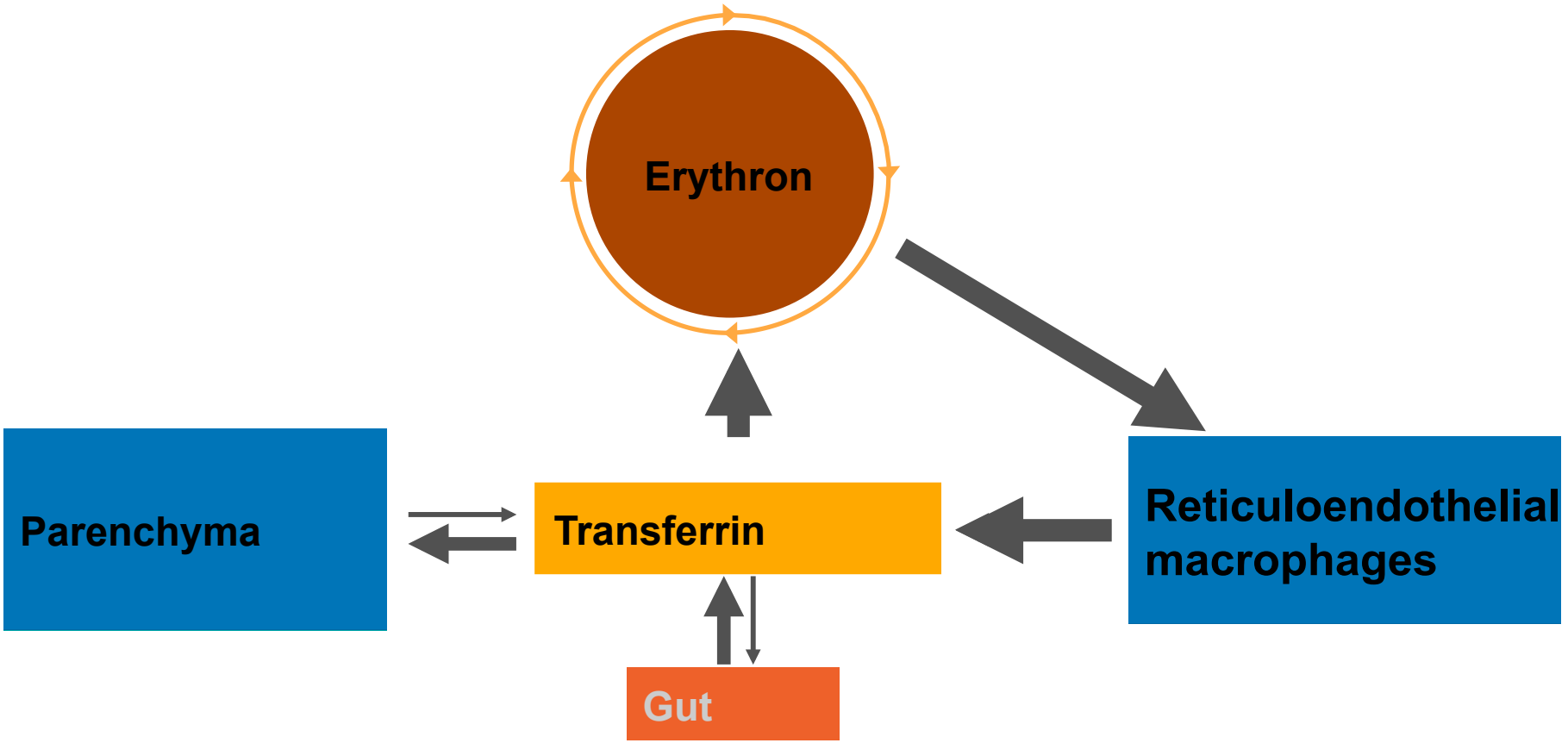
F. Lanza, P. Tosi, S. Tura, A. Zaccaria, P.L. Zinzani

La ferrochelazione, oggi e domani.

Agenda

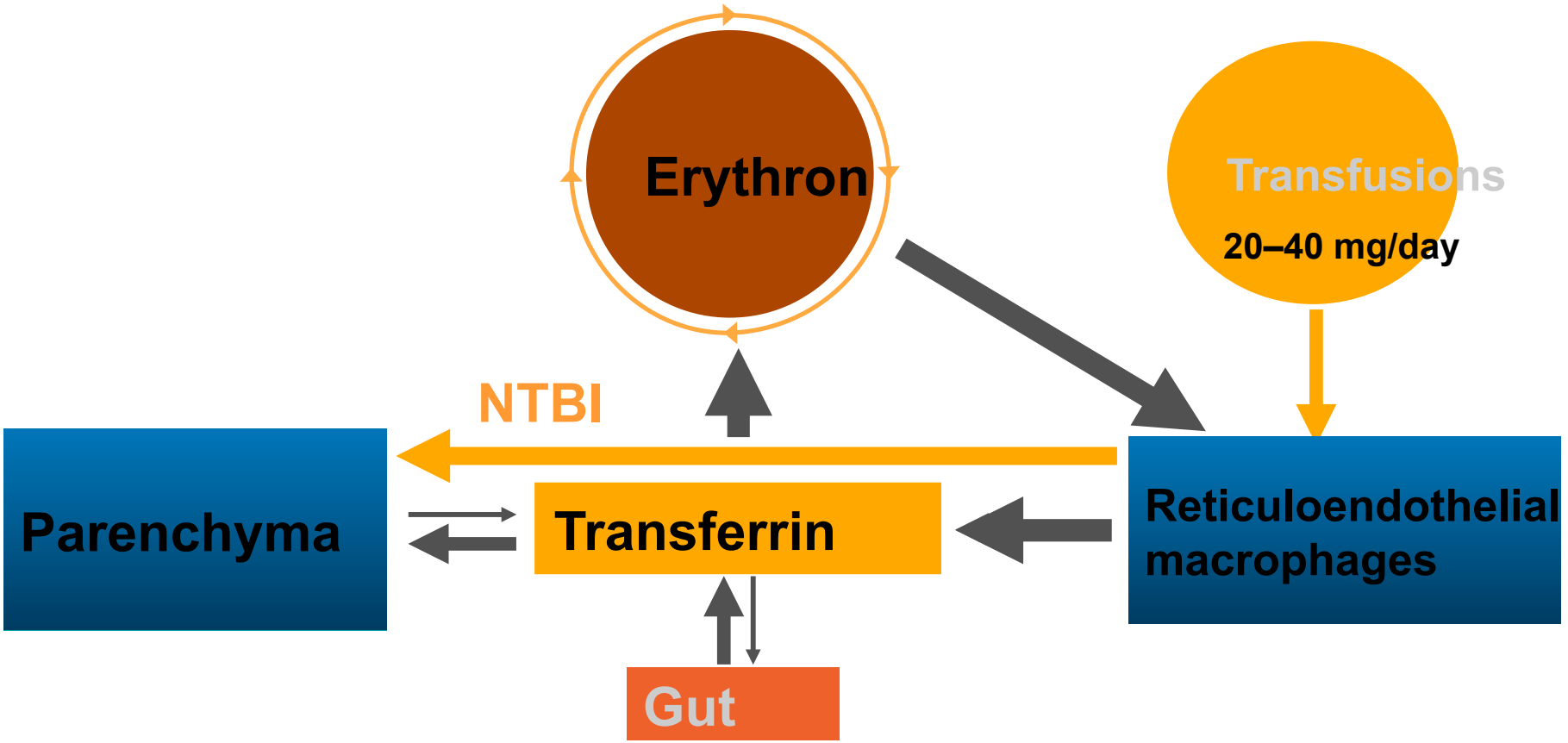
- Iron toxicity
- Differences between Thalassemia and MDS
- Today guidelines
- Future approaches

Iron Distribution and Turnover



Hershko C, et al. *Ann NY Acad Sci*. 1998;850:191-201.

Imbalance of Distribution and Turnover of Body Iron With Transfusion Therapy

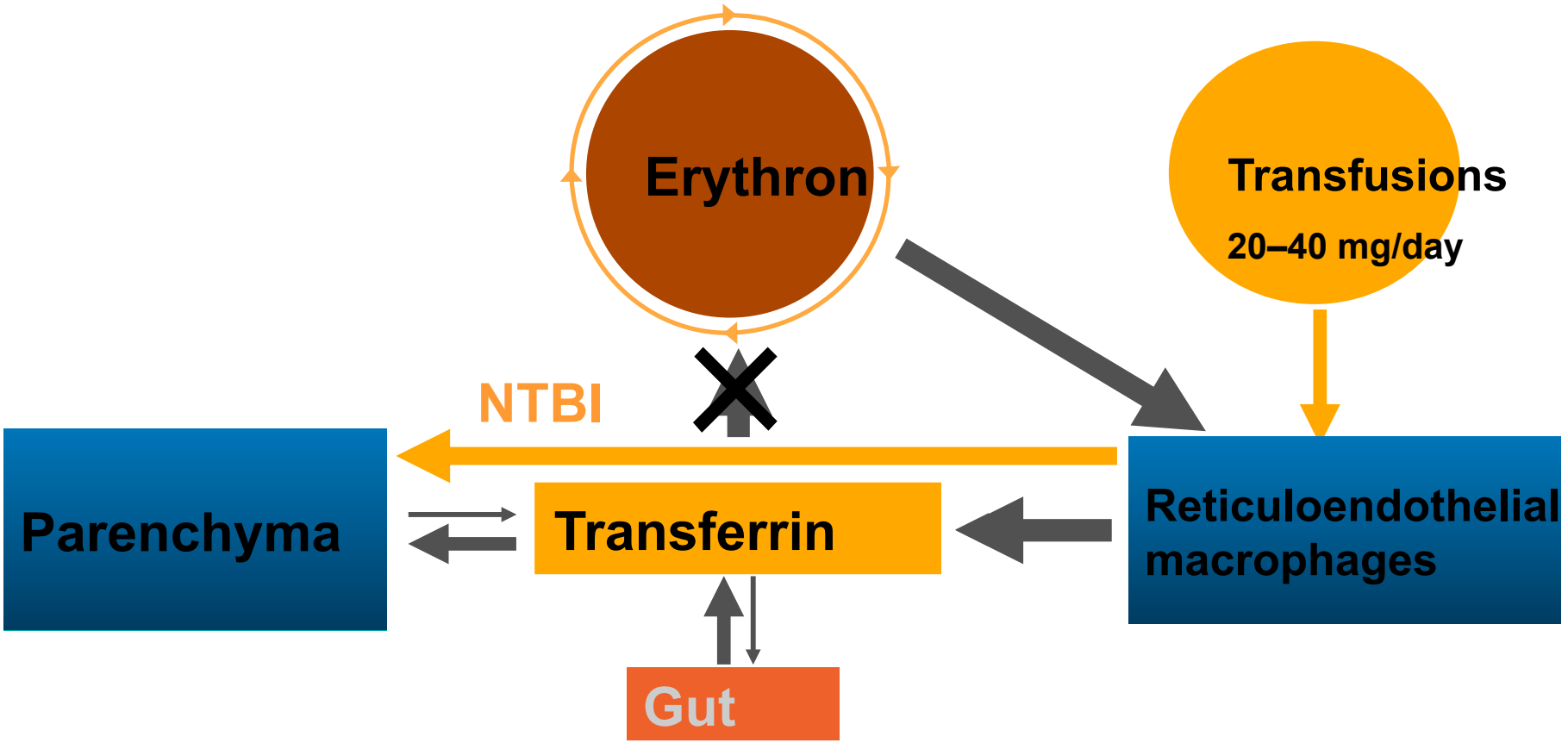


Iron balance is disturbed by blood transfusion because the body cannot remove the excess iron

NTBI=non–transferrin-bound iron.

Hershko C, et al. *Ann NY Acad Sci*. 1998;850:191-201.

Imbalance of Distribution and Turnover of Body Iron With Transfusion Therapy



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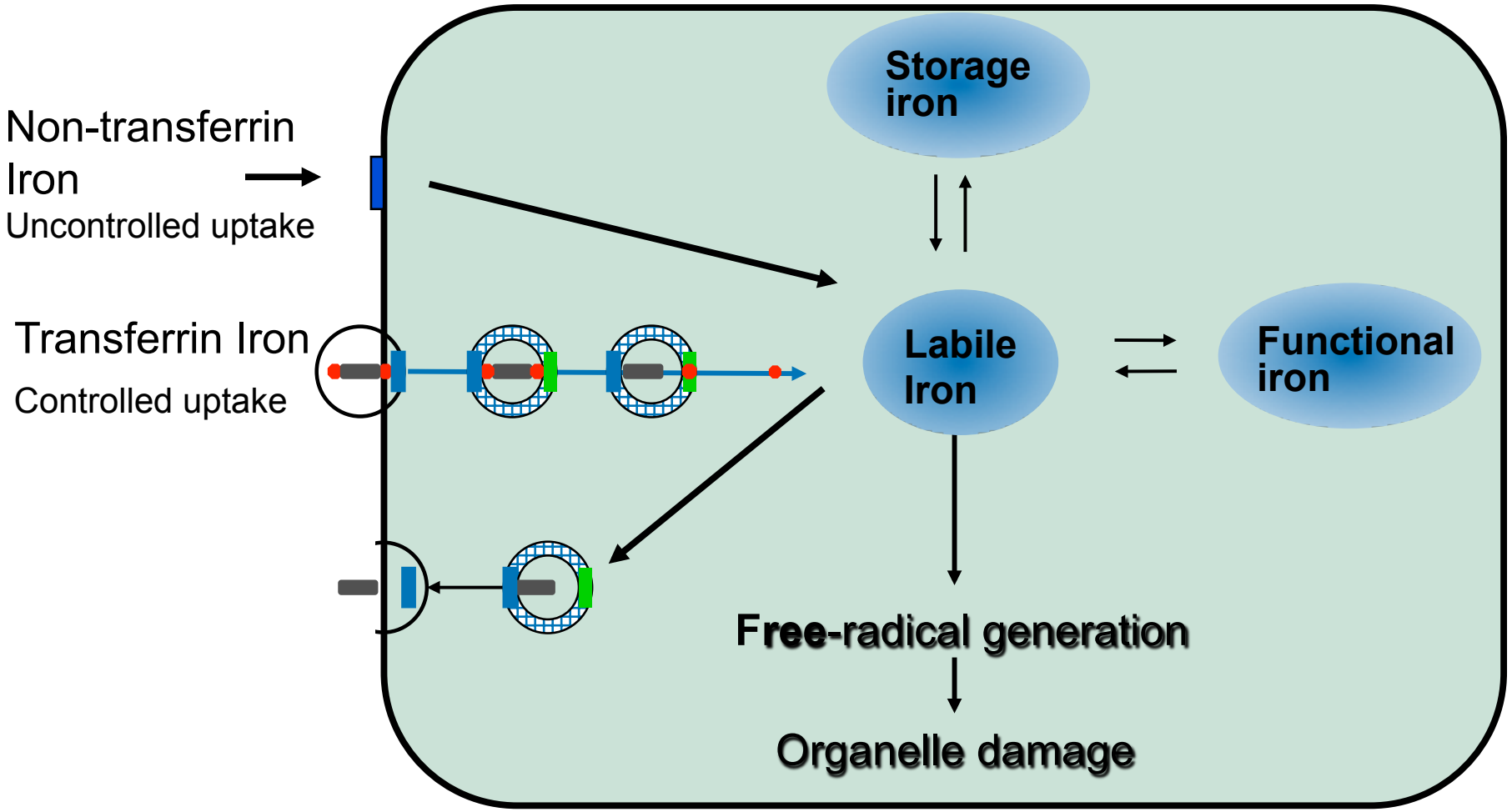
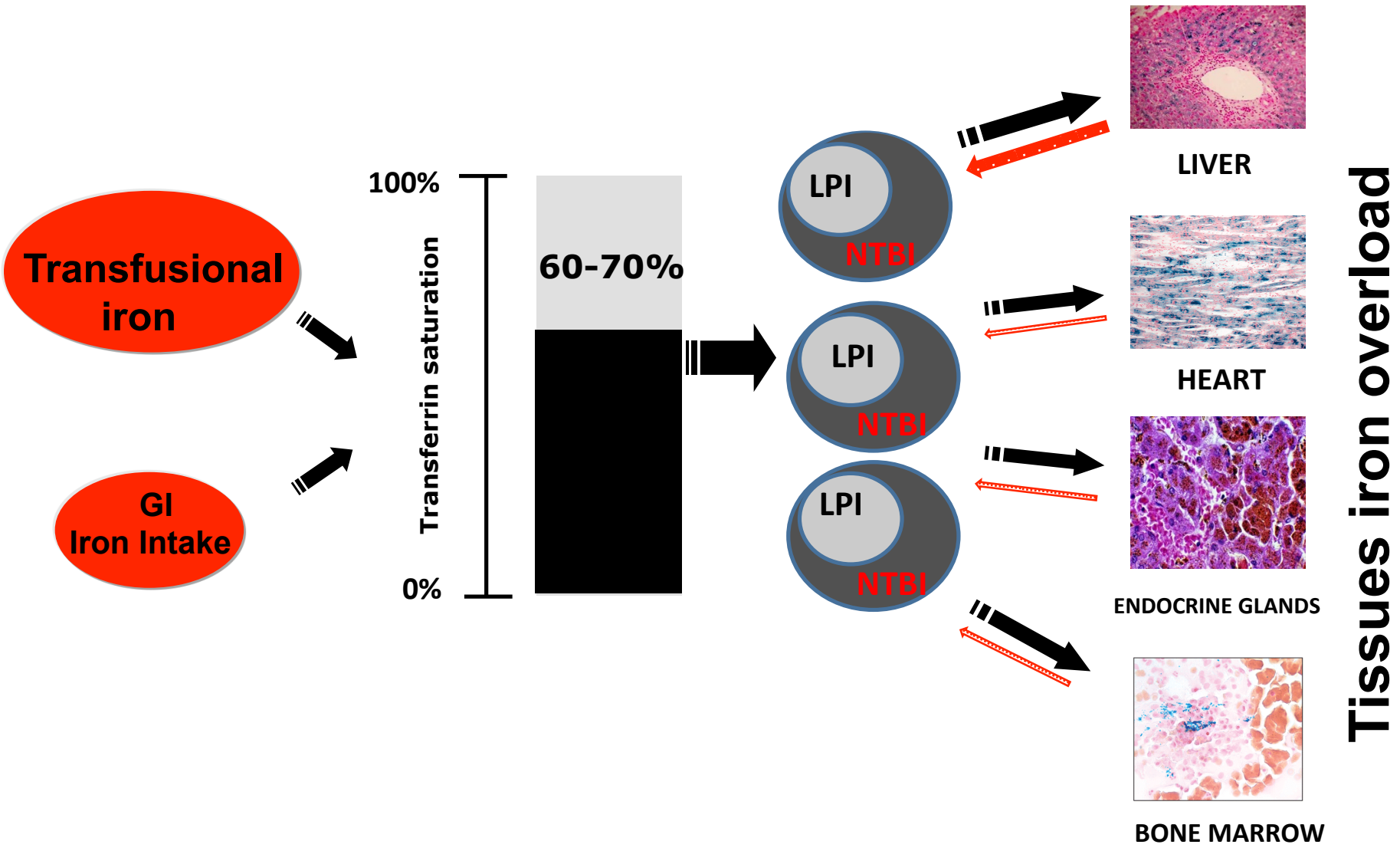
Uncontrolled Uptake of Labile Iron Leads to Cell and Organ Damage





Modified from Angelucci & Pilo
Ann N Y Acad Sci. 2016 Mar;1368(1):115-21

Iron-dependent damage

Haber-Weiss reaction

$$O_2^{\cdot -} + H_2O_2\ O_2 \xrightarrow[cat]{Fe} O_2 + OH^- + OH^{\cdot}$$

Fenton reaction

$$O_2^{\cdot -} + Fe^{3+} \longrightarrow O_2 + Fe^{2+}$$

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH^{\cdot}$$

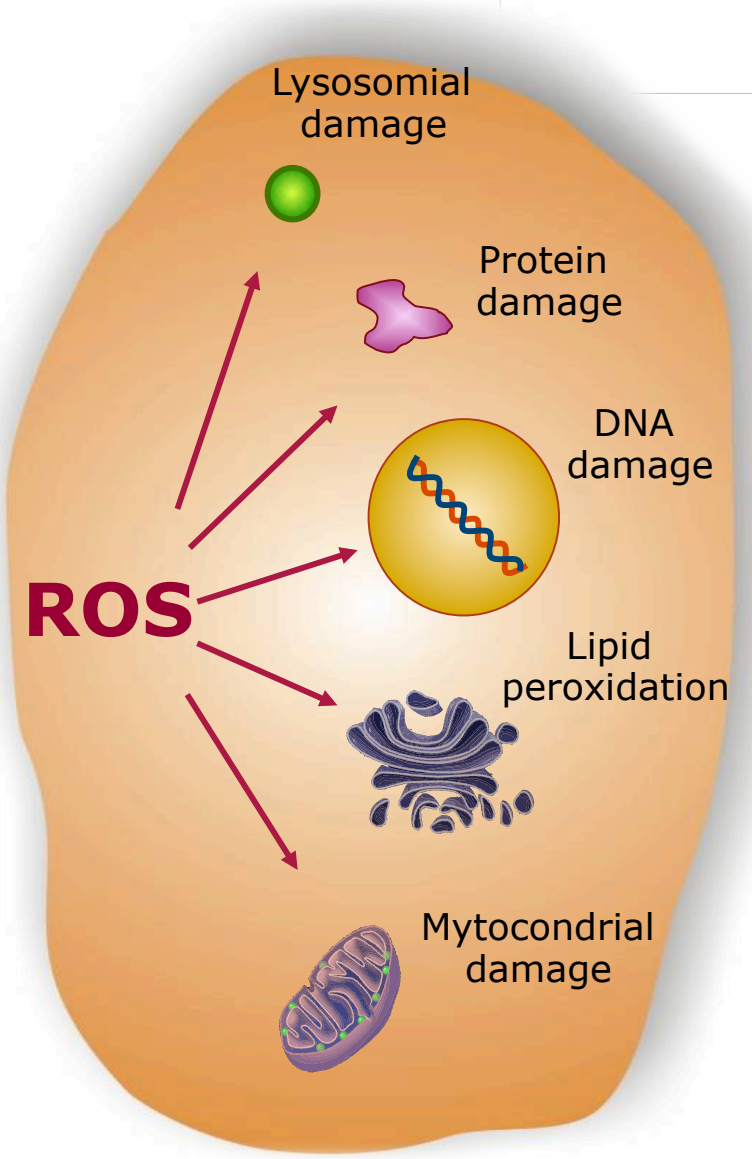
Lipoperoxide formation

$$LH + OH^{\cdot} \rightarrow H_20 + L^{\cdot} \rightarrow L^{\cdot} + LH \rightarrow LOO^{\cdot}$$

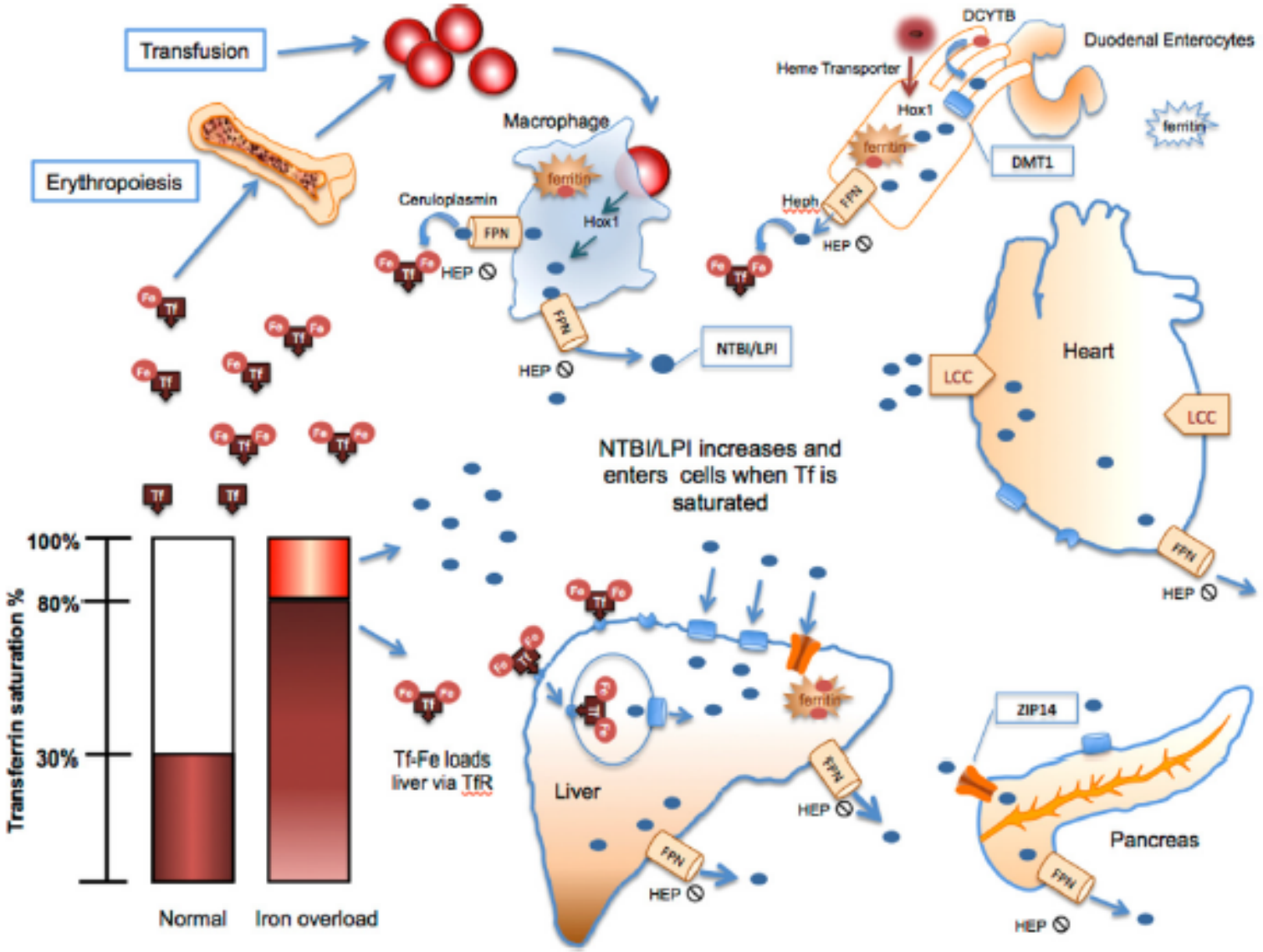
$$LOO^{\cdot} + LH \longrightarrow LOOH + L^{\cdot}$$

$$LOOH + Fe^{2+} \longrightarrow OH^- + LO^{\cdot} + Fe^{3+}$$

$$LOOH + Fe^{3+} \longrightarrow LOO^{\cdot} + H^+ + Fe^{3+}$$

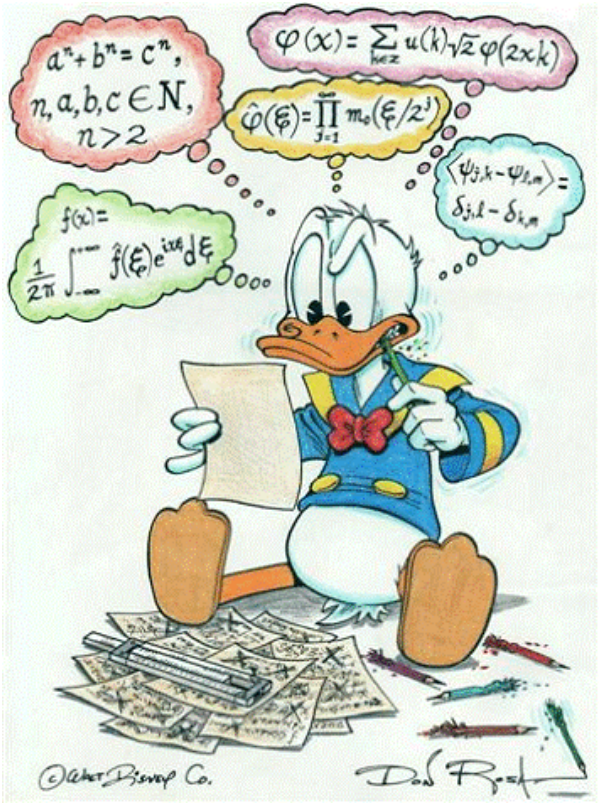


Jomova et al. Toxicology. 2011;283:65


Transfusion
Erythropoiesis
Macrophage
ferritin
Hox1
Ceruloplasmin
FPN
HEP
NTBI/LPI
DCYTB
Duodenal Enterocytes
Heme Transporter
DMT1
Heph
Heart
LCC
NTBI/LPI increases and enters cells when Tf is saturated
100%
80%
30%
Transferrin saturation %
Normal
Iron overload
Tf-Fe loads liver via TfR
Liver
ZIP14
Pancreas

…pituitary, pancreatic and cardiac iron detected by MRI reflects **time-averaged exposure to toxic reactive iron** since loading of these organs essentially only occurs when NTBI/LPI enters through ion channels and transporters.

Coates, Carson Wood & Berdoukas. Management of Iron Overload in Hemoglobinopathies: What is the 1 Appropriate Target 2 Iron Level?. Annals of the New York Academy of Sciences 2016



Fe Toxicity tissue =

$$\sum \underline{\text{Tissue Reactive Iron}} \times \underline{\text{Genetics}} \times \underline{\text{Environmental Factors}} \times \underline{\text{Time}}$$

Coates TD. Free Radic Biol Med 2014

Fe Toxicity tissue =

Tissue Reactive Iron **x** Genetics **x** Environmental Factors **x** Time

ΣTissue Reactive Iron	Tissue toxicity sums (Σ) ROS generation
Genetics	The marrow pathology Differences in iron transport Antioxidant defense mechanisms
Environmental Factors	Nutritional status Blood transfusions Drugs that may modulate iron toxicity Co morbidities (Viral infections, ecc) Administration of chelating agents
Time	Time of exposition

Perspective

"Iron toxicity depends on many factors in addition to the level of iron per se"

- There is a different relation (iron and damage) for different tissues
- Tissue toxicity sums (Σ) over time (ΔTime)
- It will likely never be possible to accurately predict toxicity from individual component factors.

Coates TD. Free Radic Biol Med 2014

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Key differences between Thalassemia and MDS and otherHemolymphopaties

- **Ethiopathogenesis**
  - monogenetic mutation vs multifactorial acquired known and unknown mutations
- **Etiopathogenesis.**
  - Hemopoietic stem cell involvement
- **Age at diagnosis**
  - no comorbidity vs comorbidity,
  - stem cell aging
- **Natural history of pathology without therapy**
  - chronic vs progression

Different pattern of iron overload in different diseases.

		TDT Suboptimal transfusion chelation regimen	TDT standardized transfusion regimen (pre transfusion HB ≥ 9)	NTDT	HH	Lower risk MDS
Iron input	**Transfusions**	+/++	+++	-/+	-	++/+++
	GI iron adsorption	+++	+	++	++	+ (?)
Patient	**Aging**	-	-	-	++	+++
	Age related comorbidity	-	-	-/+	+/++	+++
	anemia	+++	+	++	-	+++
Erythropoiesis	**ineffective**	+++	+++	++	-	+/++
	Hyperplastic	+++	+	+++	-	+/++
		↓	↓	↓	↓	↓
Major causes of death		**Anemia Cardiac disease**	**Cardiac disease Liver disease**	**Cardio-vascular disease Liver disease (?)**	**Liver disease**	**Cardiac disease Infectious disease Liver disease. Acute leukemia**

Angelucci E., Urru S.A.M., Pilo F., Piperno A. Myelodysplastic syndromes and iron chelation therapy. Mediterr J Hematol Infect Dis 2017, 9(1): e2017021, DOI: http://dx.doi.org/10.4084/MJHID.2017.021

Fe Toxicity tissue =

Tissue Reactive Iron **x** Genetics **x** Environmental Factors **x** Time

		Thal vs MDS	
		Worse in Thal	Worse in MDS
ΣTissue Reactive Iron	Tissue toxicity sums (Σ) ROS generation		+ +
Genetics	The marrow pathology Differences in iron transport Antioxidant defense mechanisms	+/-	+++ +/- +++
Environmental Factors	Nutritional status Blood transfusions Drugs that may modulate iron toxicity Co morbidities (Viral infections, ecc) Administration of chelating agents	+	++ +++ ++ ++
Time	Time of exposition	+++	

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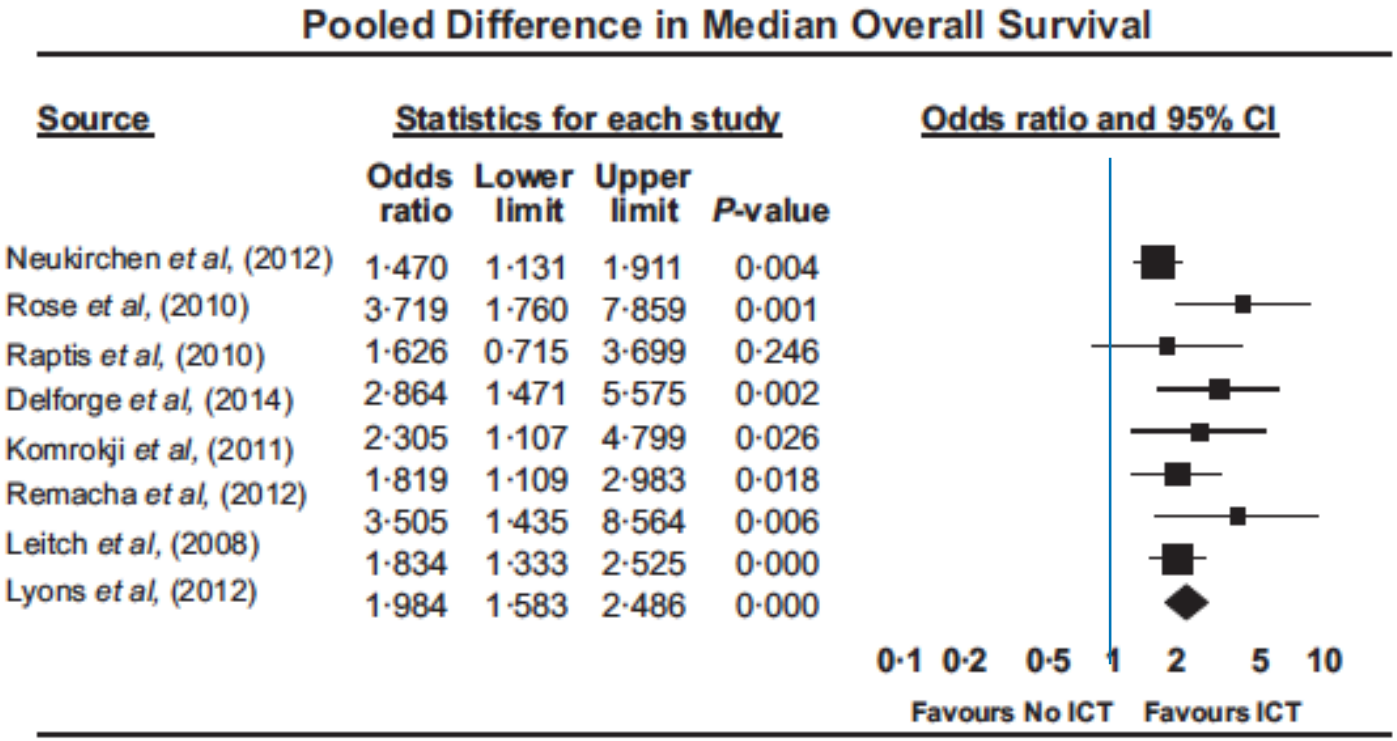
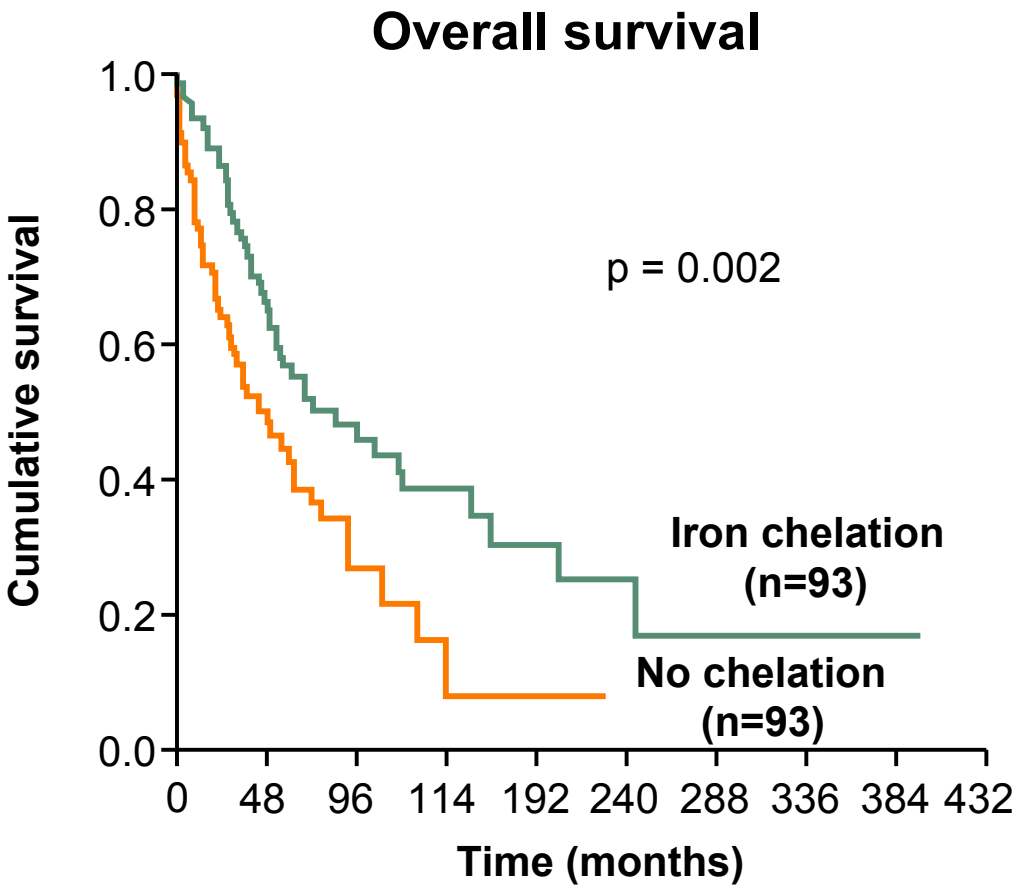
Iron chelation and survival in MDS Meta-analysis



Mainous AG 3rd, Tanner RJ, Hulihan MM, Amaya M, Coates TD. **The impact of chelation therapy on survival in transfusional iron overload: a meta-analysis of myelodysplastic syndrome.** Br J Haematol 2014 Dec; 167(5):720-3.

Iron Chelation Therapy improves Survival in MDS Patients: Matched-pair Analysis



Median cumulative survival
Chelation: 75 months
No chelation: 49 months

Fox *et al. Blood*. 2009;114:[abstract 1747].

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Comparison of 24-month outcomes in chelated and non-chelated lower-risk patients with myelodysplastic syndromes in a prospective registry

Roger M. Lyons[a,b,*], Billie J. Marek[b,c], Carole Paley[d], Jason Esposito[d], Lawrence Garbo[b,e], Nicholas DiBella[b,f], Guillermo Garcia-Manero[g]

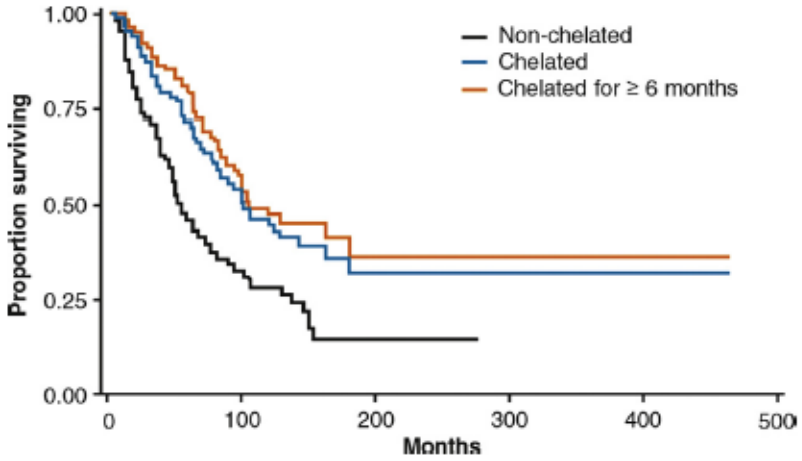


Fig. 1. Overall survival. Chelated patients had longer overall survival compared with non-chelated patients. Kaplan–Meier curves for overall survival showed median (25th, 75th percentile) time to death from MDS diagnosis in the non-chelated, chelated, and chelated ≥6 months groups was 52.2 (24.0, 136.2), 99.3 (54.1, not attained [NA]), and 104.4 months (63.4, NA), respectively ($p < .0001$ for non-chelated vs. both chelated groups).

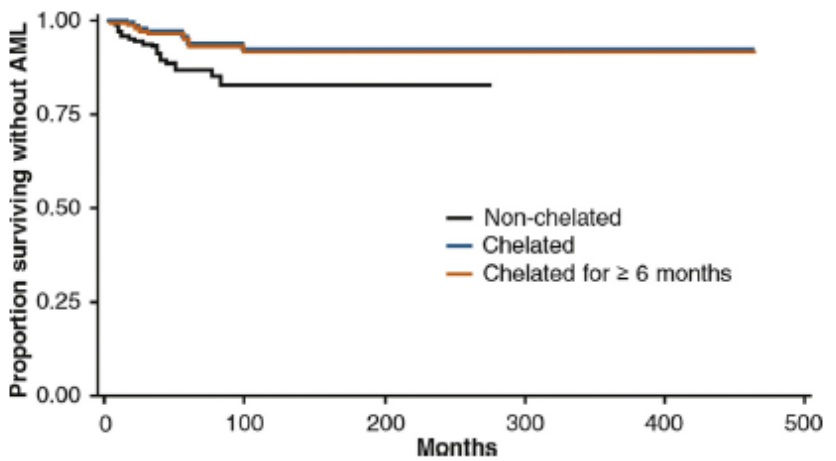


Fig. 3. Progression to AML. Time to progression to AML trended longer in chelated patients. Kaplan–Meier curves for progression to AML showed a mean (standard deviation) time to progression of 27.3 (20.3), 40.6 (25.3), and 40.8 months (27.0) in the non-chelated, chelated, and chelated ≥6 months groups, respectively. Curves for the chelated groups were practically identical and overlapped. No statistical difference was observed among groups. AML, acute myeloid leukemia.

Ann Hematol (2015) 94:779–787
DOI 10.1007/s00277-014-2274-y

ORIGINAL ARTICLE

Evolution of iron overload in patients with low-risk myelodysplastic syndrome: iron chelation therapy and organ complications

Ángel F. Remacha · Beatriz Arrizabalaga · Ana Villegas · María Soledad Durán · Lourdes Hermosín · Raquel de Paz · Marta Garcia · Maria Diez Campelo · Guillermo Sanz · On behalf of the IRON-2 Study Group

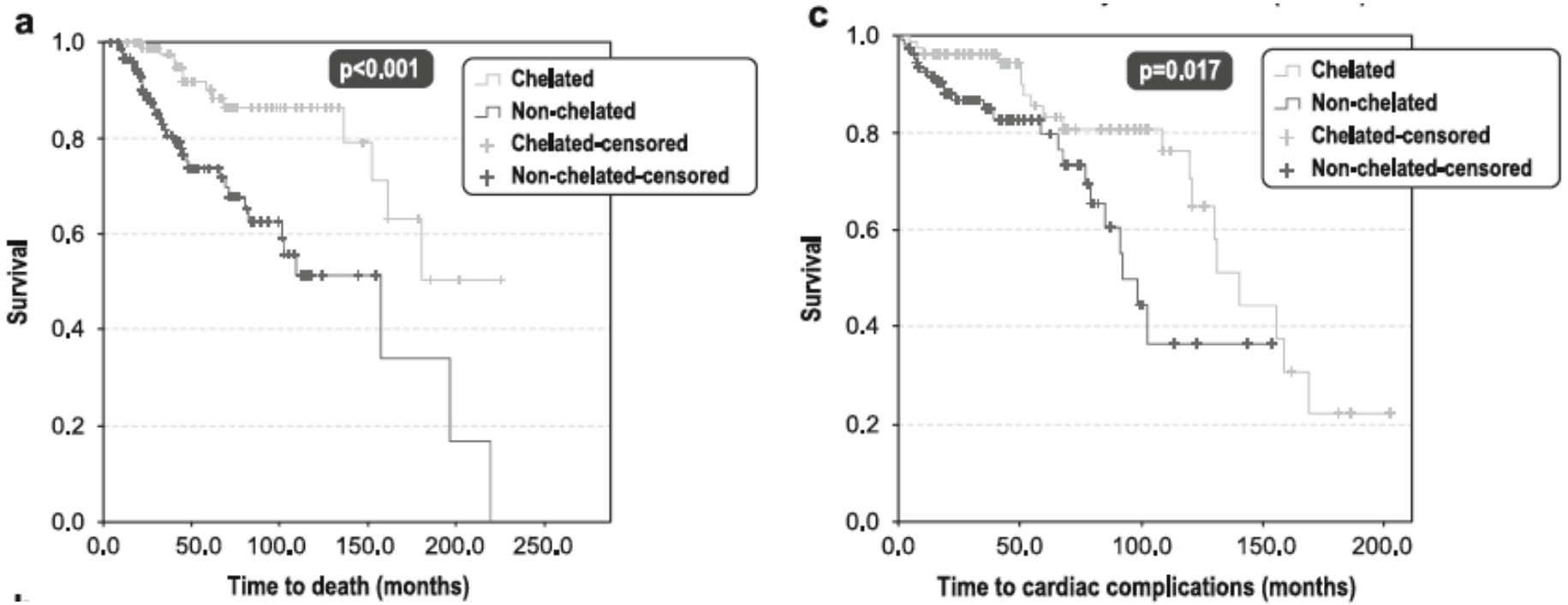


Fig. 1 Overall survival (a), leukemia-free survival (b), cardiac event-free survival (c)

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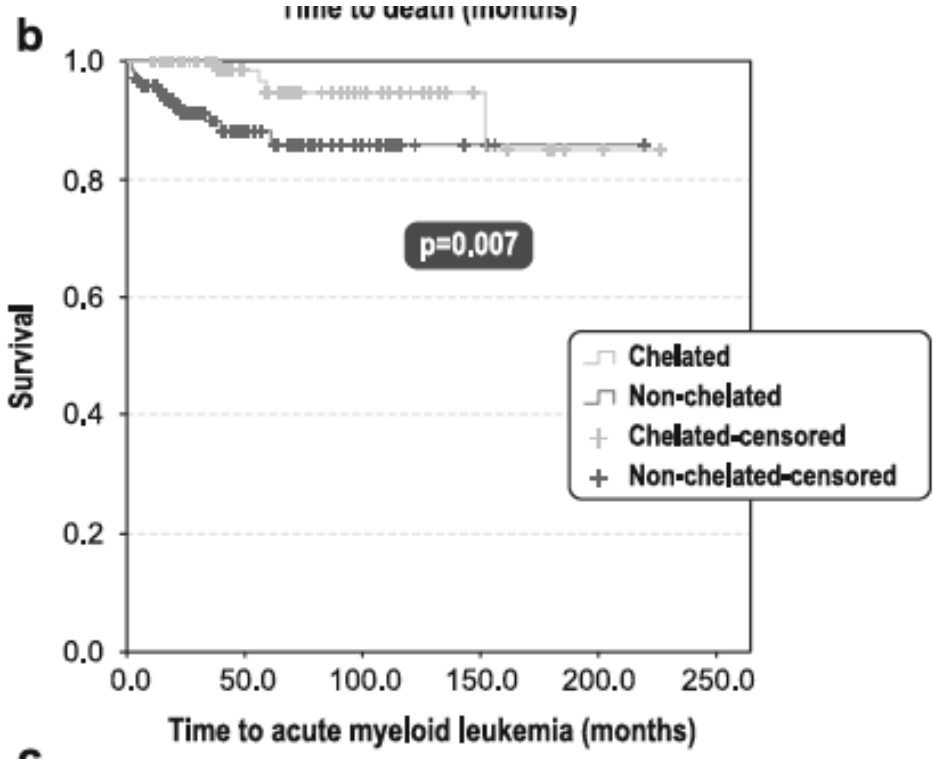

Fig. 1 Overall survival (**a**), leukemia-free survival (**b**), cardiac event-free survival (**c**)

Countries	Transfusion status	Serum ferritin (ng/mL)	Patient profile	Target serum ferritin level
Italian (Alessandrino et al., 2002)	≥ 50 RBC units	NR	• Life expectancy > 6 months	NR
UK (Bowen et al., 2003)	~ 25 RBC units (5 g iron)	NR	• Pure sideroblastic anemia • del 5q	< 1000
US (NCCN) (v2. 2011)	20-30 RBC units (≥5-10 g iron)	> 2500	• IPSS Low or Int-1 • potential transplant patients	For pts with SF >2500, aim to decrease to <1000
International (Gattermann et al., 2005)	transfusion-dependent	> 1000-2000	• RA, RARS, del 5q • IPSS Low or Int-1	NR
Japanese (Suzuki et al., 2008)	> 40 Japanese units	> 1000	• Life expectancy > 1 year	500-1000
Canadian (Wells et al. 2008)	transfusion-dependent	> 1000	• RA, RARS, del 5q • IPSS Low or Int-1 • IPSS Int-2 or High (if SF >1000 and • SCT candidates/life expectancy >1yr)	NR; reduce dose when < 2000; discontinue chelator when < 1000
Spanish (Arrizabalaga et al., 2008)	transfusion-dependent	> 1000	• IPSS Low or Int-1 • WPSS Very low, Low, or Int • Spanish prognostic index Low risk	NR
Austrian (Valent et al., 2008)	transfusion-dependent	> 2000	• Life expectancy > 2 years	NR
Israeli (Mittelman et al., 2008)	20-25 RBC units	> 1000	• Low or Int-1 (IPSS) • Candidates for SCT	< 500 to < 1000
MDS Foundation (Bennett et al., 2008)	2 RBC units/month for ≥1 year	> 1000	• Life expectancy > 1 year	NR
Italian update (Santini et al., 2010)	≥ 20 RBC units (4 g iron)	NR	• Low or Int-1 (IPSS) • Int-2, High when responding to disease-modifying agent or candidates for SCT	NR

Indication to start chelation

1. Bulky iron accumulation (serum ferritin / number of transfusions)

2. Life expectancy

Indication to start chelation

1. Bulky iron accumulation (serum ferritin / number of transfusions)

2. Life expectancy

Development of organ damage require:

- overload (bulky disease)
- time (years)

Fe Toxicity tissue =

Tissue Reactive Iron **x** Genetics **x** Environmental Factors **x** Time

		Thal vs MDS	
		Worse in Thal	Worse in MDs
ΣTissue Reactive Iron	Tissue toxicity sums (Σ) ROS generation		+ +
Genetics	The marrow pathology Differences in iron transport Antioxidant defense mechanisms	+/-	+++ +/- +++
Environmental Factors	Nutritional status Blood transfusions Drugs that may modulate iron toxicity Co morbidities (Viral infections, ecc) Administration of chelating agents	+	++ +++ ++ ++
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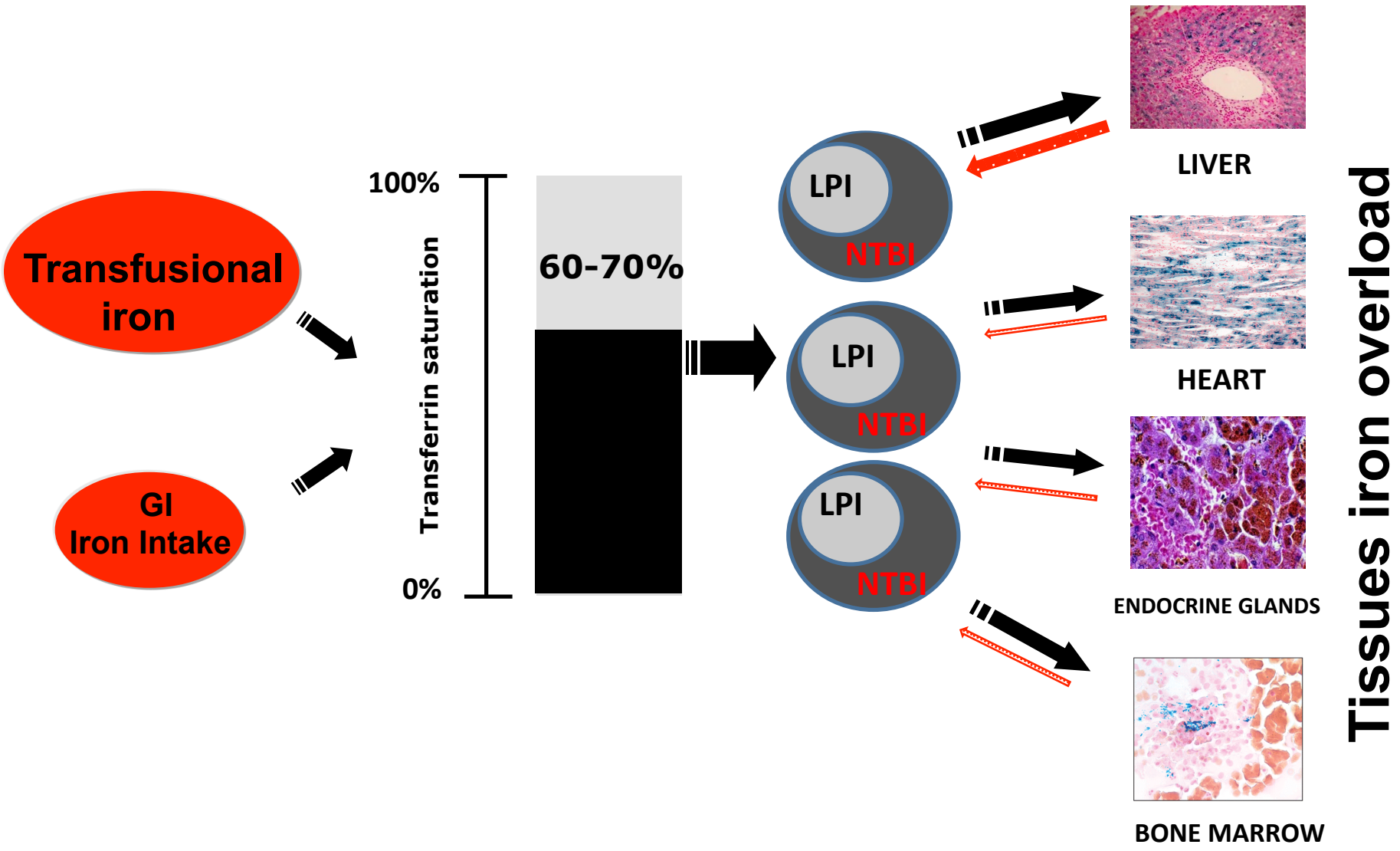

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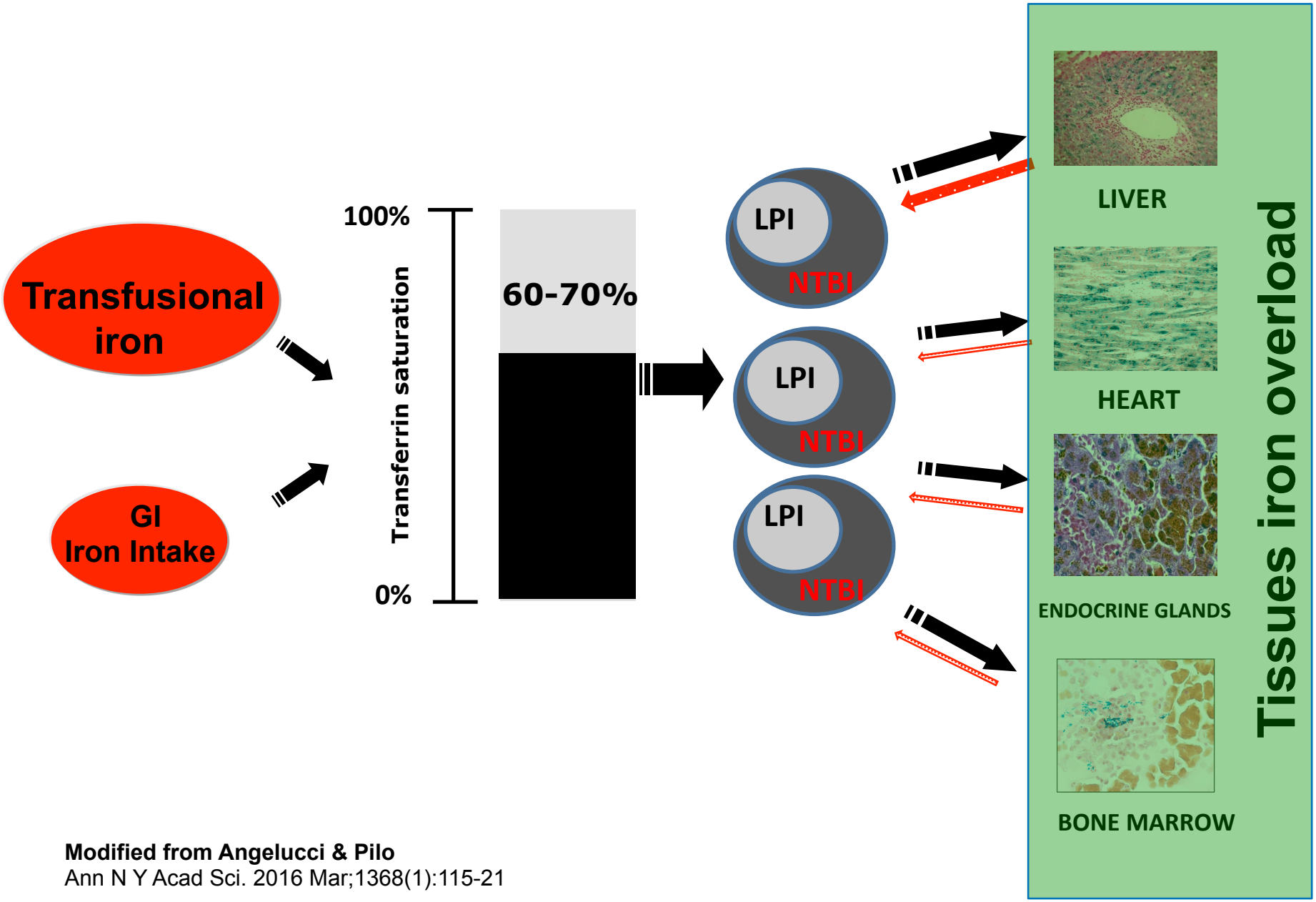

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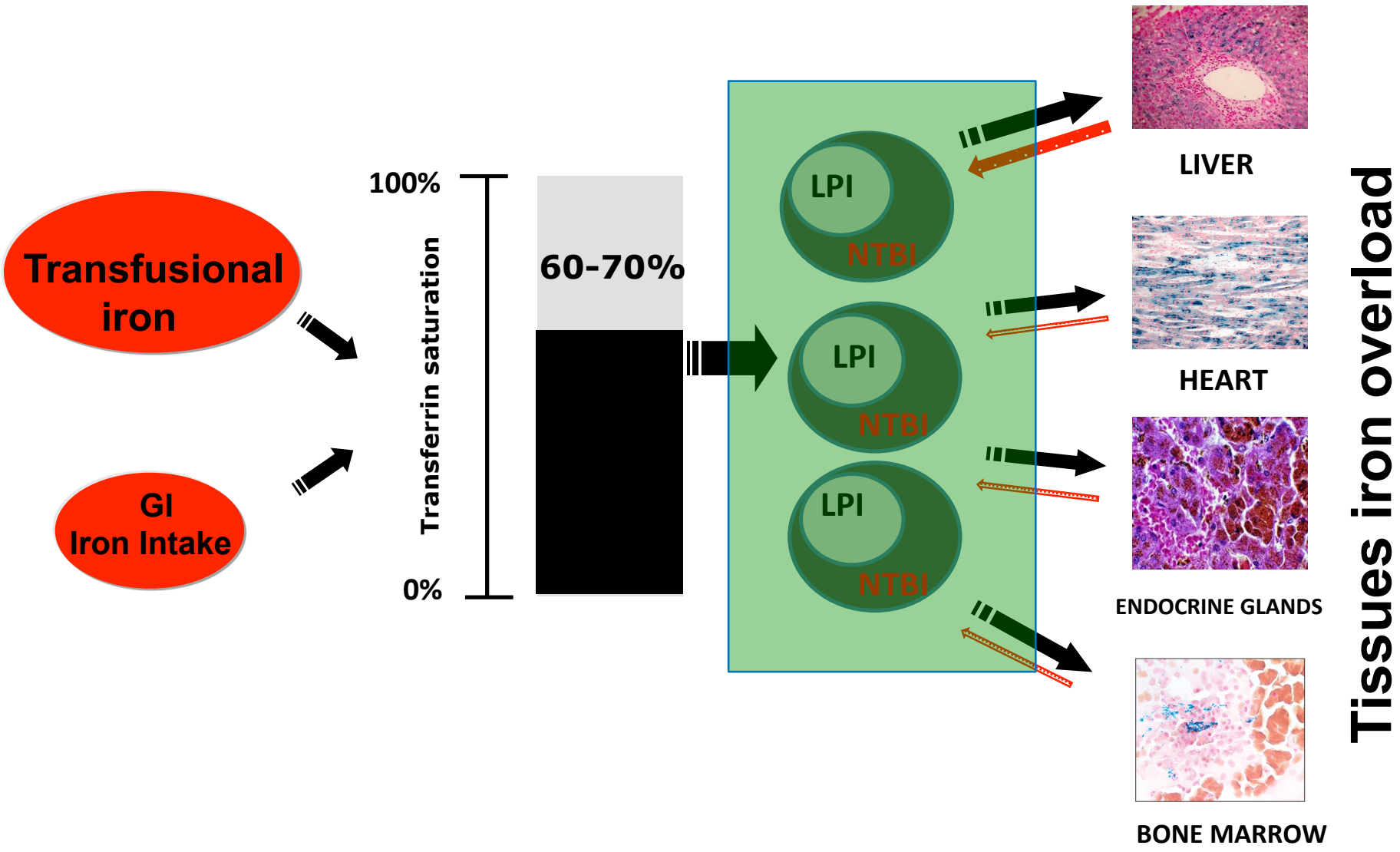

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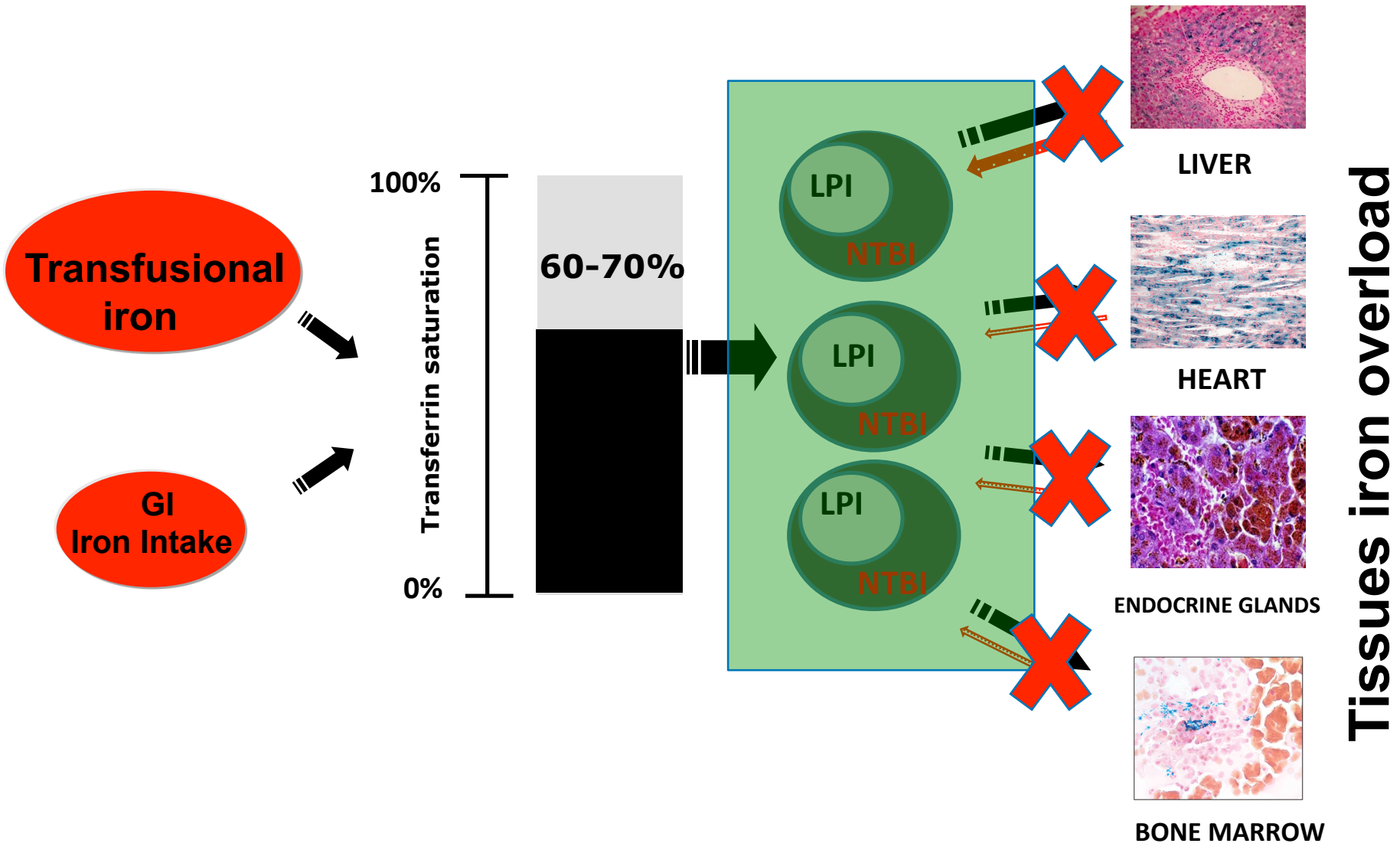

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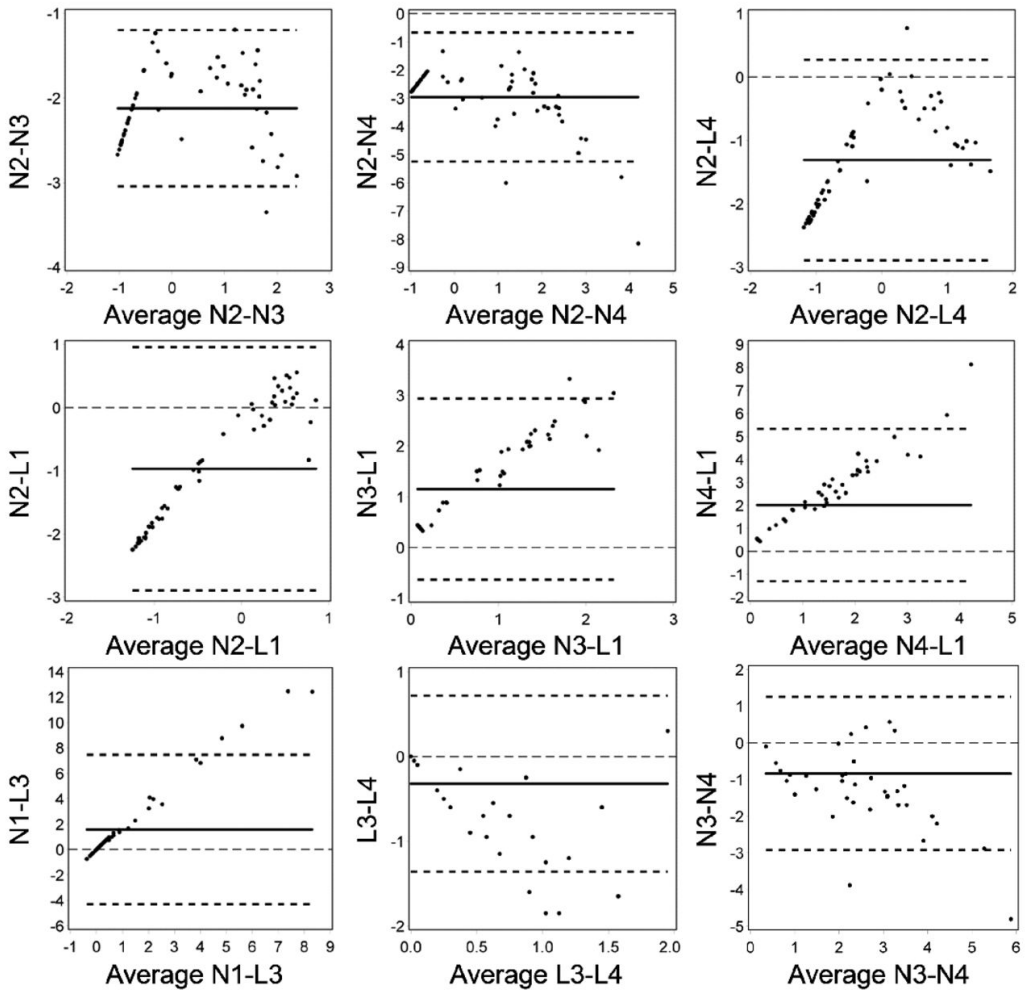
Bland-Altman plots showing differences in mean NTBI or LPI levels (µmol/L) between two methods versus the average of the mean values of these two methods.



Louise de Swart et al. Haematologica 2016;101:38-45

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Clinical Protocol

Title: Early and low dose Deferasirox (3.5 mg/kg FCT) to suppress NTBI and LPI as early intervention to prevent tissue **iron** overload in lower risk **MDS**.

IRON – MDS

ID Study: IRON - MDS
EudraCT number: ……

INVESTIGATOR SPONSOR
Fondazione Italiana Sindromi Mielodisplastiche ONLUS (FISM)

COORDINATING INVESTIGATOR/S	Dr. Emanuele Angelucci, Genova, Italia
WRITING COMMITTEE AND SCIENTIFIC SUPPORT	Dr Mario Capasso, Napoli, Italia Prof Matteo Della Porta, Milano, Italia Prof Domenico Girelli, Verona, Italia Dr Ester Oliva, Reggio Calabria, Italia Dr Federica Pilo, Cagliari, Italia Prof. Valeria Santini, Firenze, Italia

Version and date of Protocol: Version 4, May 2, 2018

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Stone, bronze, gold, and silver come and go; iron always has the last word

Thank you for your kind attention