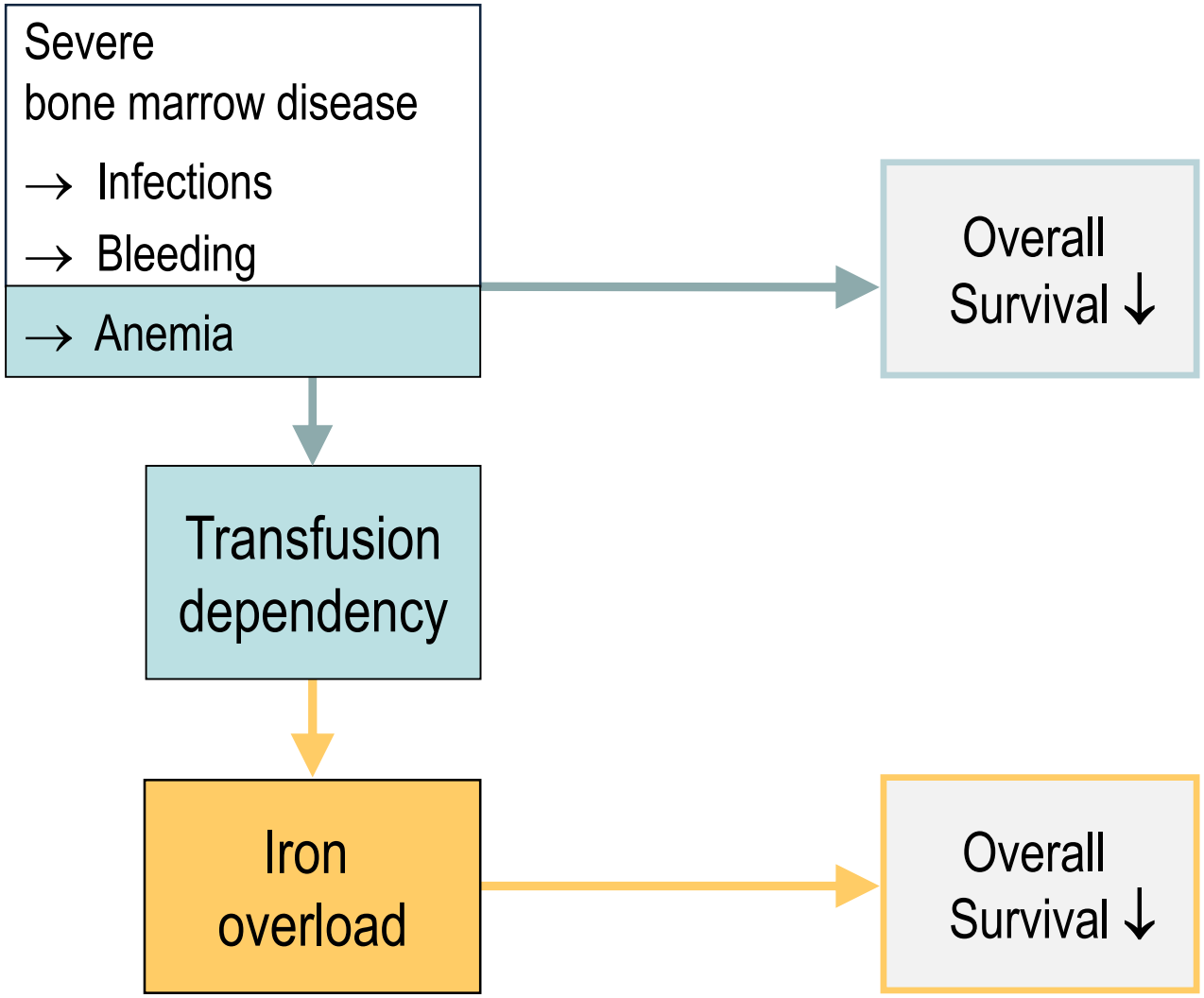
**OS of transfusion-dependent patients by baseline SF status** (n=1,000)



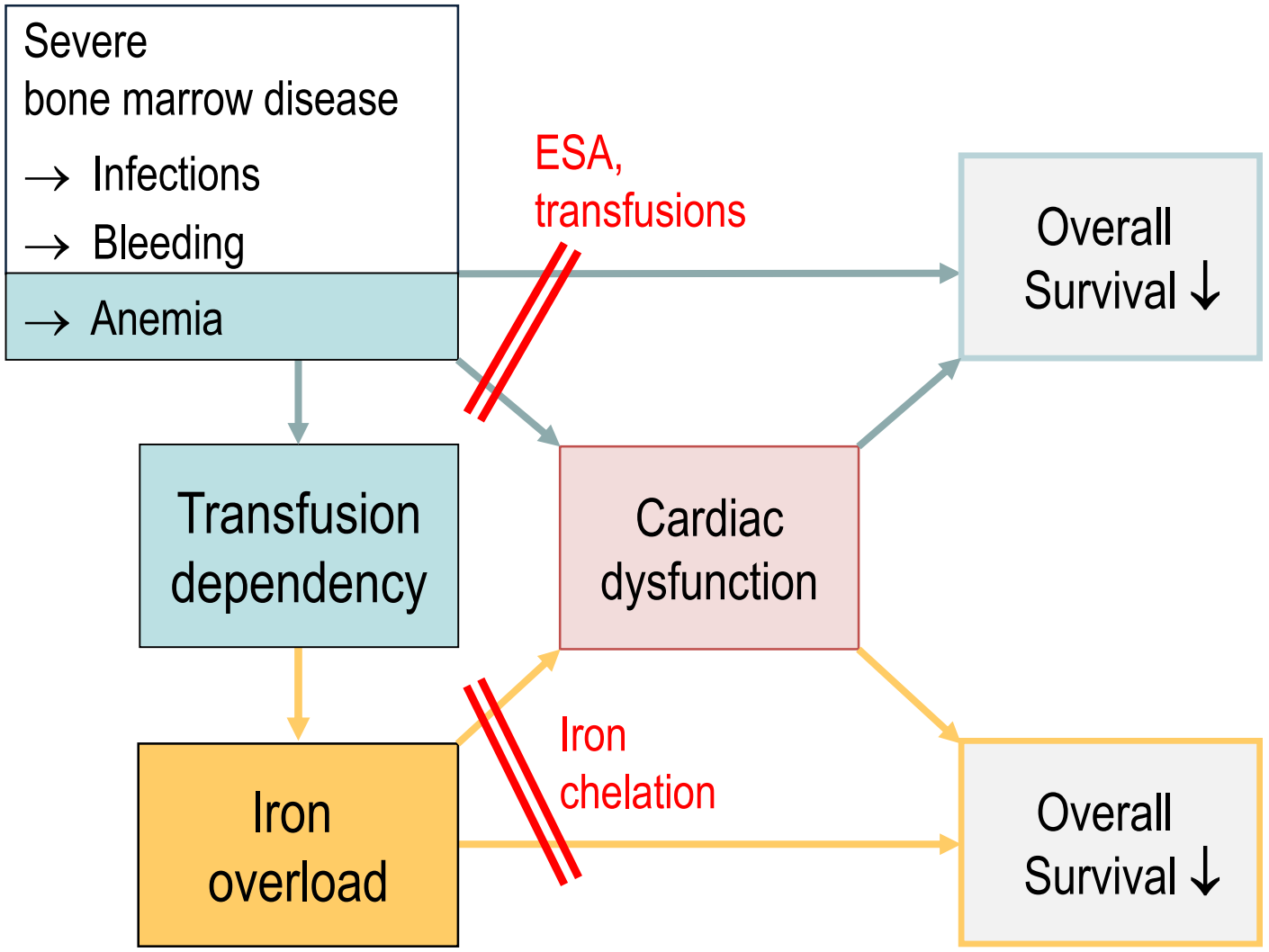

Besides transfusion burden, increasing levels of SF also had independent impact on the OS of transfusion-dependent patients with lower-risk MDS

de Swart L, et al. Blood. 2011;118:abstract 2775.

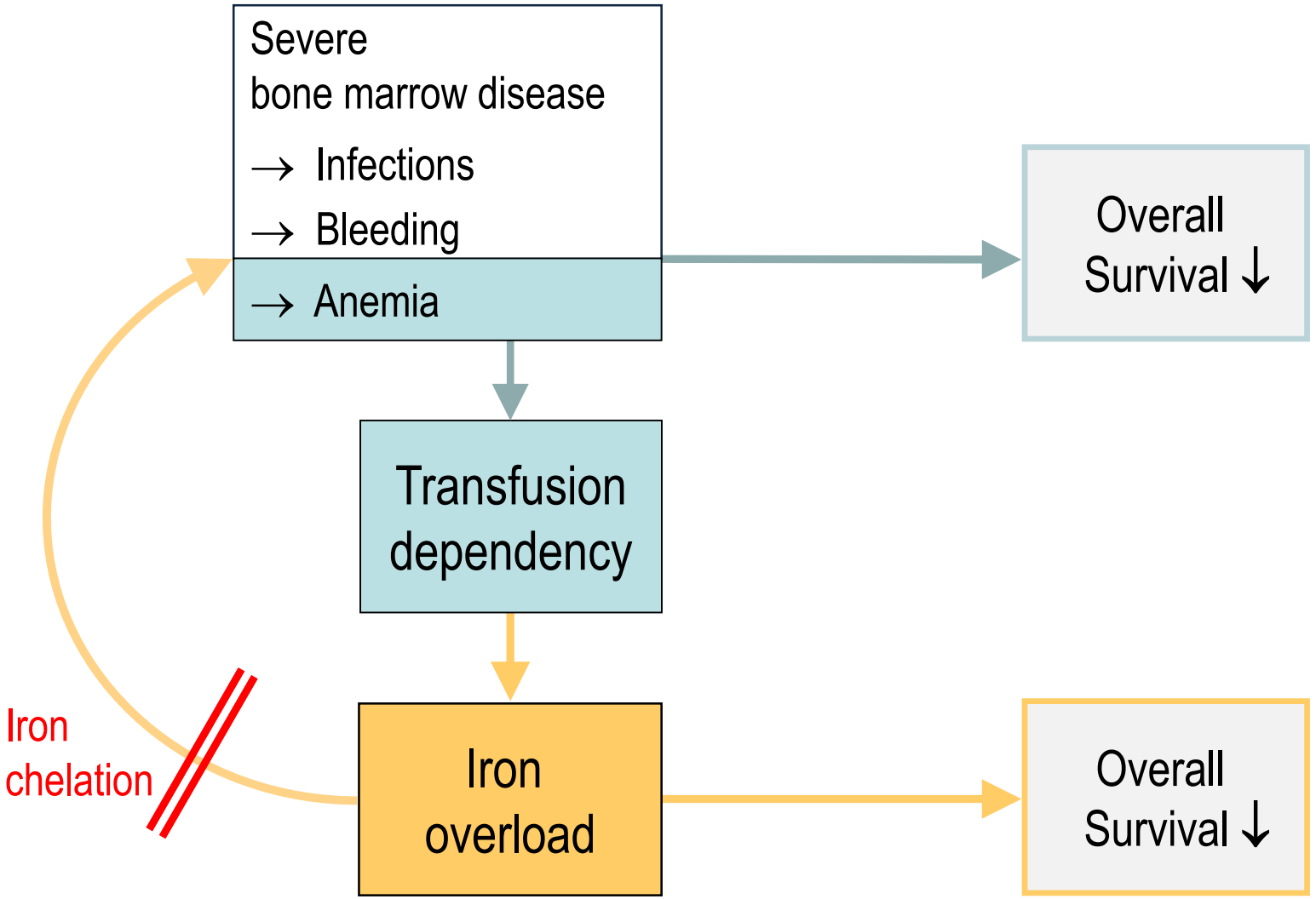
# Possible relationship between bone marrow failure, iron overload and prognosis in patients with MDS



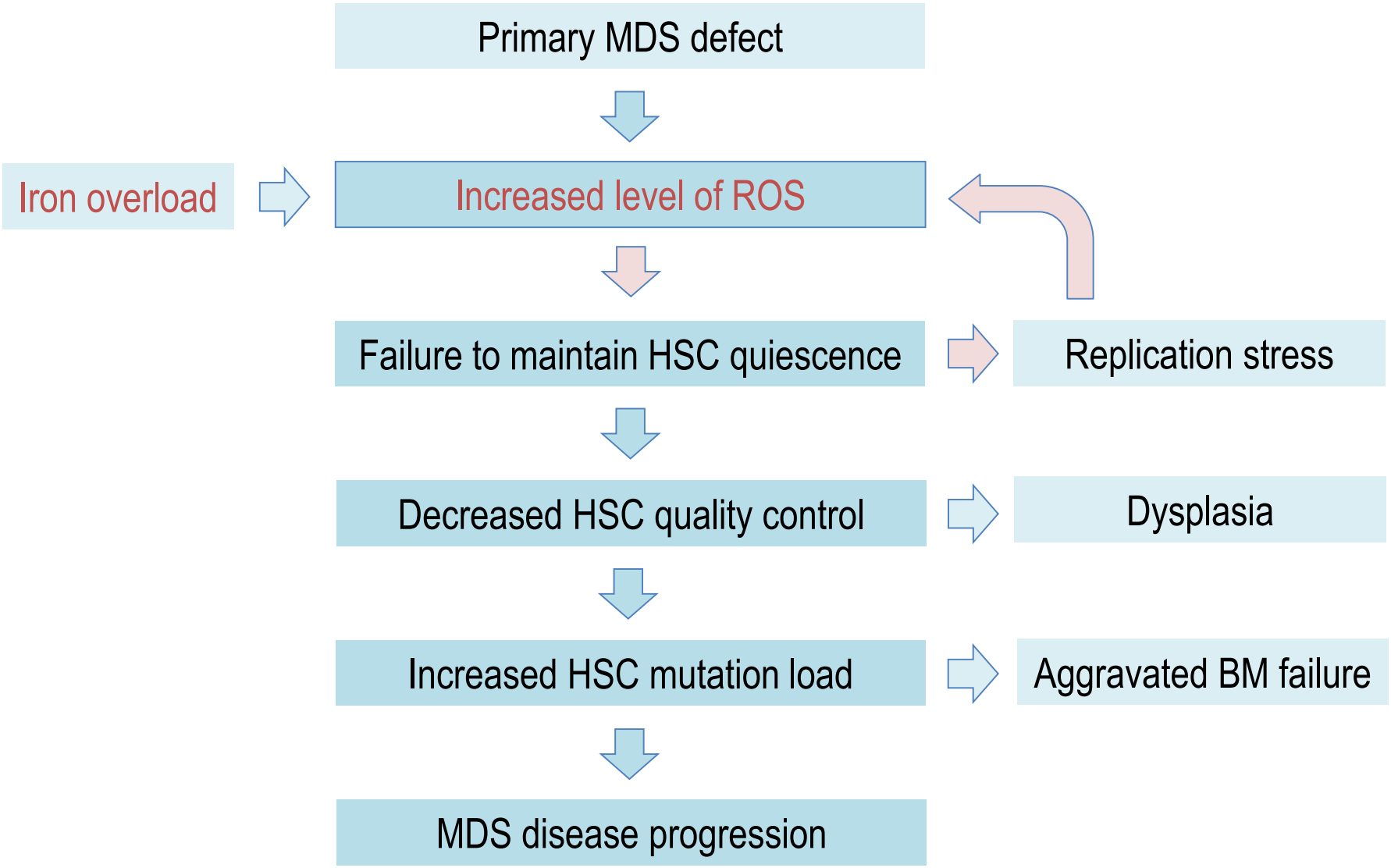
# Possible relationship between bone marrow failure, iron overload and prognosis in patients with MDS



# Iron overload may also aggravate bone marrow failure in MDS



# Role of increased ROS in MDS pathophysiology?



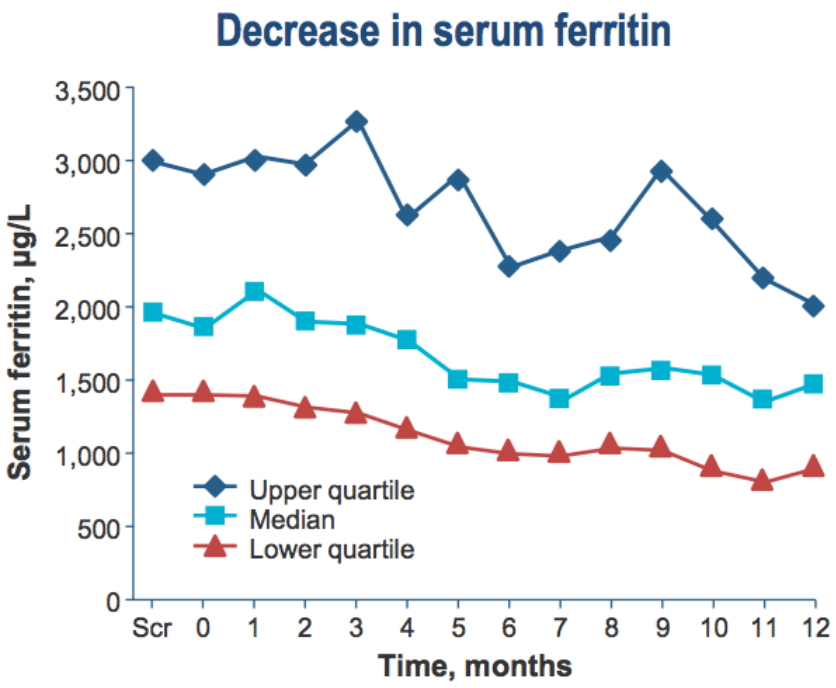
# Deferasirox can improve hematopoiesis in MDS

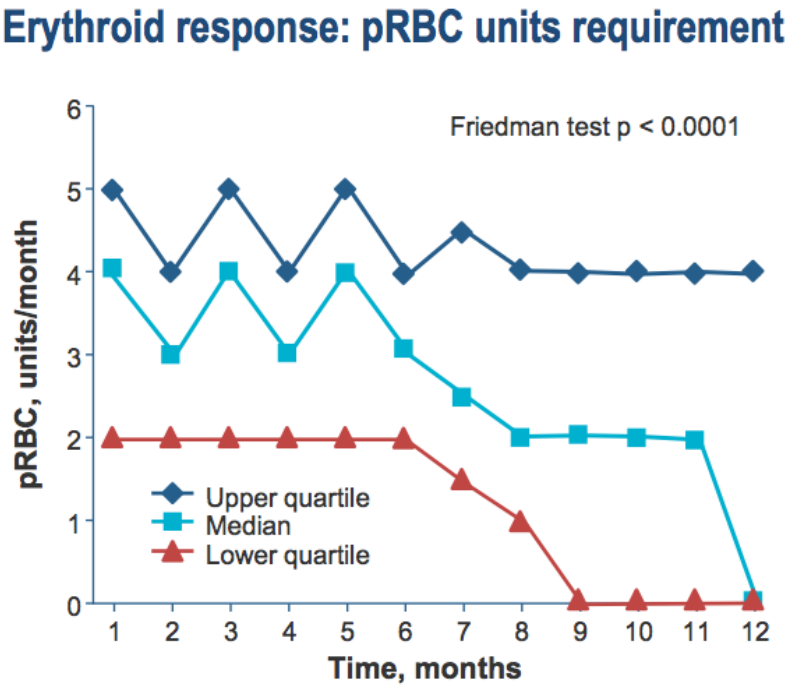
| Study | Risk IPSS | RBC response | Neutrophil response | PLT response |
|---|---|---|---|---|
| List A et al. 2012 [1] | Low/Int-1 | **15%** (n=173) | 15% (n=52) | 22% (n=77) |
| Gattermann N et al. 2012 [2] | Low/Int-1 | **21.5%** (n=247) | 22% (n=50) | 13% (n=100) |
| Nolte F et al. 2012 [3] | Low/Int-1 | **11%** (n=50) | NR | NR |
| Angelucci E et al. 2014 [4] | Low/Int-1 | Transfusion independence in **15.5%** (n=152) | NR | NR |

[1] List A et al. J Clin Oncol. 2012; 30:2134-9
[2] Gattermann N et al., Haematologica 2012; 97:1364-71
[3] Nolte et al., Ann Hematol. 2013; 92:191-8
[4] Angelucci E et al. Eur J Hematol 2014; 92:527-36

# Deferasirox for transfusion-dependent patients with MDS
## GIMEMA MDS0306 Trial

- Multicenter prospective study of 152 patients with lower-risk MDS
- All patients transfusion-dependent (≥ 20 RBC units); median 37 (22-63)
- Serum ferritin (median) decreased from 1966 ng/ml to 1475 ng/ml (p<0.0001)

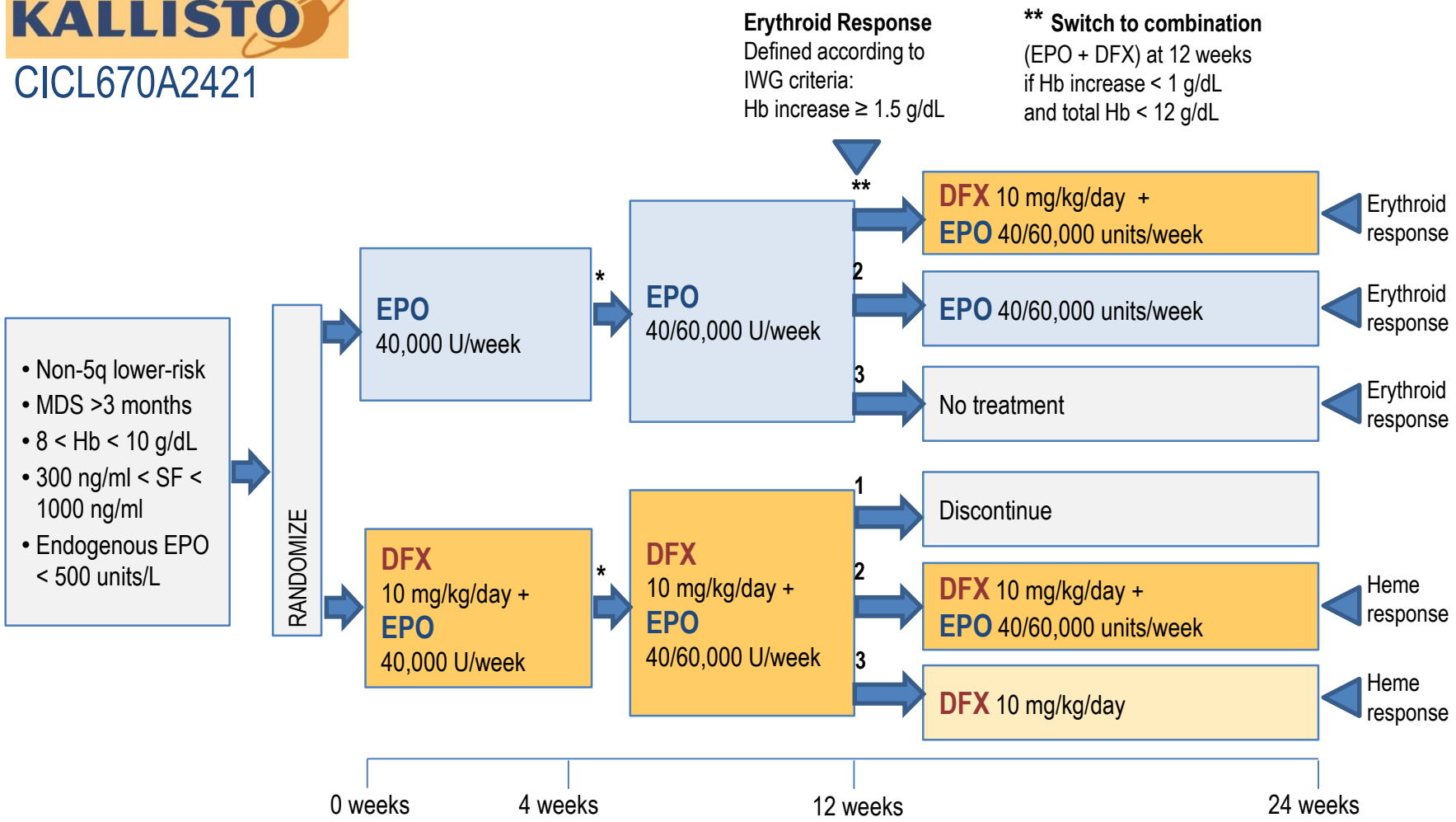



Angelucci et al., Eur J Haematol 2014;92:527-36

KALLISTO

CICL670A2421




*** Dose adjustments at 4 weeks according to EPO Guidelines**:

Hb increase < 1 g/dL and total Hb < 12 g/dL,

➔ Increase EPO dose to 60,000 units / week

Hb increase ≥ 1 g/dL and total Hb < 12 b/dL,

➔ Continue EPO dose

Hb increase ≥ 1 g/dL and total Hb > 12 g/dL,

➔ Hold EPO dose

**Dose adjustments at 12 weeks according to EPO Guidelines**:

**1**) Hb increase < 1 g/dL and total Hb < 12 g/dL,

➔ Discontinue EPO

**2**) Hb increase ≥ 1 g/dL and total Hb < 12 b/dL,

➔ Continue EPO dose

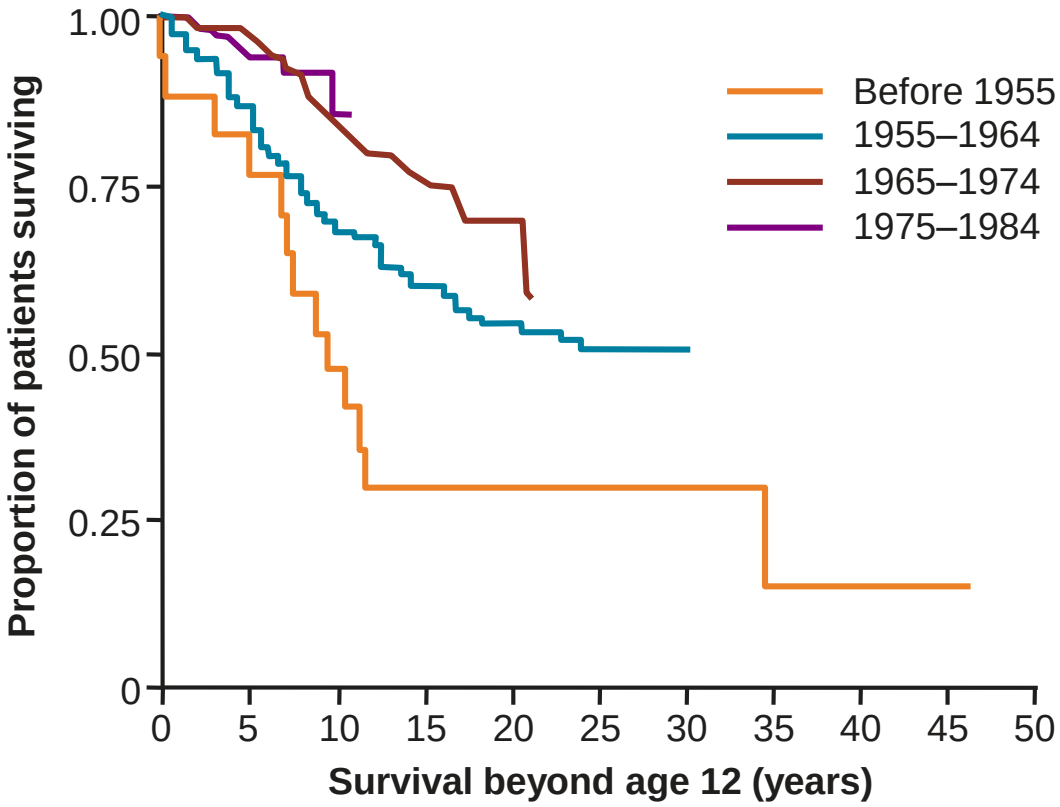
**3**) Hb increase ≥ 1 g/dL and total Hb > 12 g/dL,

➔ Hold EPO dose

# Mögliche Folgen der Eisenüberladung

| | |
|---|---|
| **Herz** | • Herzinsuffizienz, Rhythmusstörungen |
| **Leber** | • Fibrose, Zirrhose, Karzinom |
| **Endokrine Organe** | • Diabetes mellitus, Hypothyreose, Hypogonadismus |
| **Infektabwehr** | • Begünstigtes Bakterienwachstum |
| **Blutgefäße** | • Gestörte Endothelfunktion |
| **bei MDS zusätzlich:** | • Verschlechterung der Knochenmarkfunktion<br>• Vermehrte Komplikationen bei allogener SZT<br>• Evtl. beschleunigte AML-Transformation |

# Einfluß der Eisenchelation auf das Überleben von Patienten mit β-Thalassaemia major



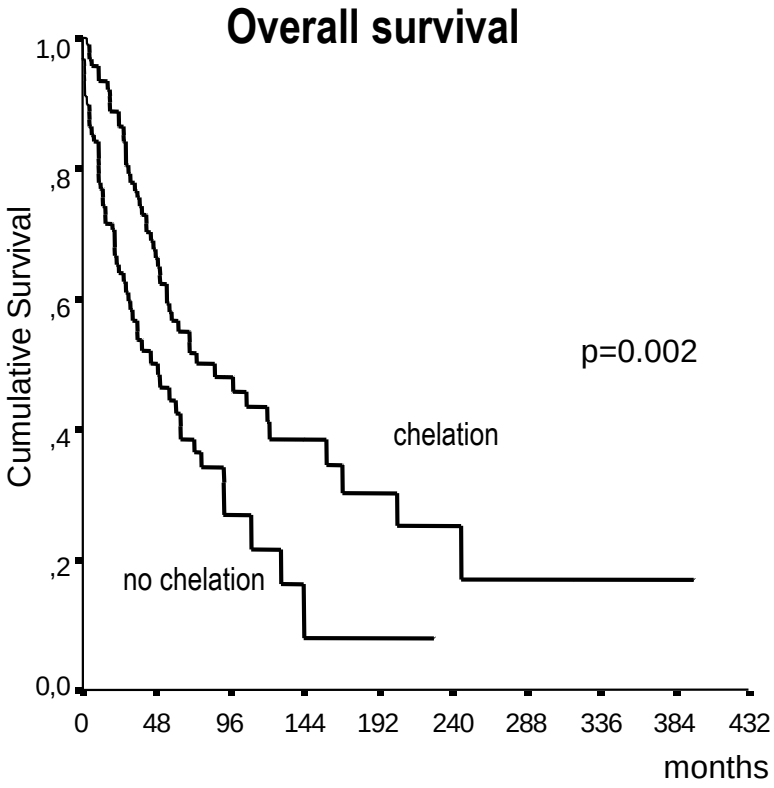

**Die verbesserten Überlebenschancen der später Geborenen beruhen auf der Behandlung der Eisenüberladung mit Deferoxamin und dem Grad der Therapietreue**

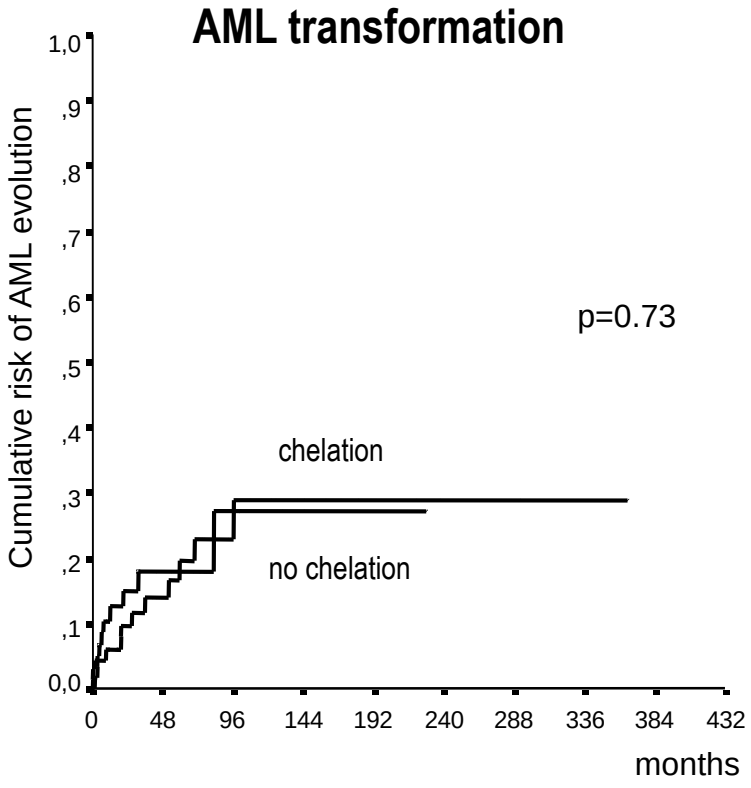
DFO, deferoxamine; β-TM, β-thalassaemia major.

Modell B, et al. Lancet. 2000;355:2051-2

# Impact of chelation therapy on survival and AML transformation

## Matched-pair analysis (93 pairs) from the Düsseldorf MDS Registry




| **Median cumulative survival** | |
|---|---|
| Chelation therapy: | **75** months |
| No chelation: | 49 months |

| **Cum. risk of AML:** | **at 2 yrs** | **at 5 yrs** |
|---|---|---|
| Chelation therapy: | 10% | 19% |
| No chelation: | 12% | 18% |

Neukirchen J et al. Leuk Res. 2012;36:1067-70

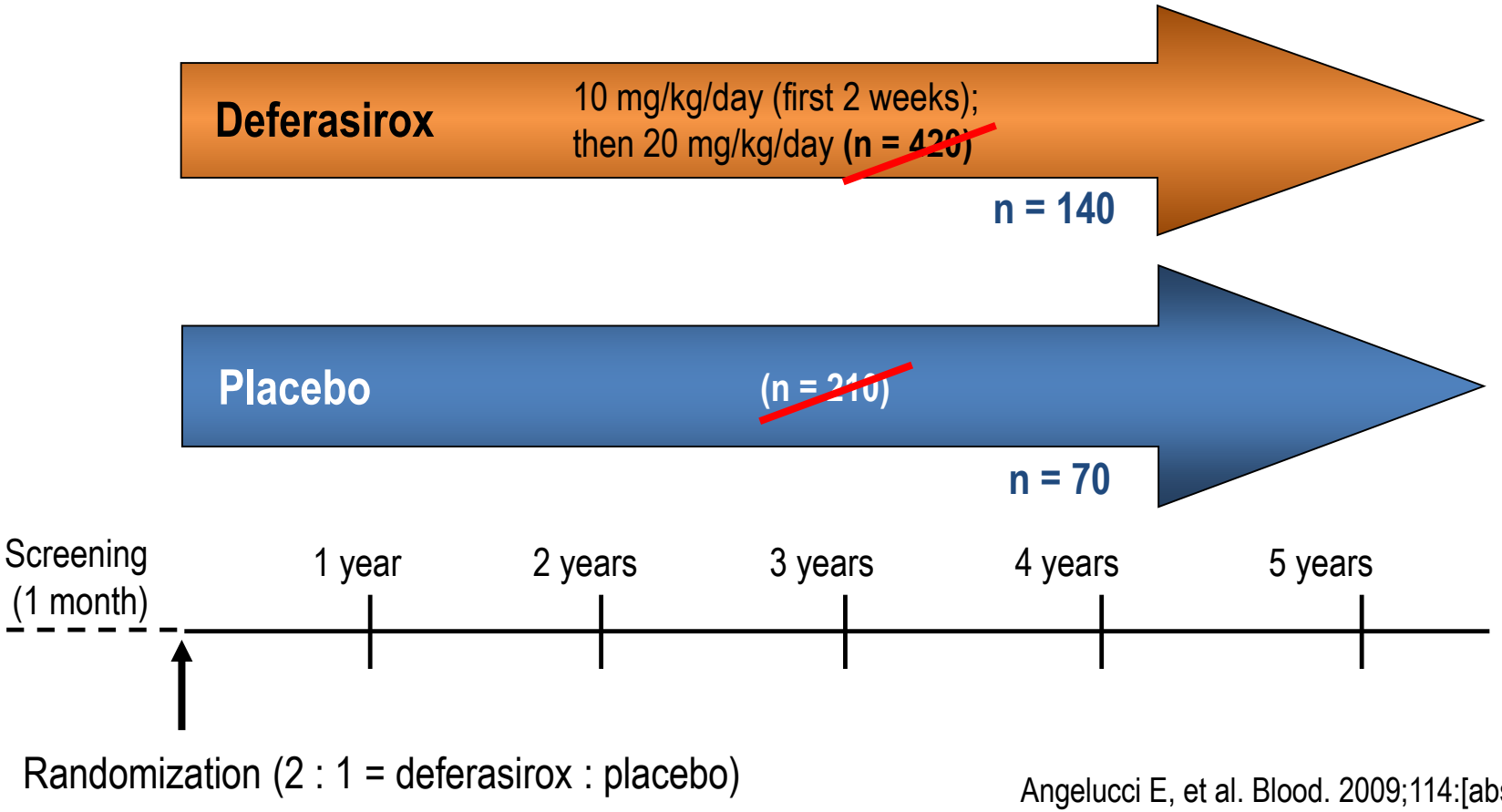
# Iron chelation may improve survival in transfusion-dependent MDS patients

| Study | N | Design | Survival | Non-chelated patients | Chelated patients | p value |
|---|---|---|---|---|---|---|
| Leitch 2008 | 36 | Retrospective | Median OS | 40 mo | Not reached | 0.003 |
| | | | 4-year survival rate | 43% | 64% | 0.003 |
| Rose 2010 | 97 | Prospective follow-up | Median OS from diagnosis | 53 mo | 124 mo | < 0.0003 |
| | | | Median OS with adequate vs weak chelation | NA | 124 vs. 85 mo | < 0.001 |
| Neukirchen 2012[a] | 188 | Matched pair analysis | Median OS | 49 mo | 75 mo | 0.002 |
| Neukirchen 2012[b] | 417 | Retrospective, registry | Median time to death in TD patients | 30 mo | 67 mo | NR |
| Komrokji 2011 | 97 | Retrospective | Median OS | 34 mo | 59 mo | 0.013 |
| Delforge 2012 | 186 | Retrospective | Median OS in Low/Int-1 | 37 mo | 126 mo | < 0.001 |
| Zeidan 2012 | 4,226 | Retrospective, registry | Median survival | 47 wk | 110 wk | 0.003 |
| | | | HR for 27-52 wks on DFX | 1 | 0.77 | NR |
| | | | HR for ≥ 53 wk on DFX | 1 | 0.34 | NR |
| Remacha 2012 | 228 | Retrospective | Median OS | 105 mo | 133 mo | 0.009 |
| de Witte T 2012 | 1,000 | Prospective, registry | Adjusted HR | 1 | 0.51 (0.19-1.32) | NS |
| Lyons 2014 | 600 | Prospective, registry | Median OS from diagnosis | 47.8 mo | All: 88 mo ICT>6 mo: 100 mo | < 0.0001 |

Delforge M, et al. Haematologica. 2012;97 Suppl 1:abstract 0898. Komorokji RS, et al. Blood. 2011;118:abstract 2776. Leitch H, et al. Clin Leuk. 2008;2:205-11. Lyons RM, et al. Blood. 2014;124:abstract 1350. [a] Neukirchen J, et al. Leuk Res. 2012;36:1067-70. [b] Neukirchen J, et al. Haematologica. 2012;97 Suppl 1: abstract 0359. Remacha A, et al. Blood. 2012;120:abstract 1723. Rose C, et al. Leuk Res. 2010;34:864-70. de Witte T, et al. EUMDS Registry. Presented at ELN 2012. Zeidan AM, et al. Blood. 2012;120:abstract 426.

# TELESTO: prospective study of deferasirox in MDS

- **Prospective, multicentre study to investigate the clinical benefit of chelation therapy with deferasirox in 210 MDS patients**
- **Primary study end-point: event-free survival (death, cardiac, and hepatic non-fatal events)**




Angelucci E, et al. Blood. 2009;114:[abstract 4854]