Iron chelation when and how?

MYELODISPLASTIC SYNDROMES: CAOS AND ORDER
IRST, Meldola
26 October 2018

Federica Pilo
U.O. Ematologia e CTMO
Ospedale Oncologico "A . Businco"
Cagliari

DISCLOSURE

- NOVARTIS ADVISORY BOARD AND HONORARIA

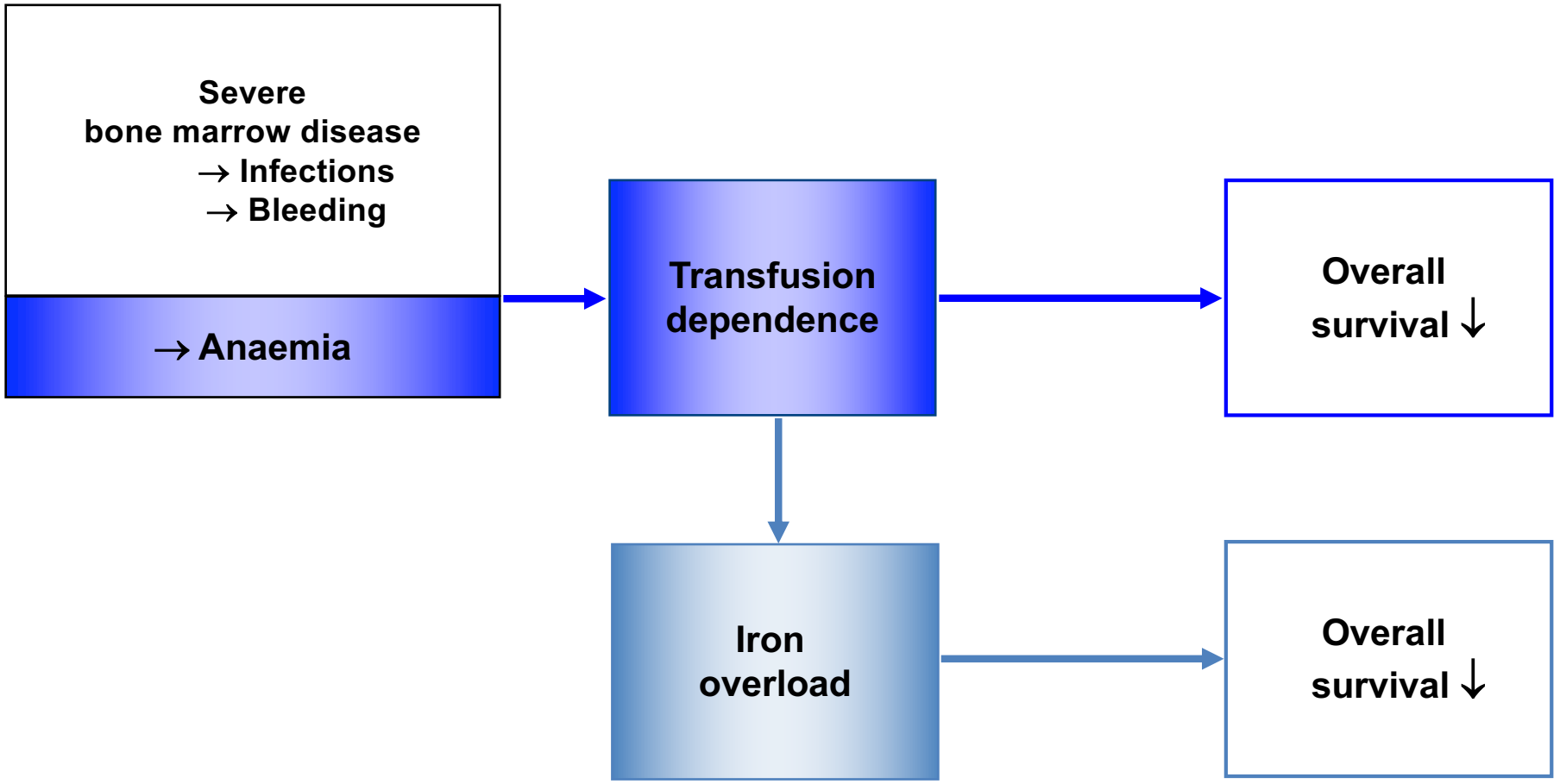
AGENDA

- What we know and what we don't know abaut iron toxicity and iron chelation
- Highlights in relationship between iron, ROS and haemopoiesis
- Clinical implications and future research directions

AGENDA

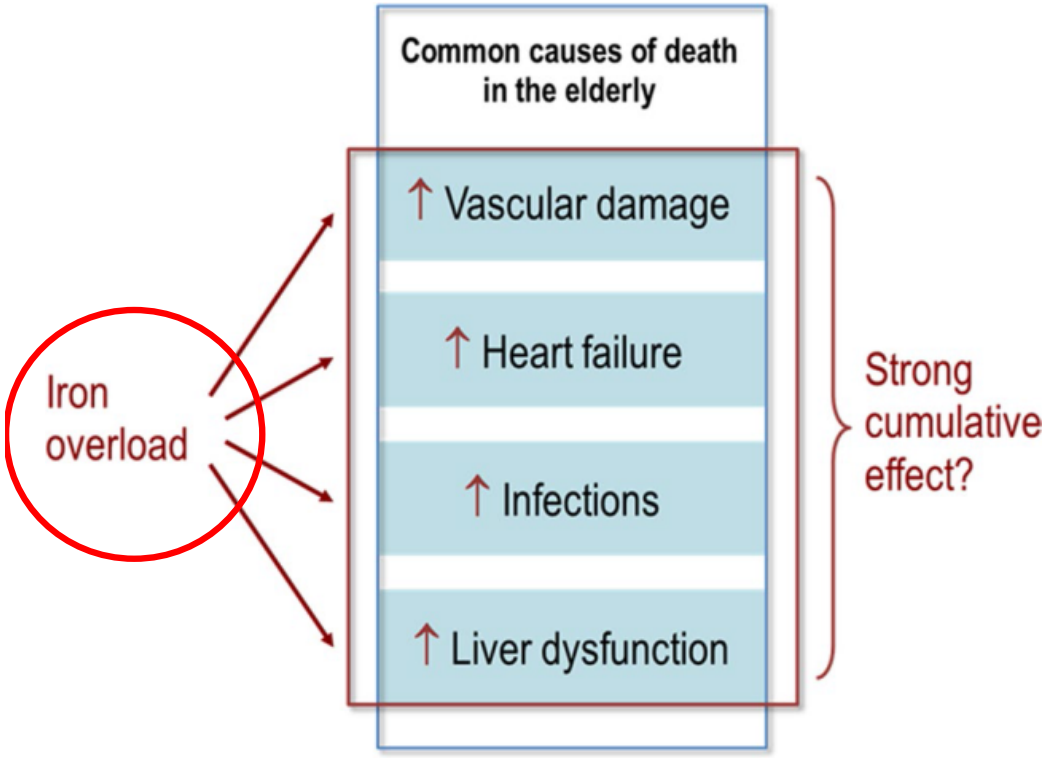
- What we know and what we don't know abaut iron toxicity and iron chelation
- Highlights in relationship between iron, ROS and haemopoiesis
- Clinical implications and future research directions

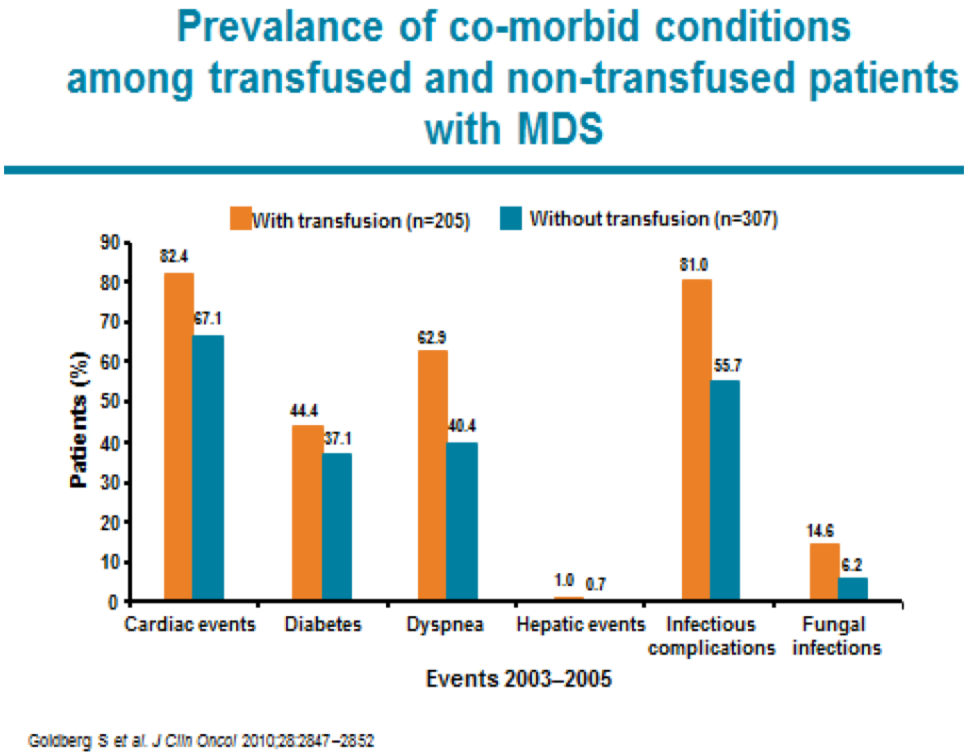
Independent impact of iron overload and transfusion dependency on survival in patients with MDS



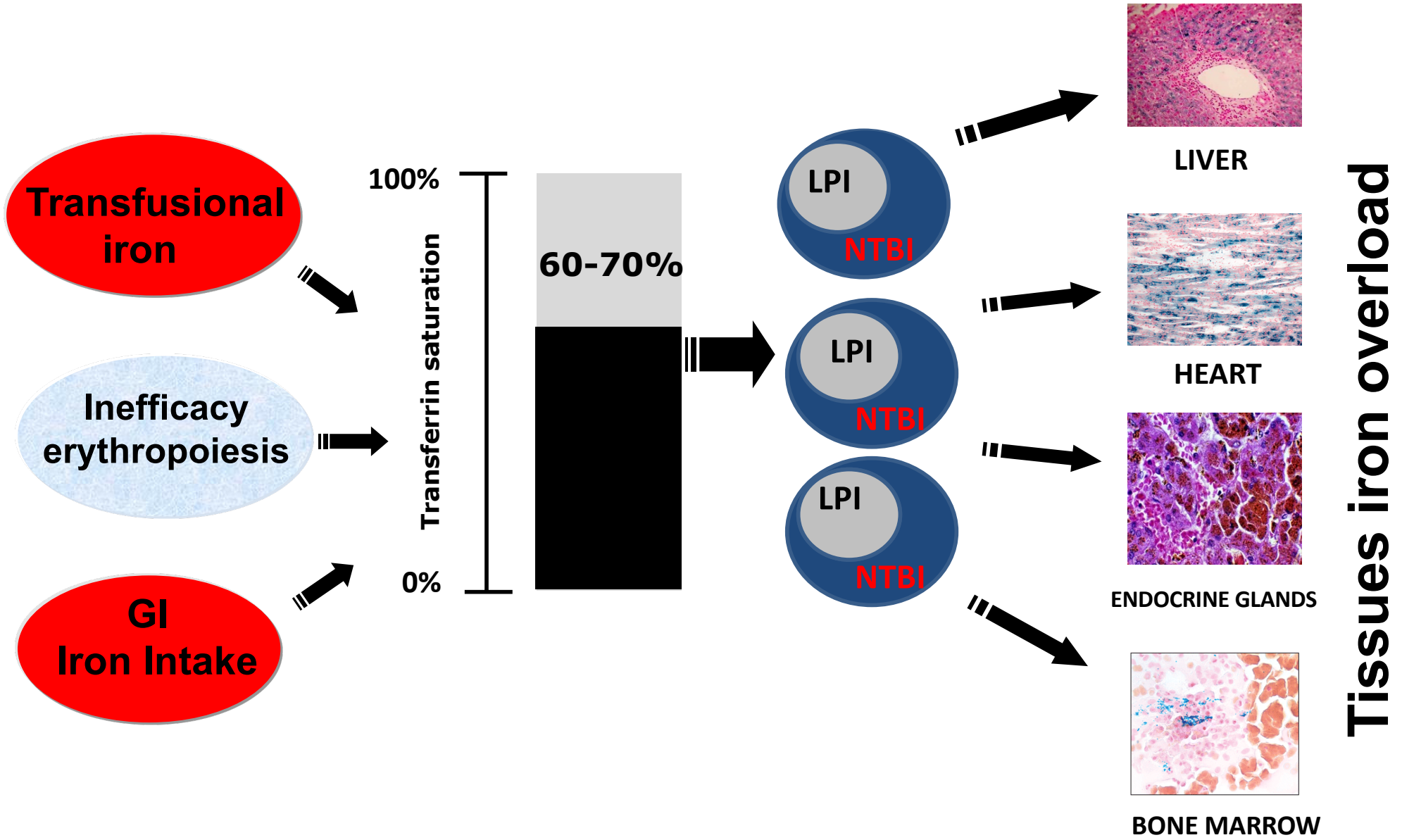
Gattermann N, Rachmilewitz EA. Ann Hematol. 2011;90:1-10.

Iron-related complications overlap with age-related clinical problems

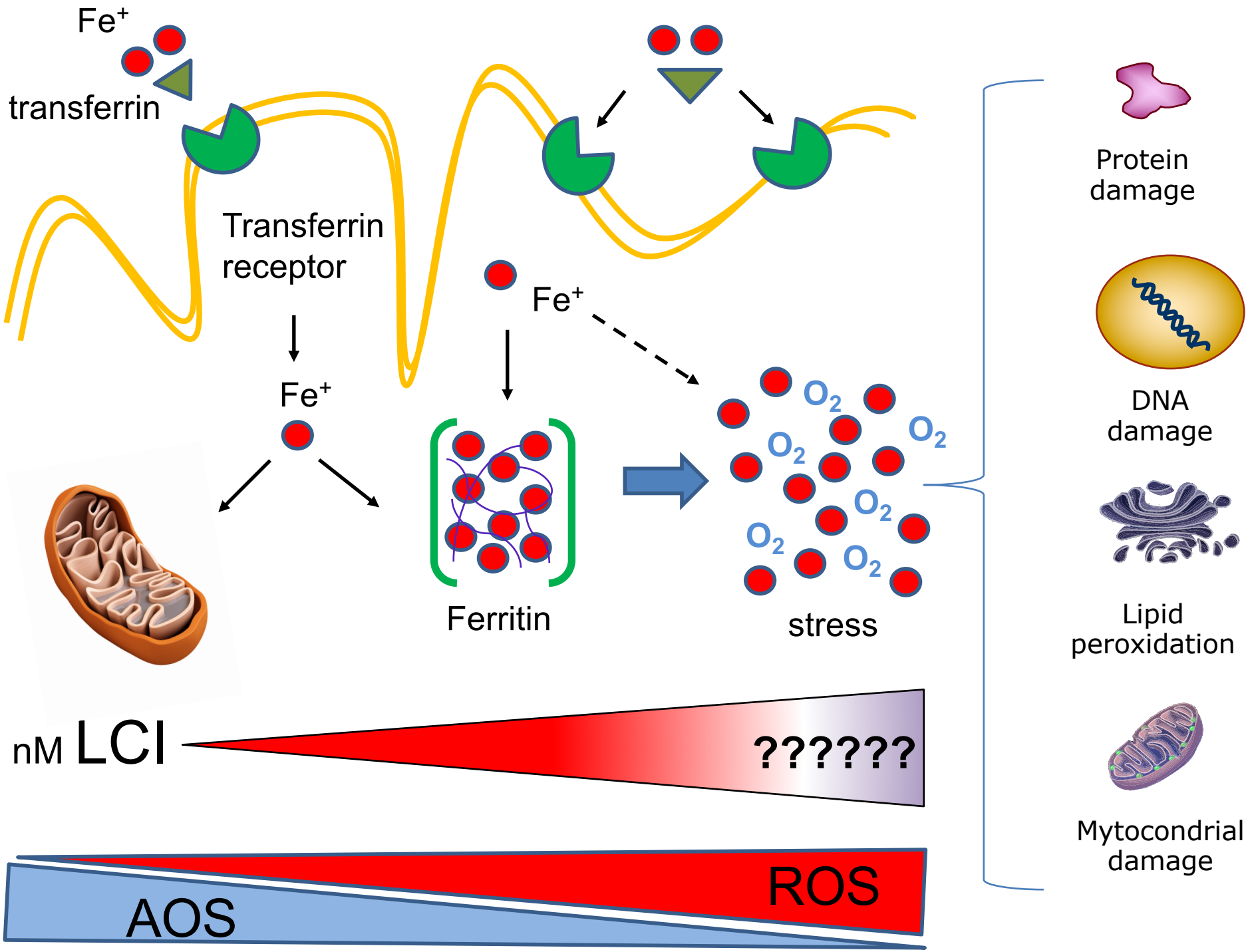




Gattermann N. Int J Hematol. 2018 Jan;107(1):55-63



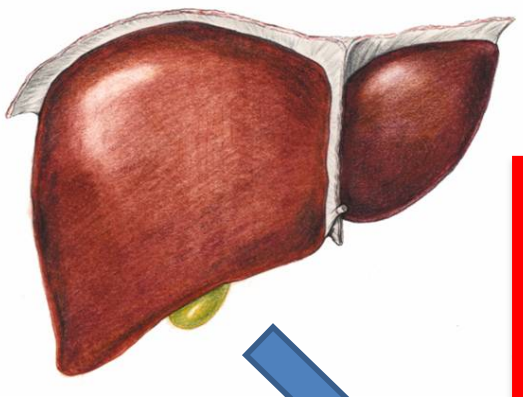
Adapted by Ann N Y Acad Sci. 2016 Mar;1368(1):115-21



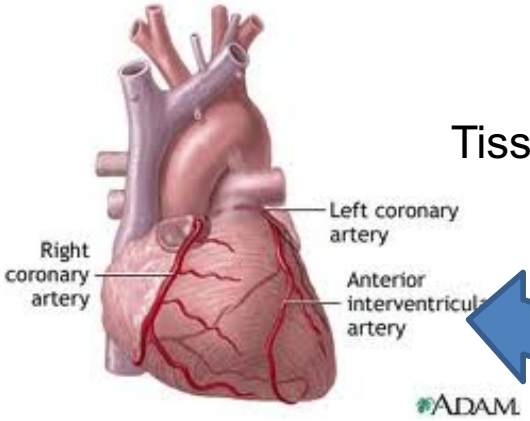
LCI: Labile cellular iron, AOS: antioxidant system, ROS: Reactive oxygen species

Pilo F. et al, paper under submission

Why Toxicity due to Iron Overload Occurs Mainly in Liver and Heart?



High levels of mitochondrial activity



Tissue damage

ROS production

Fe Toxicity tissue =

ΣTissue Reactive Iron **x** Genetics **x** Environmental Factors **x** ΔTime

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	Duration of exposition

Coates TD. Free Radic Biol Med 2014

Fe toxicity tissue =

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

1) there is a different relation for different tissues

2) tissue toxicity sums (Σ) over time (ΔTime)

3) it will likely never be possible to accurately predict toxicity from individual component factors.

Coates TD. Free Radic Biol Med 2014

Cardiac function and Iron

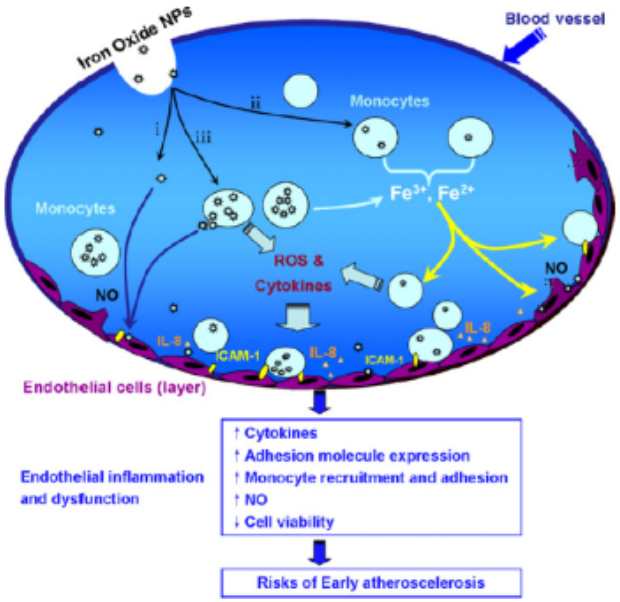
- Heart failure, like other iron-related organ damage, may not only depend on tissue iron concentrations but also on the duration of chronic exposure to non-transferrin-bound iron and labile plasma iron which generate oxidative stress

$$\text{Fe toxicity}_{\text{tissue}} \cong \sum^{\text{time}} \text{tissue reactive iron} \times \text{genetics} \times \text{environmental factors} \times \Delta\text{time}$$

- The **heart is more vulnerable to iron toxicity than the liver**
- clinically relevant cardiac dysfunction occurs at much lower iron concentrations than detectable with normal methods such as Ferritin or MRI

Gattermann N. Int J Hematol. 2018 Jan;107(1):55-63
Coates et al Ann. N.Y. Acad. Sci. 1368 (2016) 95–106

Vascular iron toxicity

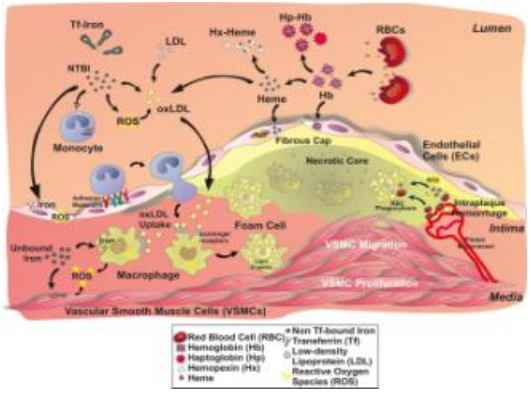


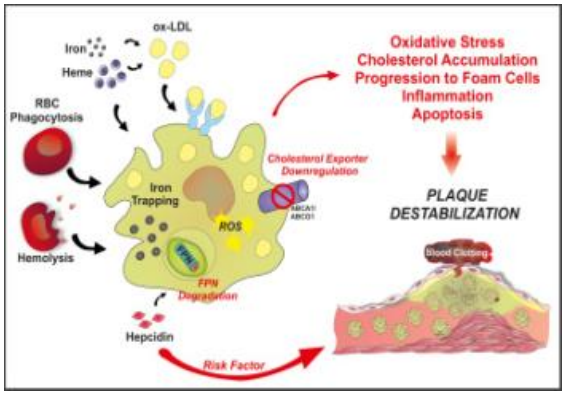
- age and iron worsen atherosclerosis

- Role of macrophages in the wall of vessels in the accumulation of iron (deriving from the destruction of the RBCs or the imbalance of iron homeostasis)

- Increased ROS production and reduced cholesterol efflux

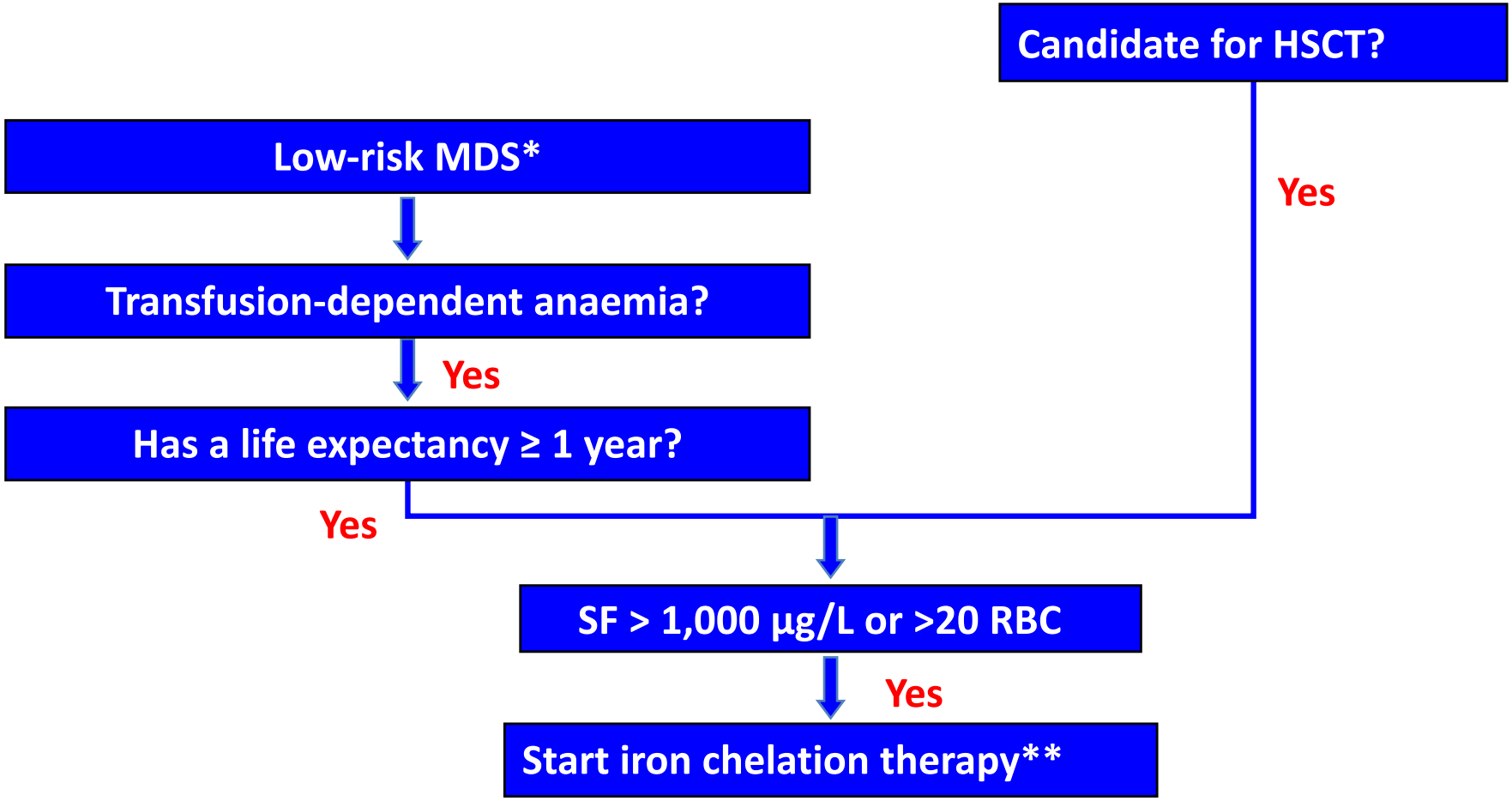
- Oxidative stress and LDL accumulation promote foam cell formation, inflammation, apoptosis, and plaque destabilization





Vinchi F, et al. Atherogenesis and iron: from epidemiology to cellular level. Front Pharmacol. 2014;5:94

Iron chelation algorithm for MDS

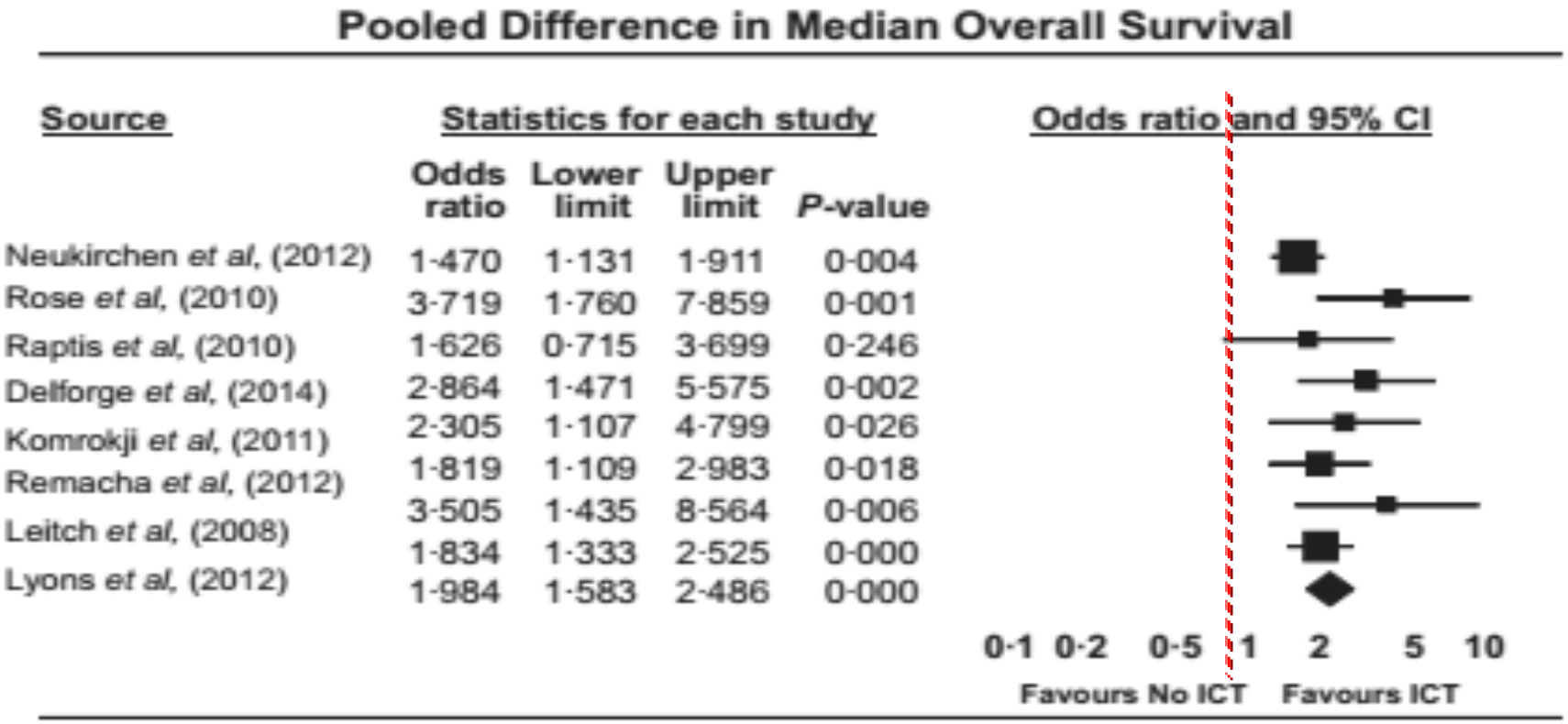


*Includes IPSS Low and Int-1.

**Duration: as needed to maintain serum ferritin < 1,000 µg/L.

Bennett JM, et al. Am J Hematol. 2008;83:858-61.
Gattermann N. Int J Hematol. 2008;88:24-9.

The impact of chelation therapy on survival in transfusional iron overload: a meta-analysis of myelodysplastic syndrome

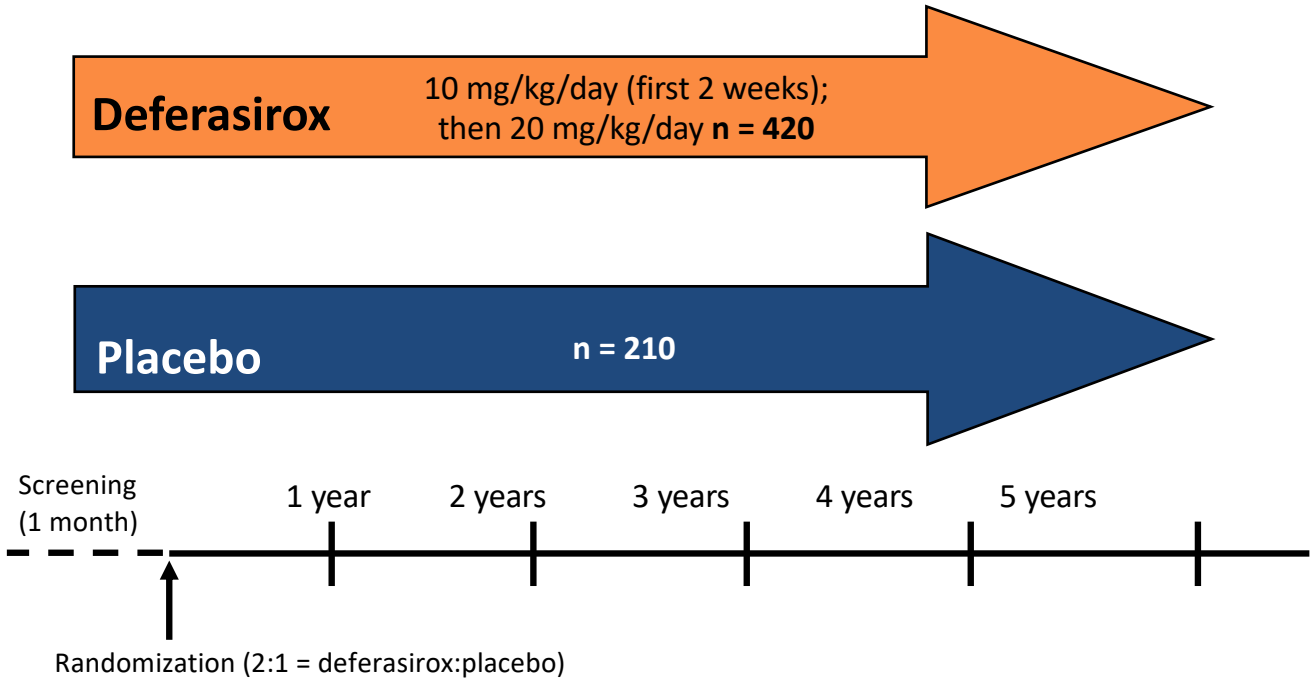


Coates TD et al 2014; 167, 697-726

bjh BRITISH JOURNAL OF HAEMATOLOGY

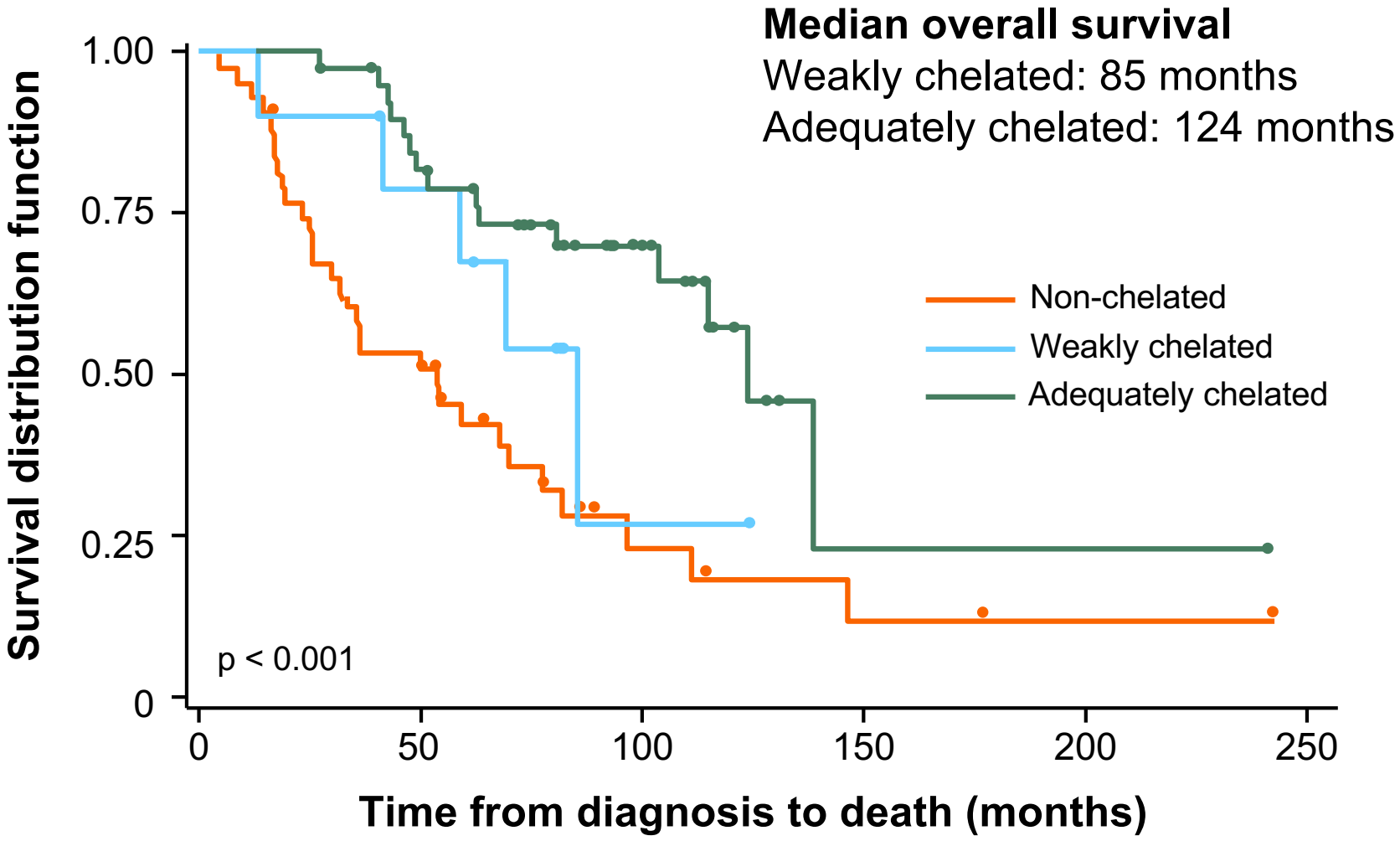
TELESTO study of deferasirox in MDS: study design

- Prospective, multicentre study to investigate the clinical benefit of chelation therapy with deferasirox in 630 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].

Adequate chelation improves survival more than weak chelation in MDS



Rose C, et al. Leuk Res. 2010;34:864-70.

AGENDA

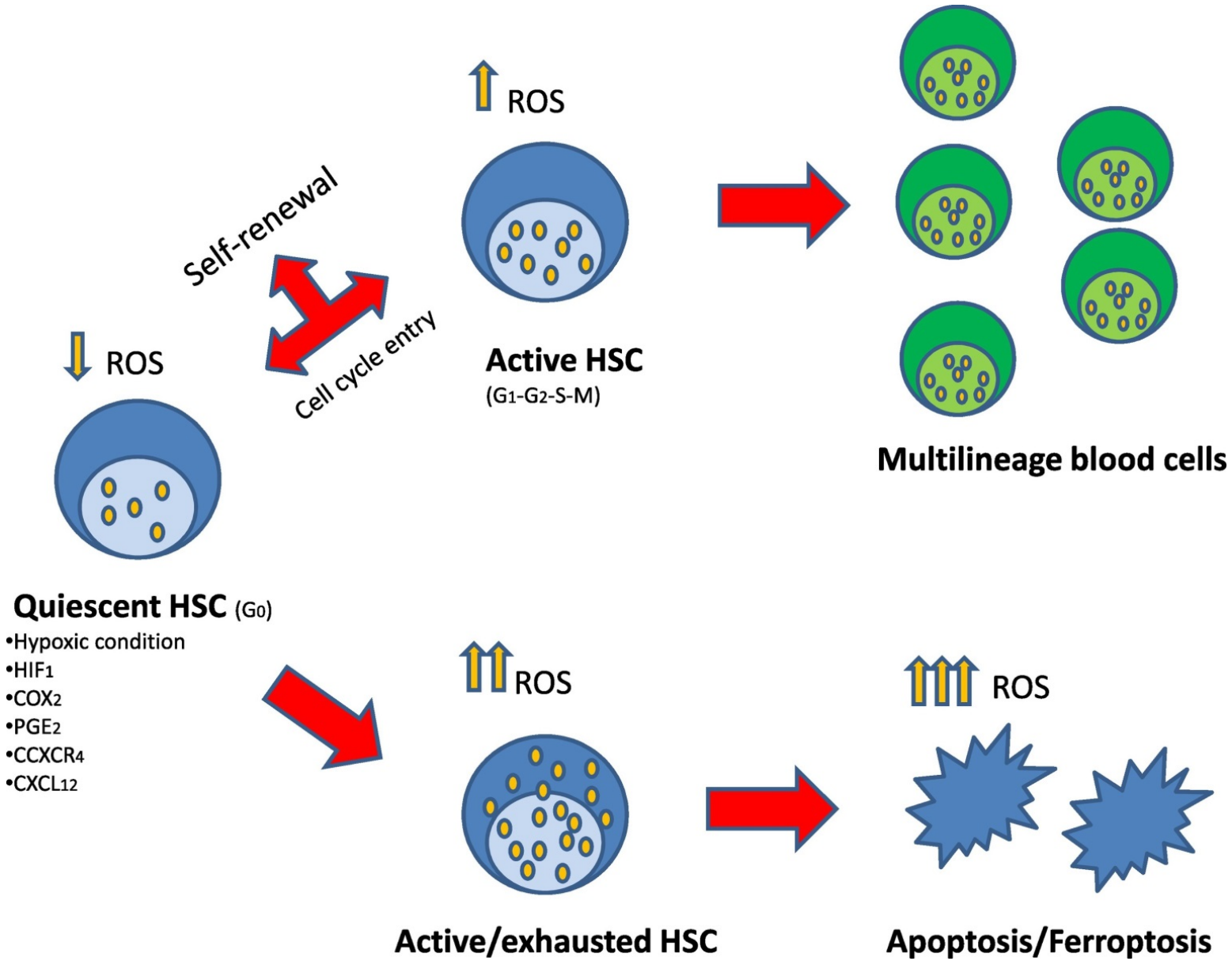
- What we know and what we don't know abaut iron toxicity and iron chelation
- Highlights in relationship between iron, ROS and haemopoiesis
- Clinical implications and future research directions

Authors	Type of study	No. of patients	MDS subtype (FAB/WHO)	Risk IPSS	RBC response	PLT response	Neutrophil response
Messa et al., 2008 [24]	Cases report	3	RA	Int-1	Minor	NA	NA
			RCMD	Int-1	Major	NA	NA
			RAEB1	High	Major	Major	NR
Capalbo et al., 2009 [25]	Case report	1	RA	Low	Major	NA	NA
Okabe et al., 2009 [26]	Case report	1	RCMD	NR	Major	Major	NR
List et al., 2009 [11]	Phase 2 study	6	NR	Low/Int-1	2 Major 1 Minor[a]	1 Major 1 Major[b]	1 Major 1 Major[b]
Badawi et al., 2010 [13]	Case report	1	RCMD	Int-1	Major[c]	NA	NA
Oliva et al., 2010 [27]	Case report	1	RA	Low	Major	NA	NA
Molteni et al., 2010 [28]	Retrospective study	6	NR	NR	5 Minor	1 Major	NA
Nishiuchi et al., 2010 [29]	Case report	1	RCMD	Int-1	Major[d]	Major[d]	NA
Breccia et al., 2010 [30]	Case report	1	RCMD	Low	Major	NR	NA
Present study	Case report	1	Refractory thrombocytemia[e]	Int-1	Major	Major	NA

RA, refractory anemia; RCMD, refractory cytopenia with multilineage displasia; RAEB1, refractory anemia with excess type I blasts; Pts, patients; NA, not applicable; NR, not reported.

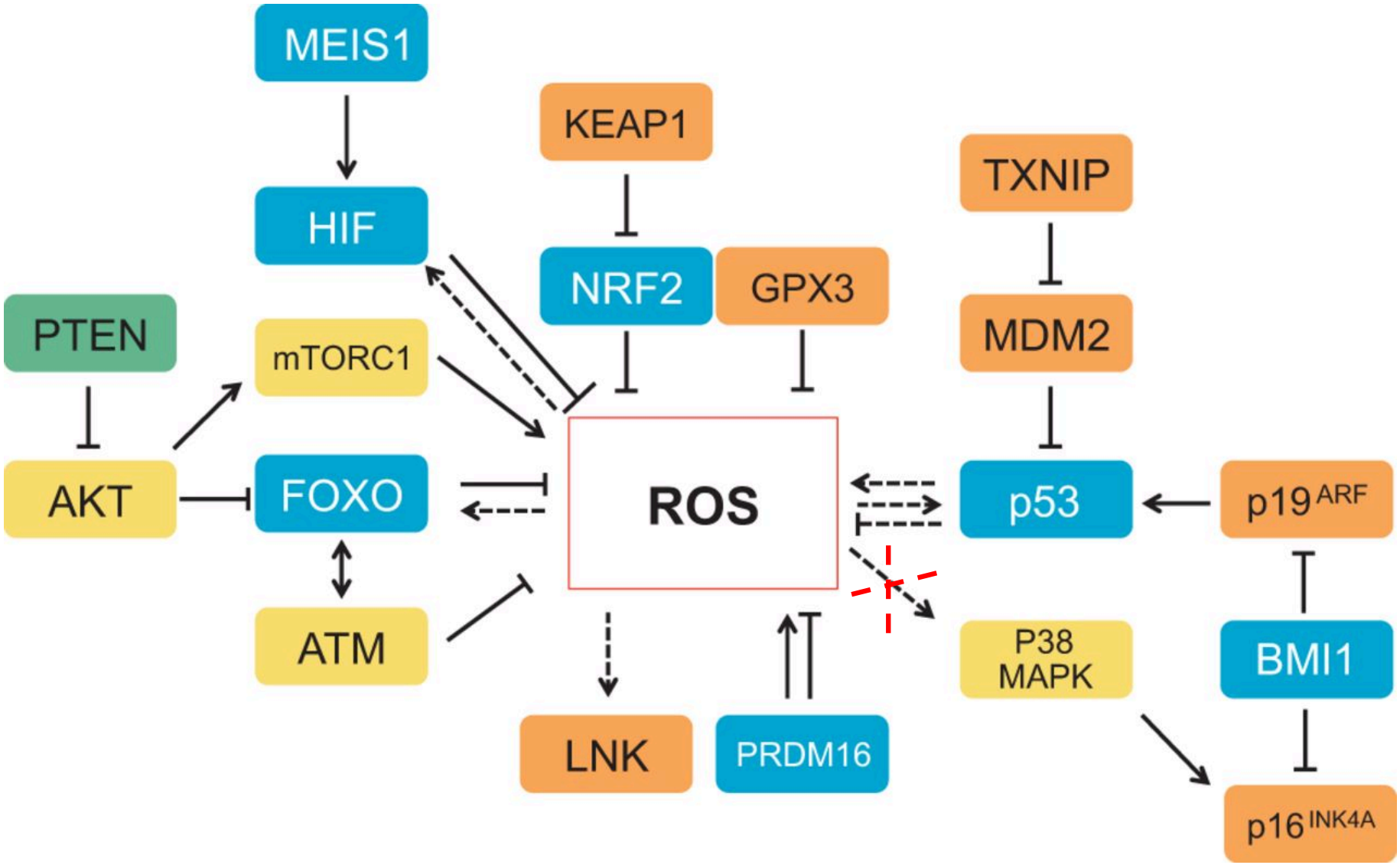
Study	Pt n°	Erythroid	Neutrophil	Pletelet
EPIC Gatterman N et al 2012	247	21%	22%	13%
US03 List A F et al 2012	176	15%	15%	22%
Maurillo et al 2014	19	19%	8%	5%
MDS0306 Angelucci et al 2014	152	11%	11%	15%

ROS balance and hemopoietic stem cel destiny



Pilo & Angelucci Blood Rev. 2018 **A storm in the niche: Iron, oxidative stress and haemopoiesis.**

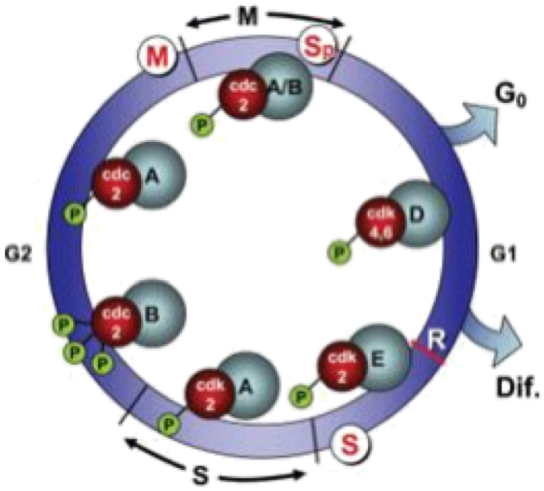
Redox sensor molecules.



Carolina L. Bigarella et al. Development 2014;141:4206-4218

Development

ROS and cell cycle
It's a question of amount and duration ???
Does DFX modulate ROS amount ???



DFX

ROS

DNA, protein, lipid damage,
Mithocondrial damage
Signal transduction

Ferroptosis

G1/S/G2/M arrest

Apoptosis

Signal transduction

Prolonged signal transduction

DFX

Enhanced proliferation

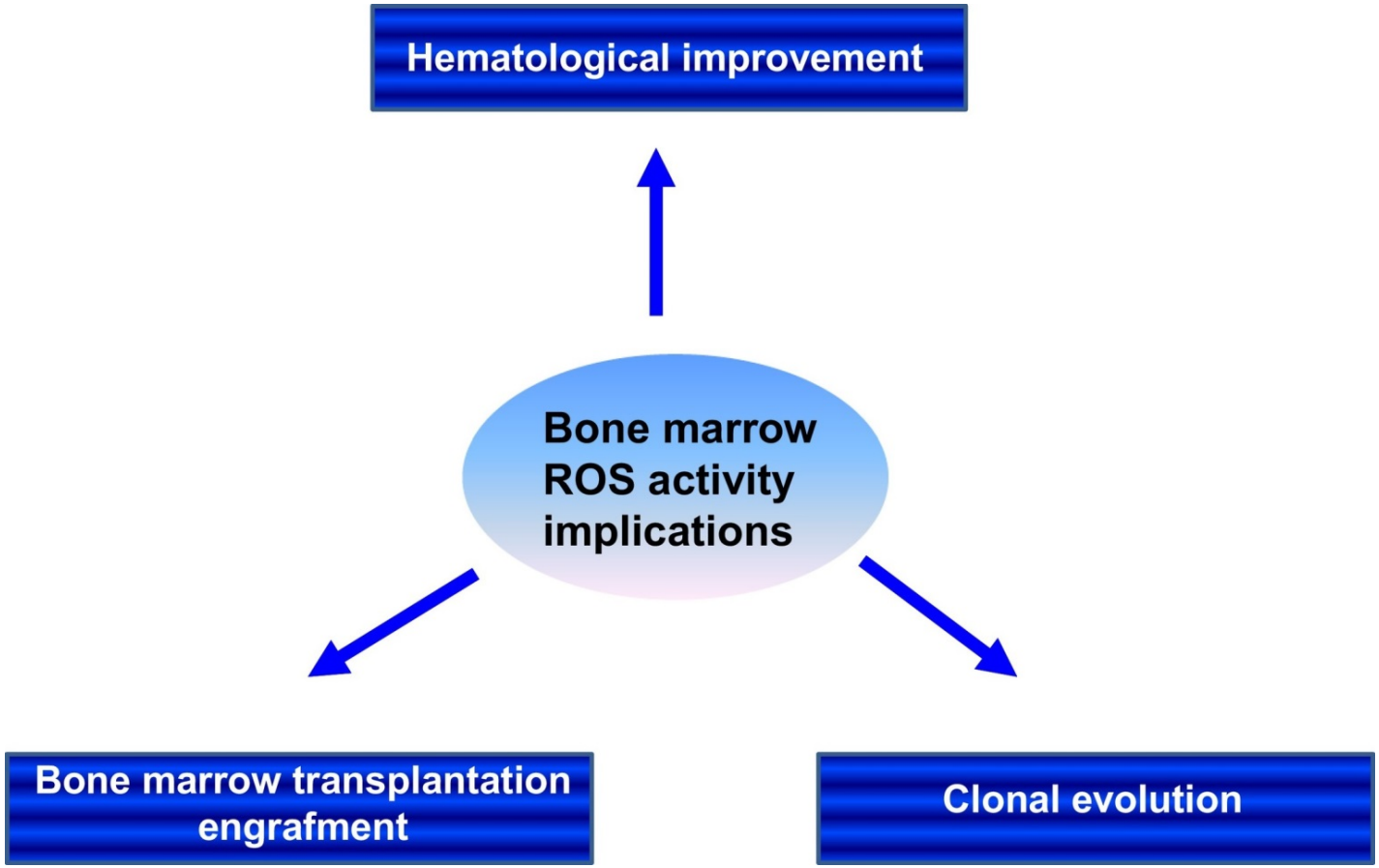
TIME

Courtesy by prof C. Piccoli

AGENDA

- What we know and what we don't know abaut iron toxicity and iron chelation
- Highlights in relationship between iron, ROS and haemopoiesis
- Clinical implications and future research directions

Process in which ROS activity could be involved



Pilo & Angelucci Blood Rev. 2018 **A storm in the niche: Iron, oxidative stress and haemopoiesis.**

Iron overload detection: new prospective

PRESENT	FUTURE
• ferritin, transferrin saturation • blood transfusion intake, • MRI	• NTBI, LPI/LCI , • ROS (peroxides, superoxide, peroxides/superoxide ratio) • Reduced glutathione (GSH) • Lipid peroxidases (MDA) • Hepcidin, GDF 11 e 15 • Erythroferrone, • 8-OHdG and OGG1 activity

The recent introduction of oxidative stress concepts leads the interest of physicians to develop and validate detection methods to identify these parameters in order to better understand the possibility of introduction of these biomarker in prospective clinical trial to predict outcome

Unusual parameters may be considered to detect the real iron tissue damage and connected them to overall survival in the near future

N°	Title	Purpose
NCT02663752	A Phase II Pilot Study to Assess the Presence of Molecular Factors Predictive for Hematologic Response in Myelodysplastic Syndrome Patients Receiving Deferasirox Therapy. Belgium multicentric study	assess the presence of genetic biomarkers predictive for hematologic response by the use of gene expression profiling of bone marrow aspirates obtained from MDS patients with or without hematological response
NCT02233504	Pilot Study to Assess Hematologic Response in Patients With Acute Myeloid Leukemia or High Risk Myelodysplastic Syndromes Undergoing Monotherapy With Exjade (Deferasirox) Abramson Cancer Center of the University of Pennsylvania	The purpose of this trial is to examine the hematologic response rate of Exjade® in patients with AML and high risk MDS and chronic iron overload from blood transfusions.
NCT00354217	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**	Balance iron burden in one-year treatment in early phase of transfusion requirement by low dose (3.5 mg/kg) DFX-FCT (prevention of iron overload) as demonstrated by hepatic iron concentration.
NCT02477631	Effect of Deferiprone on Oxidative-Stress and Iron-Overload in Low Risk Transfusion-Dependent MDS Patients Sheba Medical Center, Israel	To evaluate the effect of Deferiprone on oxidative stress parameter - Reactive oxygen species (ROS)

ongoing studies , ClinicalTrials.gov

Thanks for your very kind attention

ACKNOWLEDGMENTS

- DR. EMANUELE ANGELUCCI
- CAGLIARI, HEMATOLOGY GROUP
  Direttore Prof. Giorgio La Nasa

federica.pilo@aob.it