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2019 Korean Society of Hematology International Conference

Deferasirox for iron overload patients: preserving organ functions

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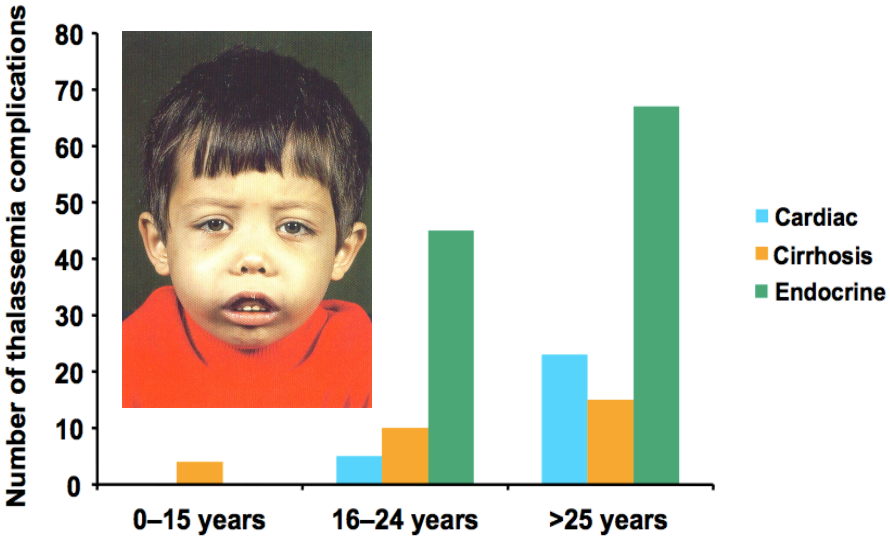
Comprehensive Cancer Center

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

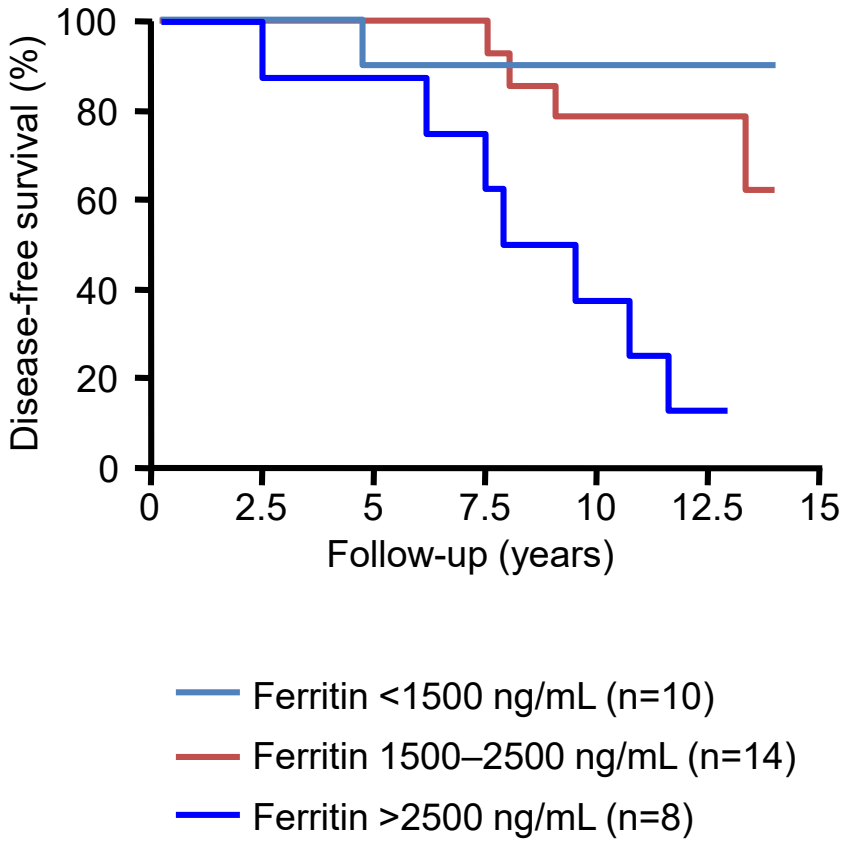
Iron **overload** has a strong **negative impact** on survival of patients with β thalassemia major

Clinical sequelae of iron overload

Pituitary → impaired growth
Heart → cardiomyopathy, cardiac failure
Liver → liver cirrhosis
Pancreas → diabetes mellitus
Gonads → hypogonadismus, infertility

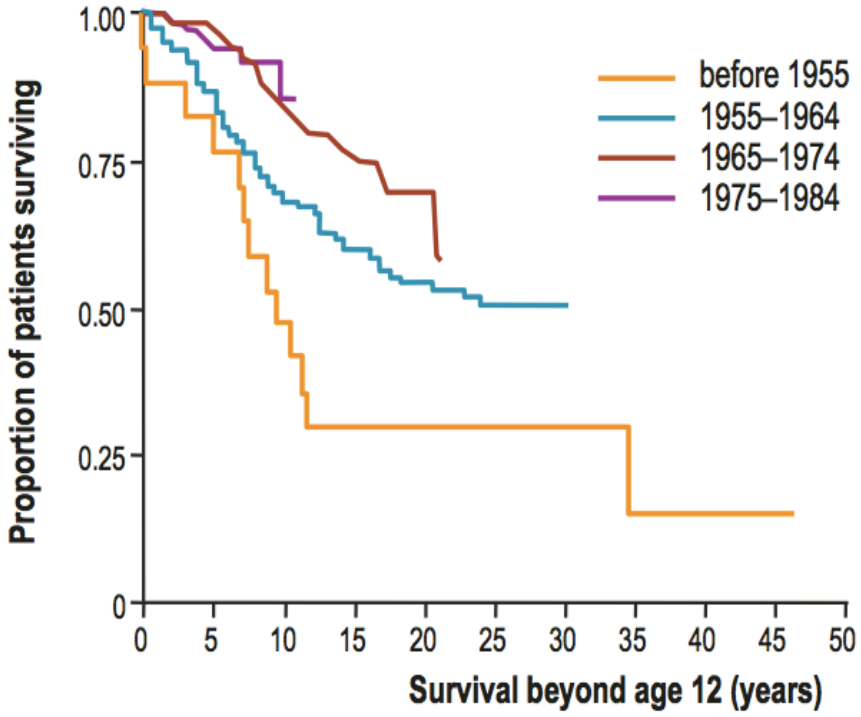


Cunningham MJ et al. *Blood* 2004;104:34–39

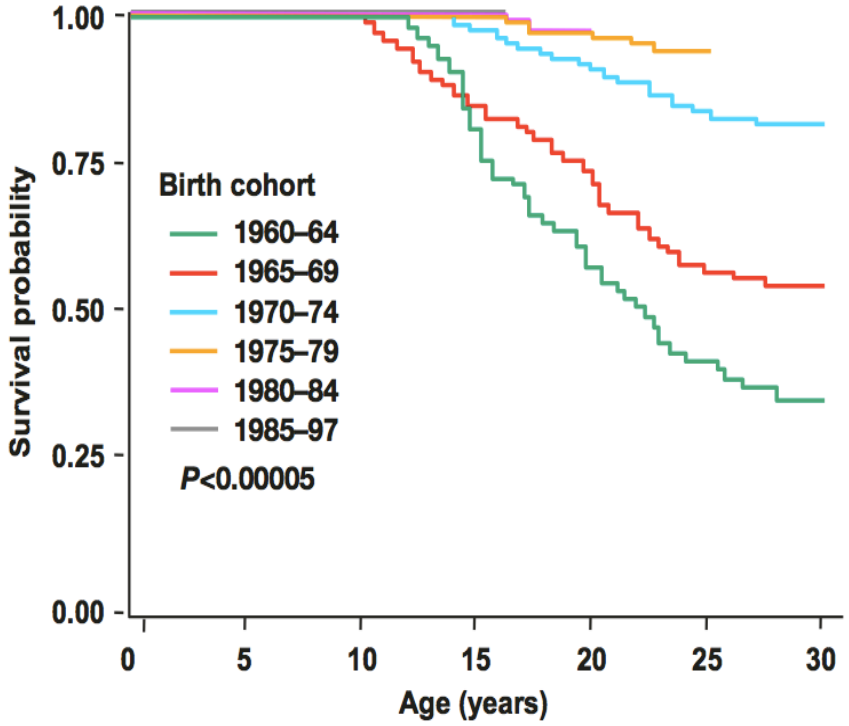


Telfer PT et al. Br J Haematol 2000;110:971–977

Iron **chelation** has a strong **positive impact** on survival of patients with β thalassemia major



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



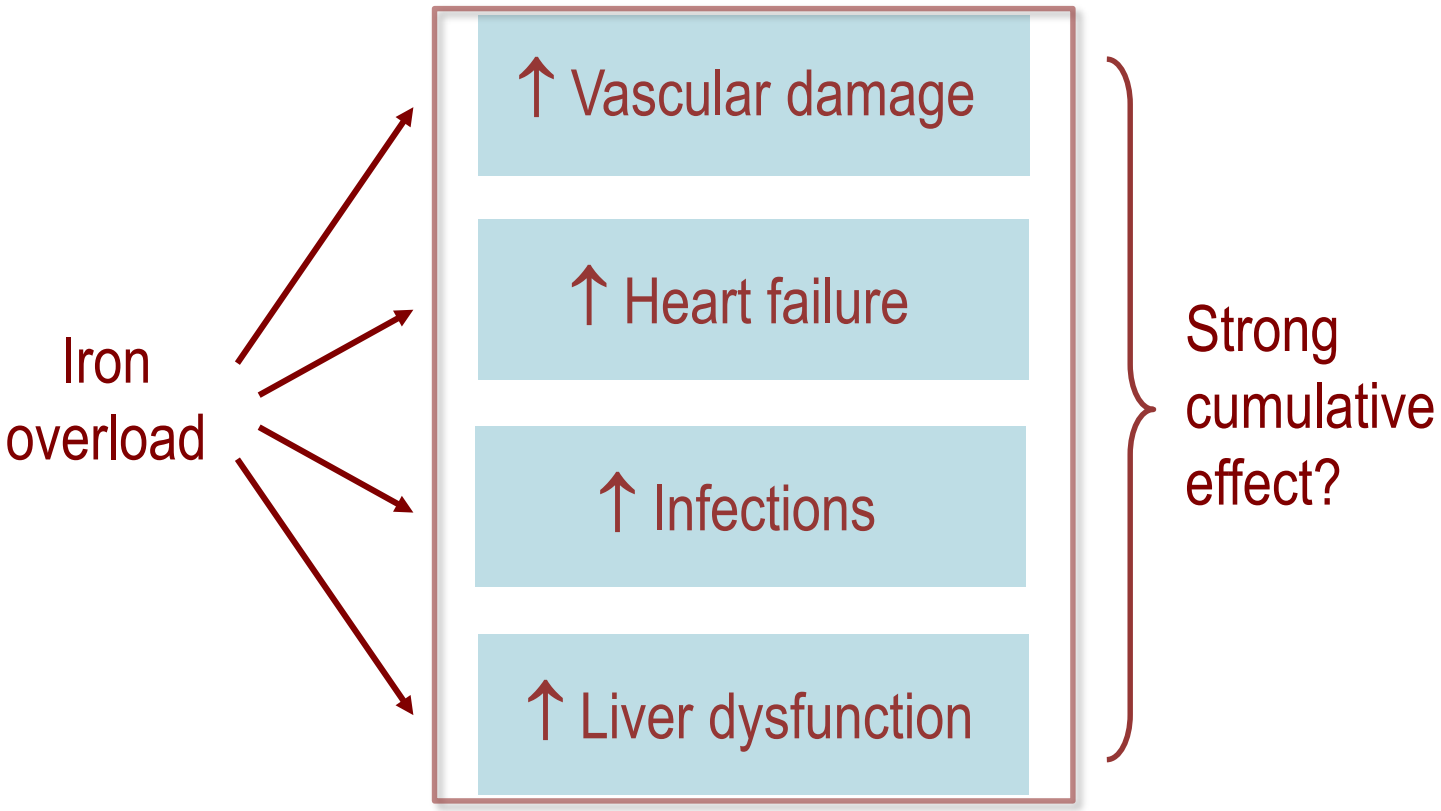
Borgna-Pignatti C et al. *Haematologica* 2004;89:1187–93

Improvement in survival by later birth date reflects the availability of DFO treatment for IOL and the extent of patient compliance with treatment

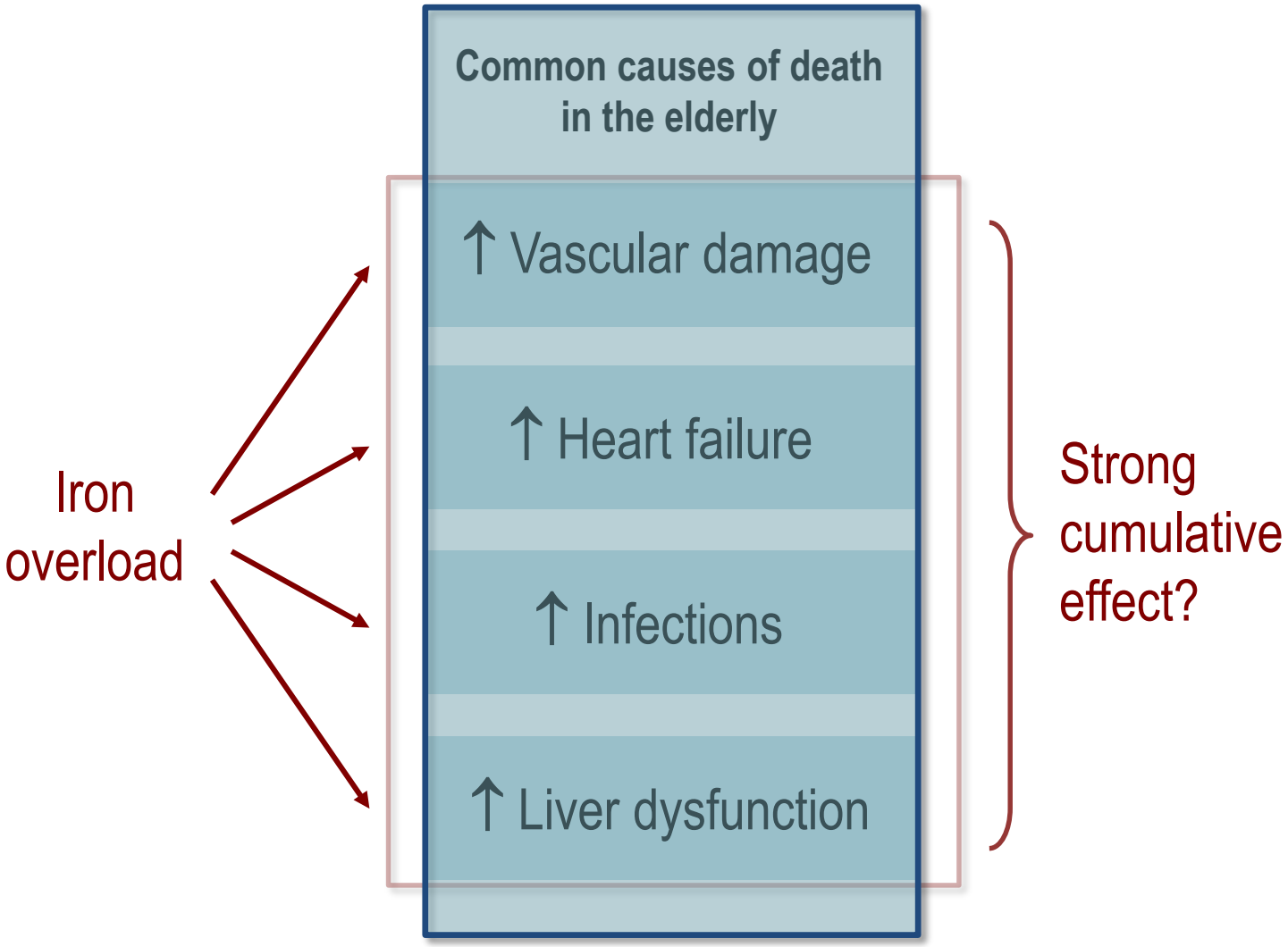
Why is it difficult to extrapolate this knowledge into the field of MDS?

- Exposure to iron overload is shorter in MDS
  - Transfusion therapy in MDS starts much later in life
  - Many patients with MDS do not live long enough to develop clinical complications of iron overload
- Iron-related complications in elderly MDS patients overlap with age-related medical problems

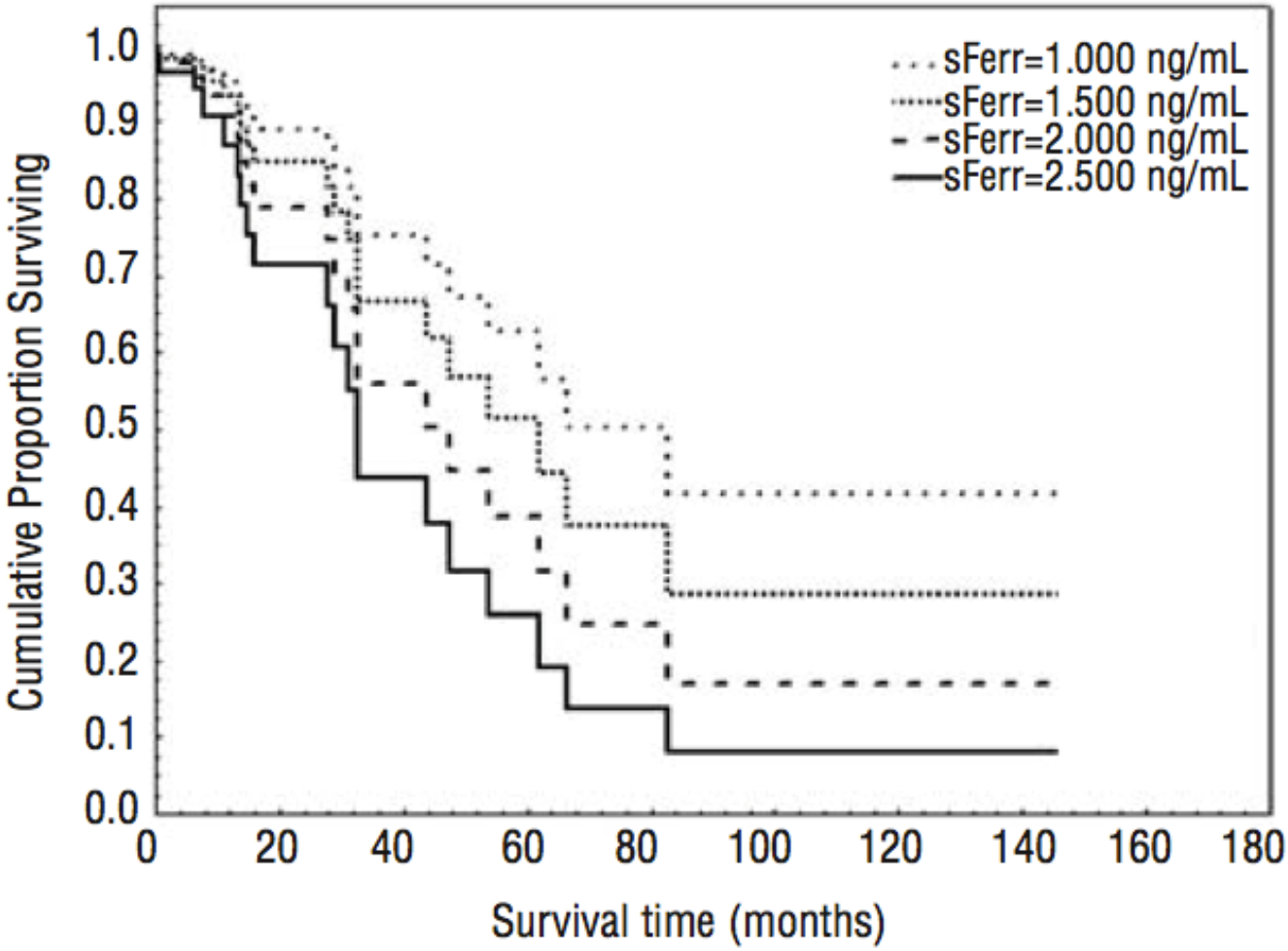
In elderly MDS patients, iron-related complications overlap with age-related medical problems



In elderly MDS patients, iron-related complications overlap with age-related medical problems



Survival of patients with MDS according to serum ferritin level

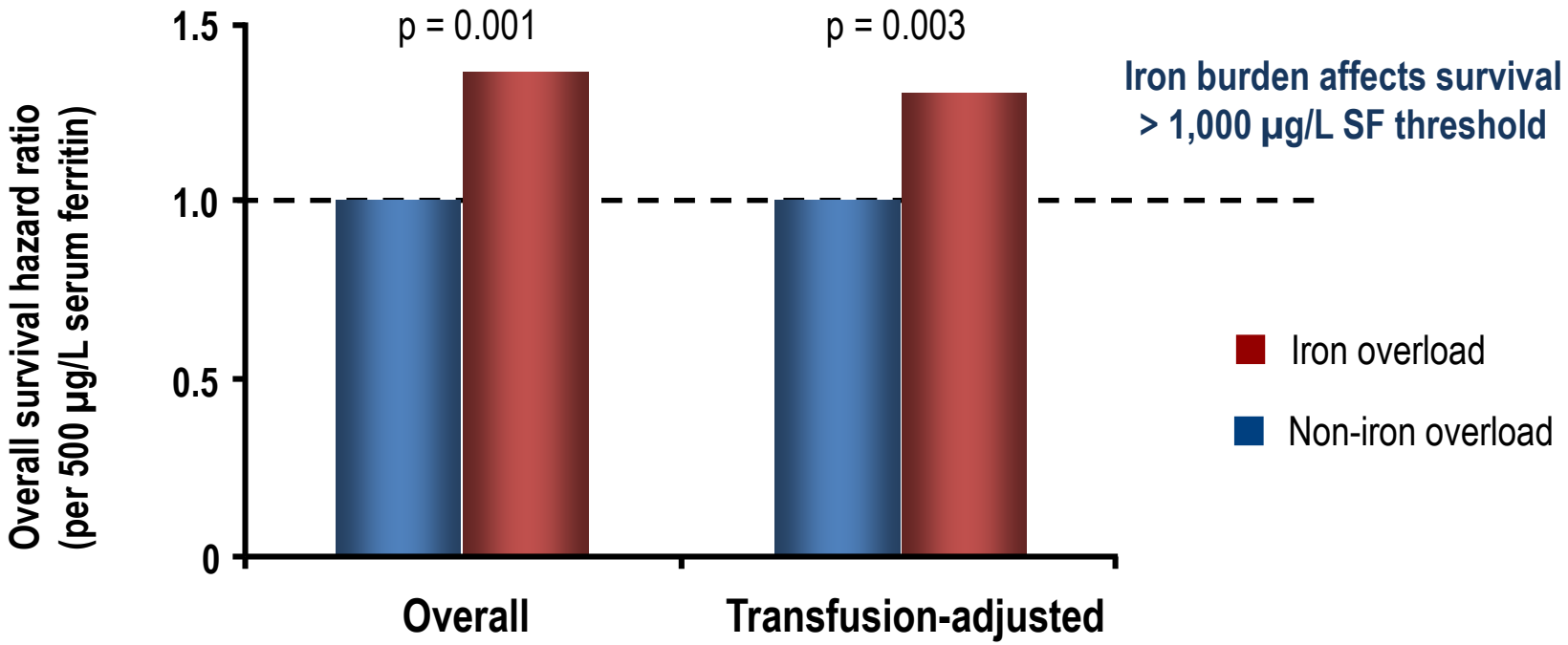


Patients with RA/RARS/5q− (HR = 1.42; p<0.001)

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

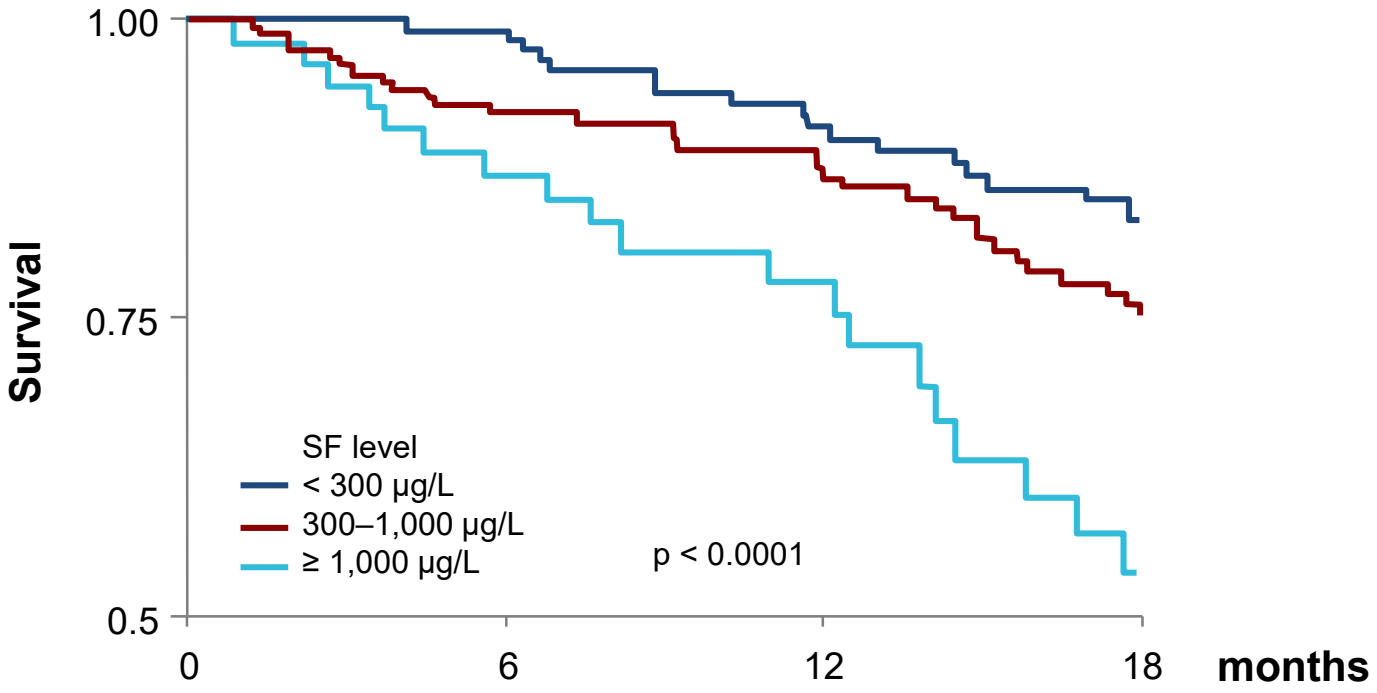


A 30% greater risk of death was evident for every 500 µg/L increase in SF above a 1,000 µg/L threshold

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

European Leukemia Net (ELN) prospective MDS registry: Independent survival impact of SF

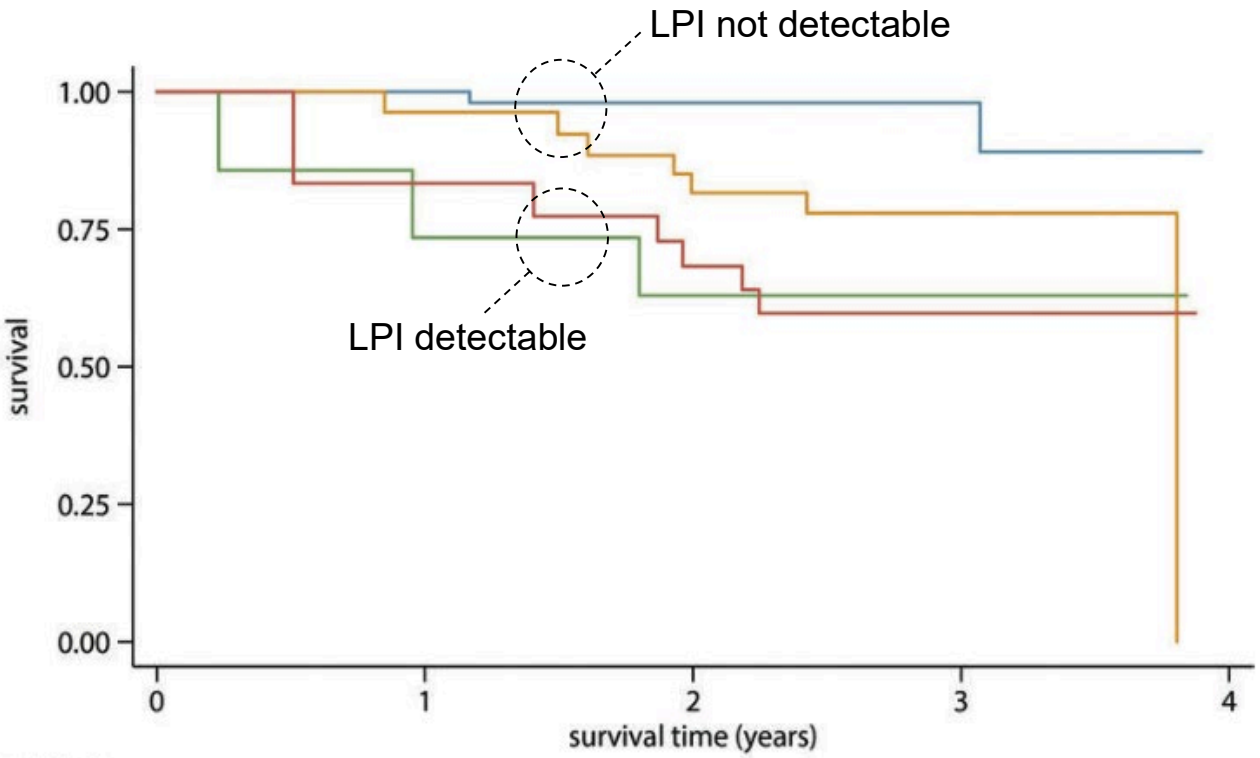
OS of transfusion-dependent patients by baseline SF status (n=1,000)



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.

ELN prospective MDS registry: Survival impact of **labile plasma iron** (LPI)



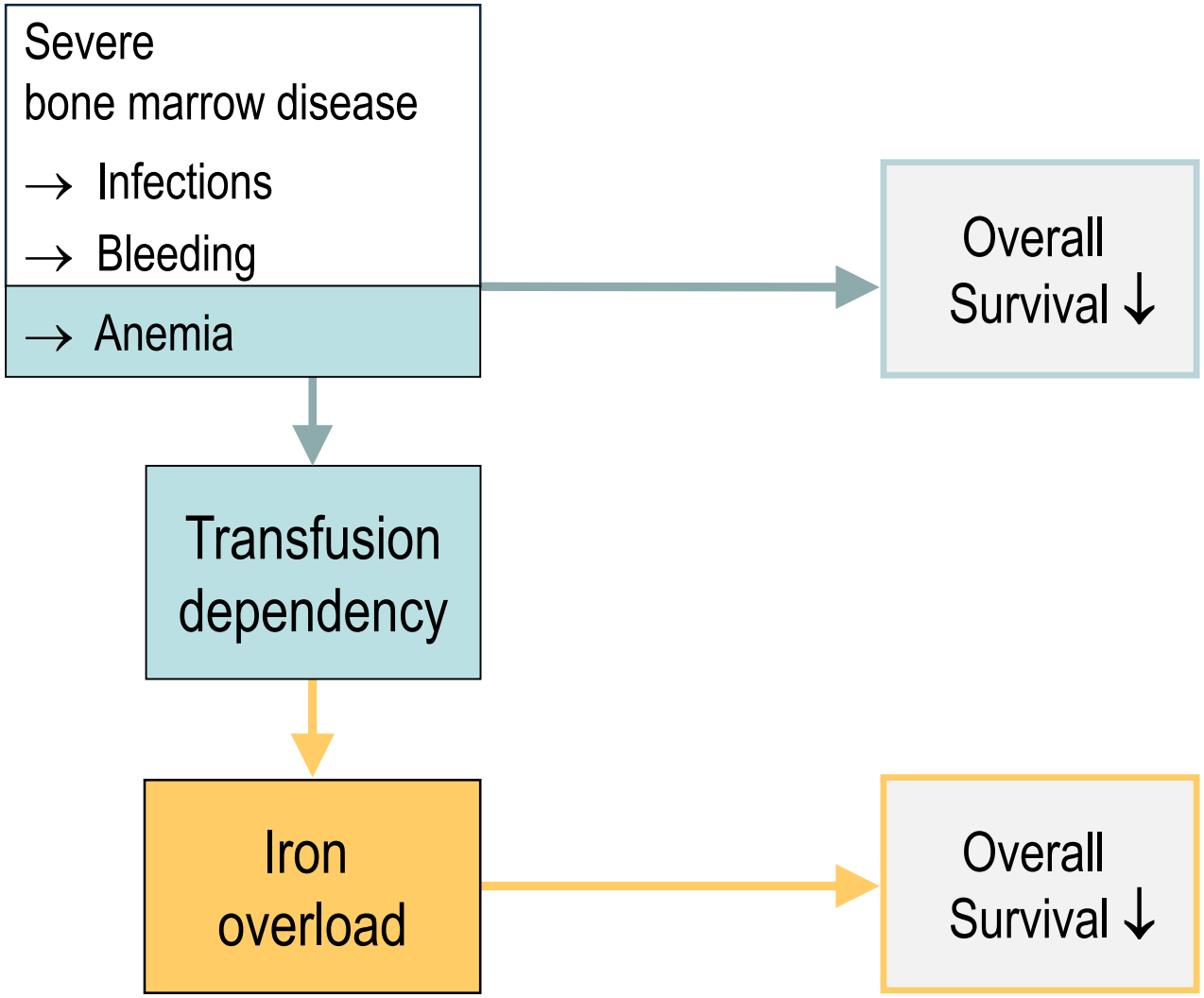
Number at risk

LPI<LLOD, TI	77	53	33	13	0
LPI>=LLOD, TI	9	6	7	5	0
LPI<LLOD, TD	12	26	24	4	0
LPI>=LLOD, TD	2	11	15	10	3

LPI<LLOD, TI
LPI>=LLOD, TI
LPI<LLOD, TD
LPI>=LLOD, TD

de Swart L, et al.
Haematologica 2018; 103:69-79

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



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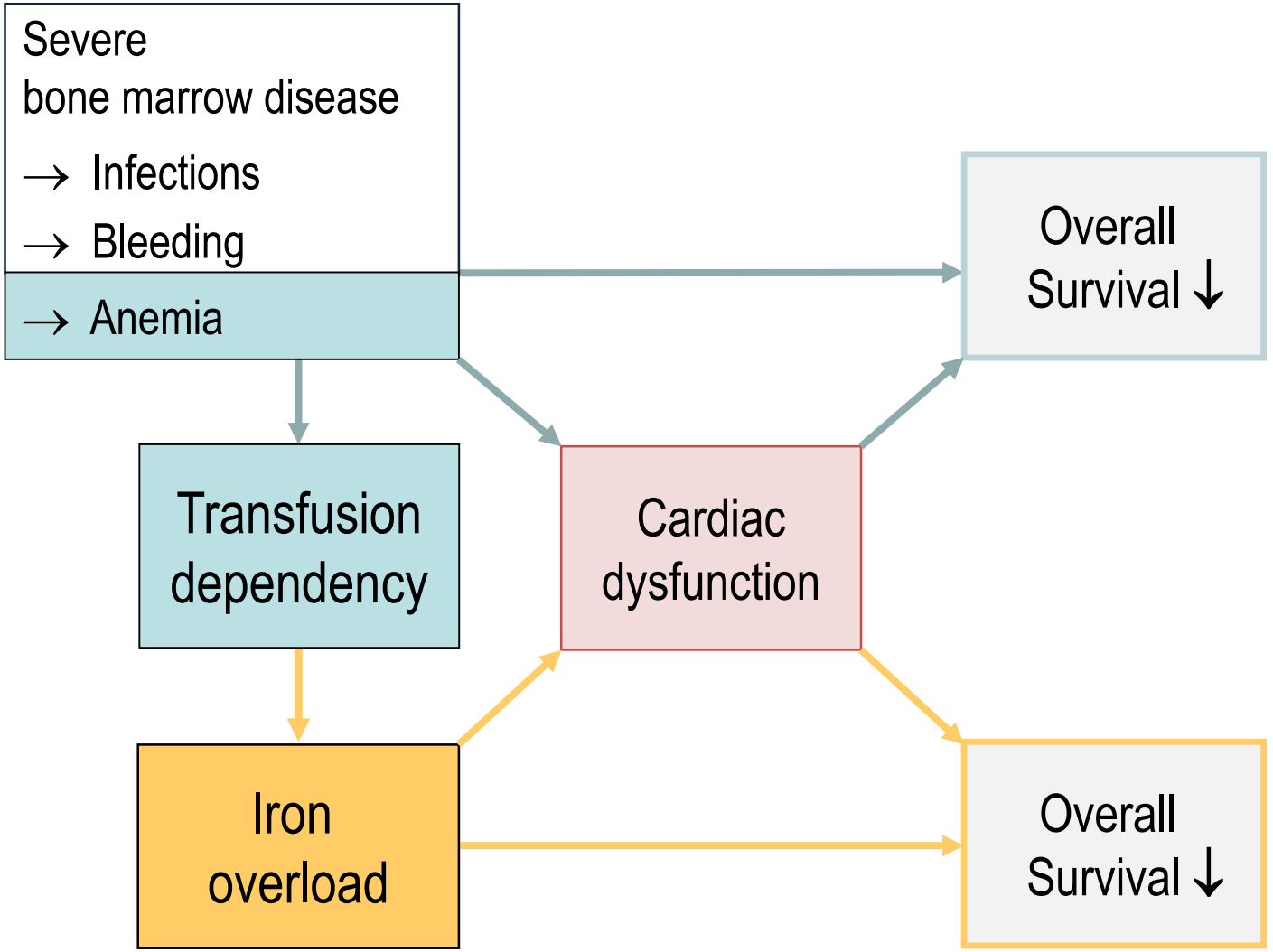
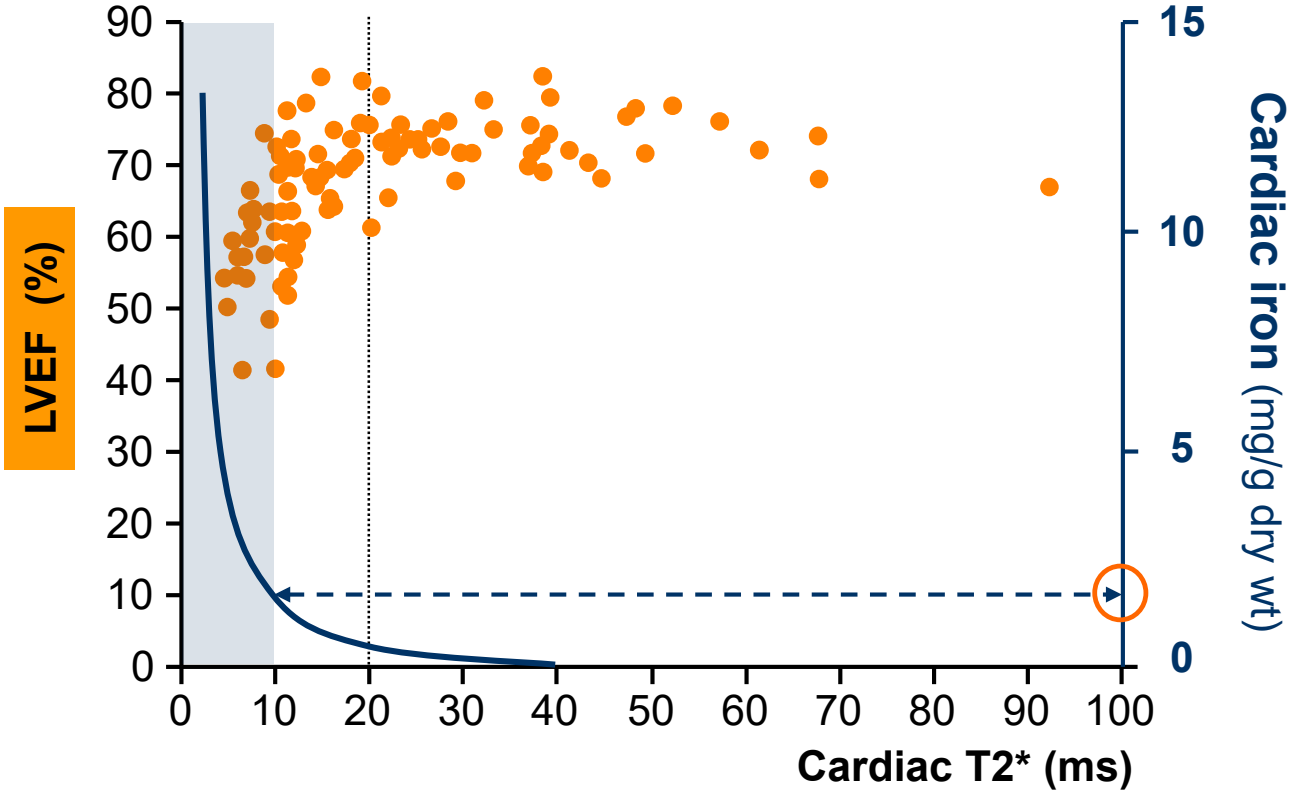


The heart is more vulnerable to iron overload than the liver

Relationship between cardiac T2*, cardiac function, and cardiac iron



Iron values derived from animal studies

Clinically relevant cardiac dysfunction occurs at much lower tissue iron concentrations than clinically relevant liver dysfunction

Wood JC, et al. Circulation 2005

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

On T2* Magnetic Resonance and Cardiac Iron

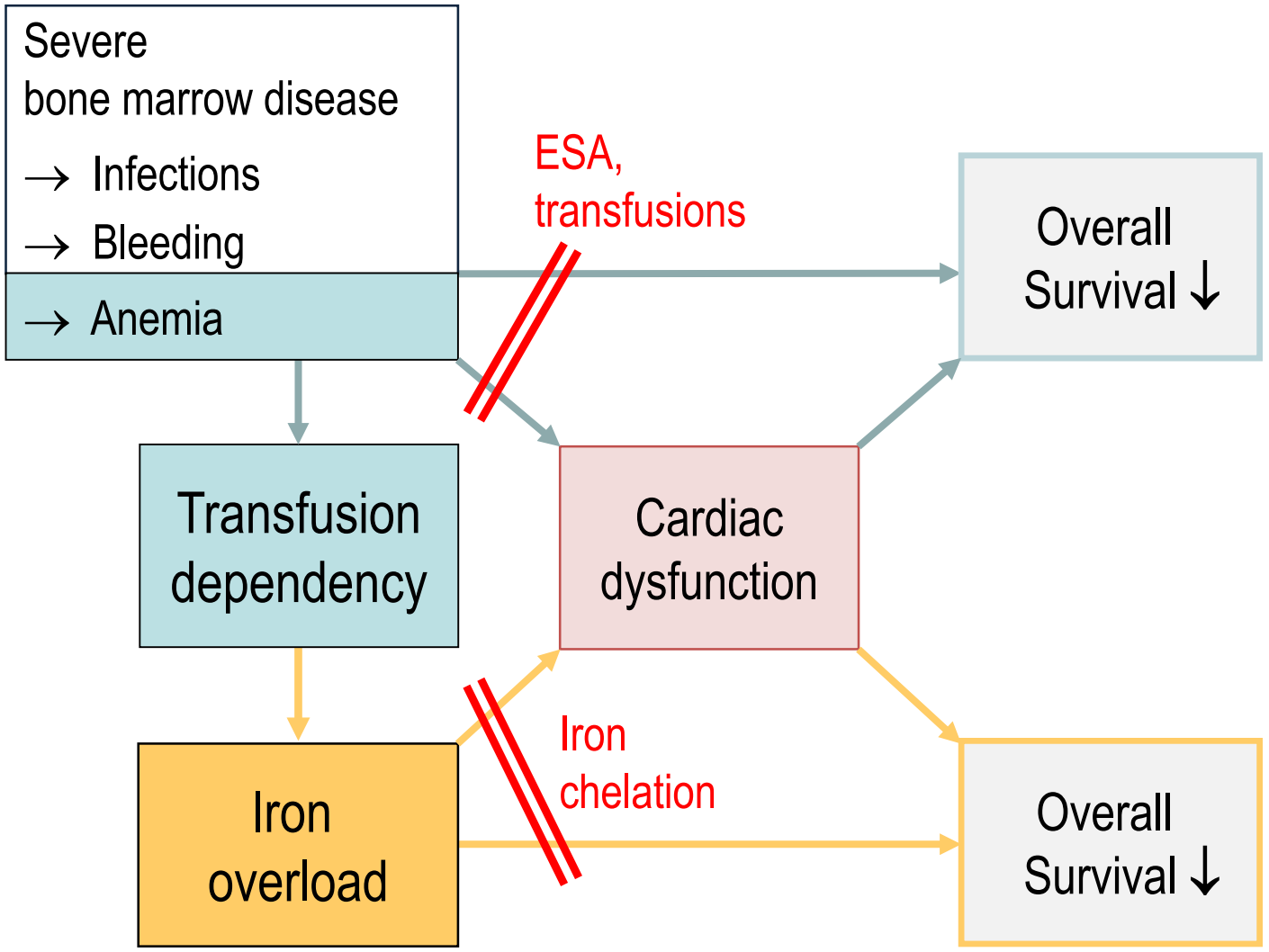
John-Paul Carpenter, MB, MRCP*; Taigang He, PhD*; Paul Kirk, MB, MRCP; Michael Roughton, MSc; Lisa J. Anderson, MD, MRCP; Sofia V. de Noronha, PhD; Mary N. Sheppard, MD, FRCPath; John B. Porter, MD, FRCP, FRCPath; J. Malcolm Walker, FRCP; John C. Wood, MD; Renzo Galanello, MD; Gianluca Forni, MD; Gualtiero Catani, MD; Gildo Matta, MD; Suthat Fucharoen, MD; Adam Fleming, BSc; Michael J. House, PhD; Greg Black, MSc; David N. Firmin, PhD; Timothy G. St. Pierre, PhD; Dudley J. Pennell, MD, FRCP

Background—Measurement of myocardial iron is key to the clinical management of patients at risk of siderotic cardiomyopathy. The cardiovascular magnetic resonance relaxation parameter R2* (assessed clinically via its reciprocal, T2*) measured in the ventricular septum is used to assess cardiac iron, but iron calibration and distribution data in humans are limited.

Methods and Results—Twelve human hearts were studied from transfusion-dependent patients after either death (heart failure, n=7; stroke, n=1) or transplantation for end-stage heart failure (n=4). After cardiovascular magnetic resonance R2* measurement, tissue iron concentration was measured in multiple samples of each heart with inductively coupled plasma atomic emission spectroscopy. Iron distribution throughout the heart showed no systematic variation between segments, but epicardial iron concentration was higher than in the endocardium. The mean±SD global myocardial iron causing severe heart failure in 10 patients was 5.98±2.42 mg/g dry weight (range, 3.19 to 9.50 mg/g), but in 1 outlier case of heart failure was 25.9 mg/g dry weight. Myocardial ln[R2*] was strongly linearly correlated with ln[Fe] (R^2=0.910, P<0.001), leading to $[Fe]=45.0\times(T2^*)^{-1.22}$ for the clinical calibration equation with [Fe] in milligrams per gram dry weight and T2* in milliseconds. Midventricular septal iron concentration and R2* were both highly representative of mean global myocardial iron.

Conclusions—These data detail the iron distribution throughout the heart in iron overload and provide calibration in humans for cardiovascular magnetic resonance R2* against myocardial iron concentration. The iron values are of considerable interest in terms of the level of cardiac iron associated with iron-related death and indicate that the heart is more sensitive to iron loading than the liver. The results also validate the current clinical practice of monitoring cardiac iron in vivo by cardiovascular magnetic resonance of the midseptum. (***Circulation***. **2011;123:1519-1528.**)

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



Iron-related **endothelial** dysfunction: an underestimated clinical problem?

frontiers in PHARMACOLOGY

REVIEW ARTICLE
published: 05 May 2014
doi: 10.3389/fphar.2014.00094

Atherogenesis and iron: from epidemiology to cellular level

*Francesca Vinchi[1,2], Martina U. Muckenthaler[1,2], Milene C. Da Silva[1,2], György Balla[3,4], József Balla[5] and Viktória Jeney[3,5]**

ASH | 57th Annual Meeting & Exposition
Orlando, FL · December 5-8, 2015

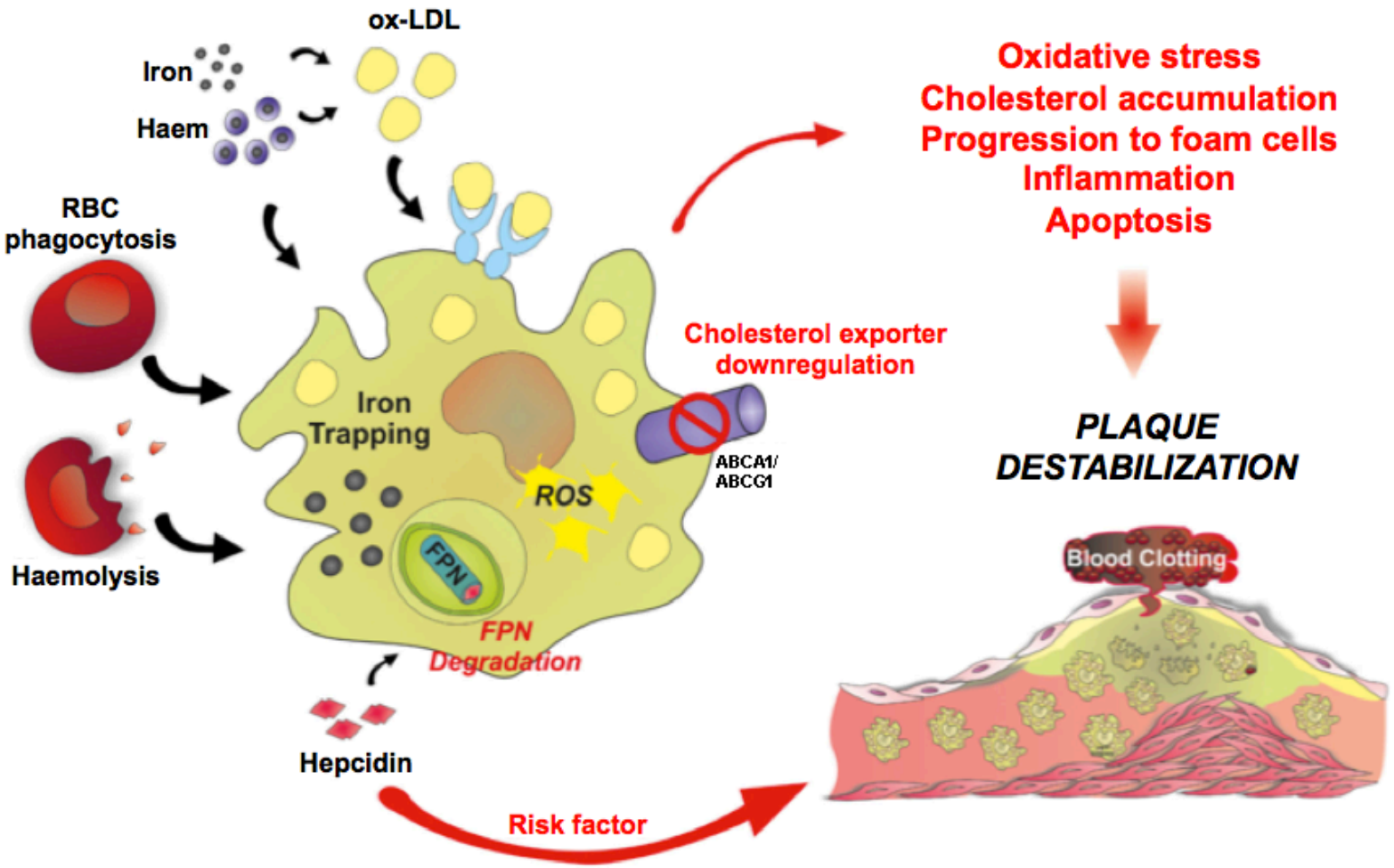
1040 High Circulating Iron Levels Are a Risk Factor for Cardiovascular Disease: Clinical Implications for Iron-Overload Conditions

Francesca Vinchi, PhD[1,2], Andreas Simmelbauer, Master student[1,2*], Milene Costa da Silva, PhD student[1,2*], Sandro Altamura, PhD[1,2*], Bruno Galy, PhD[3*], Matthias W. Hentze, MD[3,4*] and Martina U. Muckenthaler, PhD[1,2]*

With increasing age, high circulating iron levels strongly enhance the severity of the atherosclerotic phenotype, indicating that systemic iron overload is a risk factor for atherosclerosis progression and predisposes to cardiovascular disease.

Vinchi F, et al. Front Pharmacol. 2014;5:94.
Vinchi F, et al. Presented at ASH 2015. Blood. 2015;126:abstract 1040.

Pathophysiological model: a role for macrophage-retained iron in atherosclerosis



Vinchi F, et al. Front Pharmacol. 2014;5:94.

American Heart Association

Iron Chelation Improves Endothelial Function in Patients With Coronary Artery Disease

Stephen J. Duffy, MB, BS, PhD; Elizabeth S. Biegelsen, MD; Monika Holbrook, MS; Judson D. Russell, BS; Noyan Gokce, MD; John F. Keaney, Jr, MD; Joseph A. Vita, MD

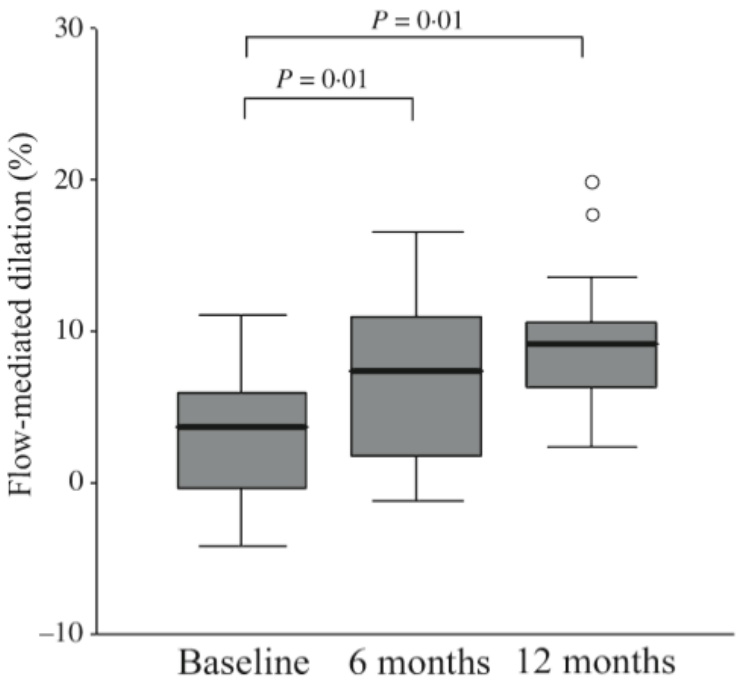
Background—Some epidemiological studies have shown that increased iron stores are associated with increased cardiovascular events. Redox-active iron may contribute to lipid peroxidation, endothelial cell activation, and generation of reactive oxygen species (especially hydroxyl radical, via Fenton chemistry). Increased oxidative stress is associated with impaired action of endothelium-derived nitric oxide in patients with atherosclerosis.

Methods and Results—To test the hypothesis that reducing vascular iron stores would reverse endothelial dysfunction, we examined the effects of the iron chelator deferoxamine (500 mg intra-arterially over 1 hour) on vasomotor function in forearm resistance vessels of patients with coronary artery disease by venous occlusion plethysmography. Patients with coronary artery disease had impaired endothelium-dependent vasodilation in response to methacholine compared with healthy control subjects ($P<0.001$). Deferoxamine infusion decreased serum iron levels ($P<0.001$). Deferoxamine improved the blood flow response to methacholine in patients with coronary artery disease ($P<0.01$ by 2-way repeated-measures ANOVA) but had no effect on the response to sodium nitroprusside. In normal volunteers, deferoxamine had no effect on the response to methacholine. The nitric oxide synthase inhibitor N^G-monomethyl-L-arginine abolished augmentation of the methacholine response associated with deferoxamine. The hydroxyl radical scavenger mannitol had no effect on the methacholine response.

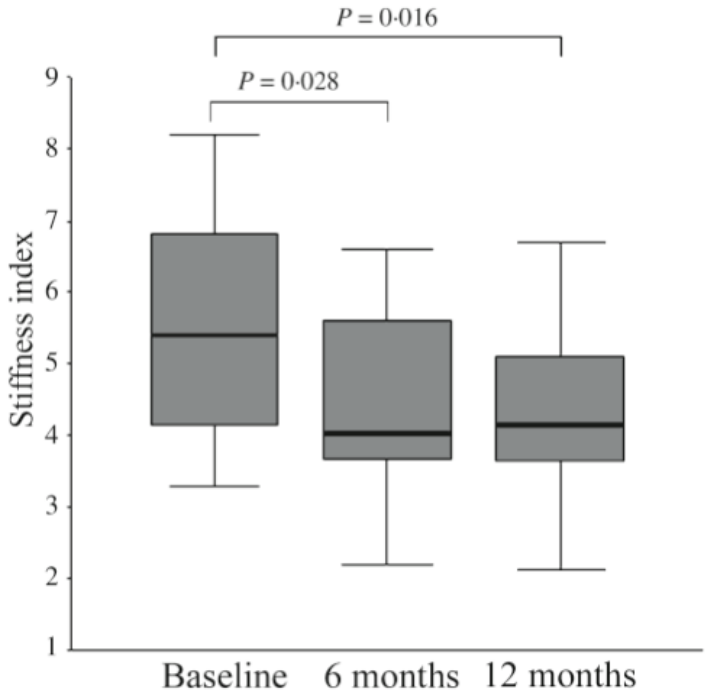
Conclusions—Deferoxamine improved nitric oxide–mediated, endothelium-dependent vasodilation in patients with coronary artery disease. These results suggest that iron availability contributes to impaired nitric oxide action in atherosclerosis. (***Circulation*. 2001;103:2799-2804.**)

Key Words: iron ■ nitric oxide ■ endothelium ■ coronary disease

Effect of deferasirox on arterial function in patients with beta-thalassemia major



Brachial artery flow-mediated dilation



Carotid arterial stiffness index

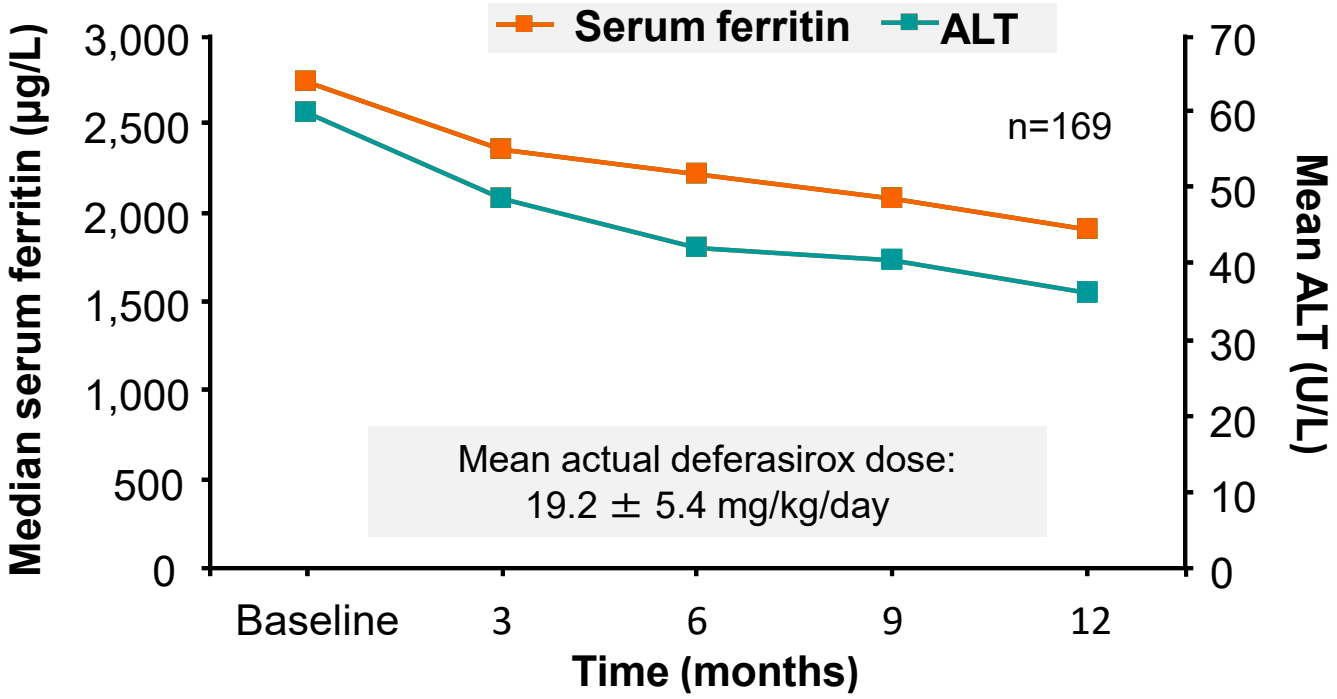
Deferasirox has the ability to

- bind labile cell iron pools in the vascular wall
- diminish reactive oxygen species formation and
- attenuate nitric oxide inactivation.

Cheung et al. (2008)
Br J of Haematol. 141:728–33

Hepatic iron overload in MDS

EPIC Study: Reduction in serum ferritin associated with improvement in ALT



At 12 months, there were significant reductions in

- **median serum ferritin** (−253 µg/L; p=0.002)
- **mean ALT** (−27.7 ± 37.4 U/L; p<0.0001)

Gattermann *et al. Leuk Res.* 2010 Sep;34(9):1143-50

Iron overload in lower international prognostic scoring system risk patients with myelodysplastic syndrome receiving red blood cell transfusions: Relation to infections and possible benefit of iron chelation therapy

Leukemia Research
Clinical and Laboratory Studies
67:75-81, 2018

Colleen A.C. Wong[a], Shannon A.Y. Wong[a], Heather A. Leitch[b,*]

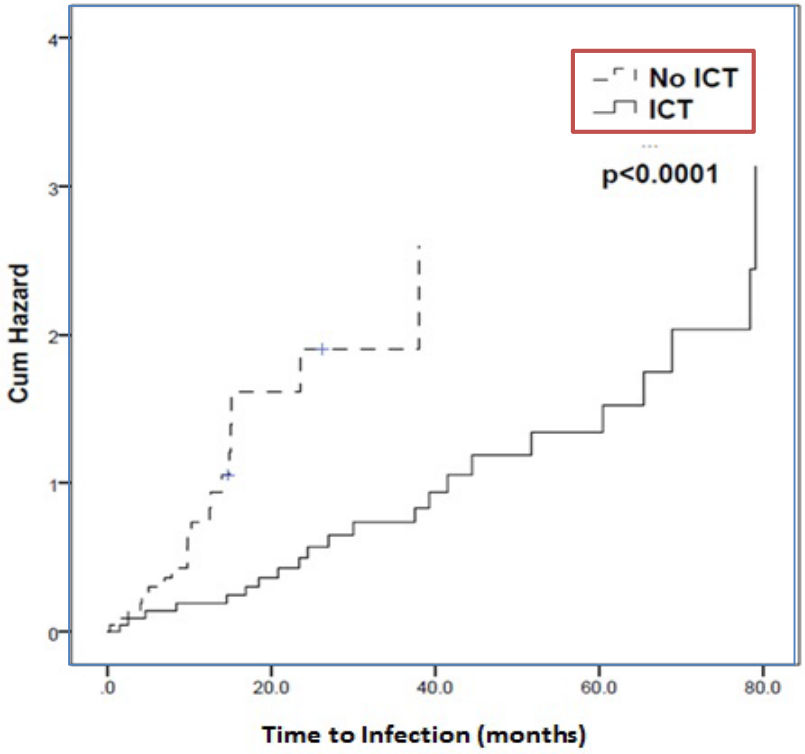


Figure 1. Time from first RBC transfusion to first infection in patients with lower IPSS risk MDS not receiving or receiving iron chelation therapy.

Clinical factors differing between ICT and non-ICT pts, respectively, were (median [range]):

- **age at 1st RBC transfusion**, 67 (31-88) and 75 (43-93) yrs
- **number of RBC units (U) transfused while lower risk**, 76 (10-675) and 24 (2-200)
- **number of RBCU/4 weeks**, 2.2 (0.5-9.1) and 2.0 (0.1-5.4)
- **serum ferritin**, 914 (49-15608) and 266 (12-5009) ng/mL
- **other treatments received**, 18 (30.5%) and 5 (6.3%)

($p \leq 0.04$ for all)

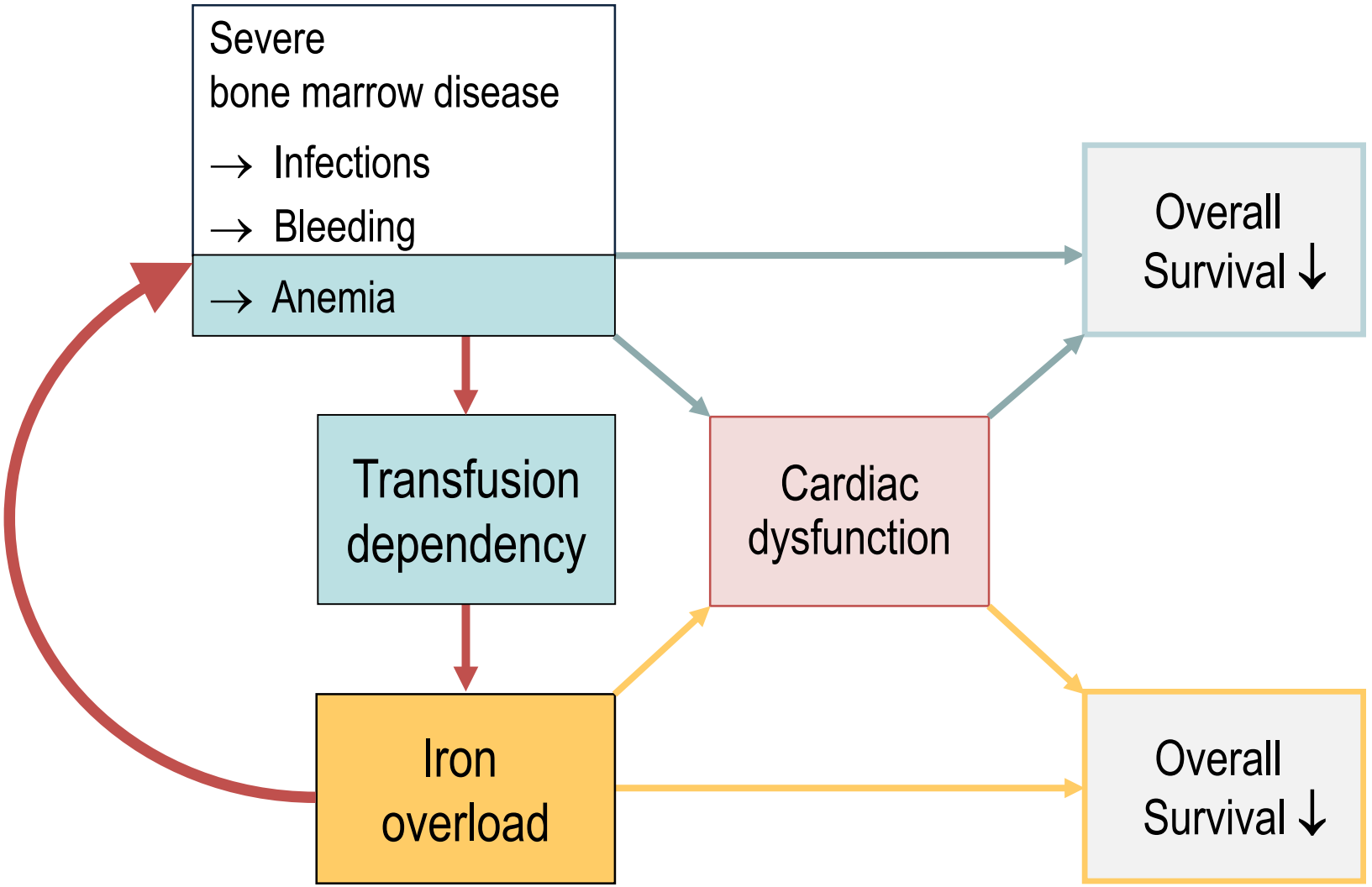
Factors not differing between groups were:

- **gender; FAB or WHO MDS diagnosis;**
- **marrow blast count;**
- **IPSS or IPSSR cytogenetic risk;**
- **IPSS or IPSSR risk;**
- **neutrophil count at first RBC transfusion or at first infection**
- **causes of death**

(p = NS for all)

In this retrospective, non-controlled analysis, for lower IPSS risk MDS patients receiving RBC transfusions, receiving iron chelation therapy was associated with superior overall survival. Though number and type of infections were similar between groups and despite similar neutrophil counts, **time to first infection was significantly longer in ICT patients**. These results should be confirmed in larger, prospective analyses.

The bone marrow may also be affected by iron overload

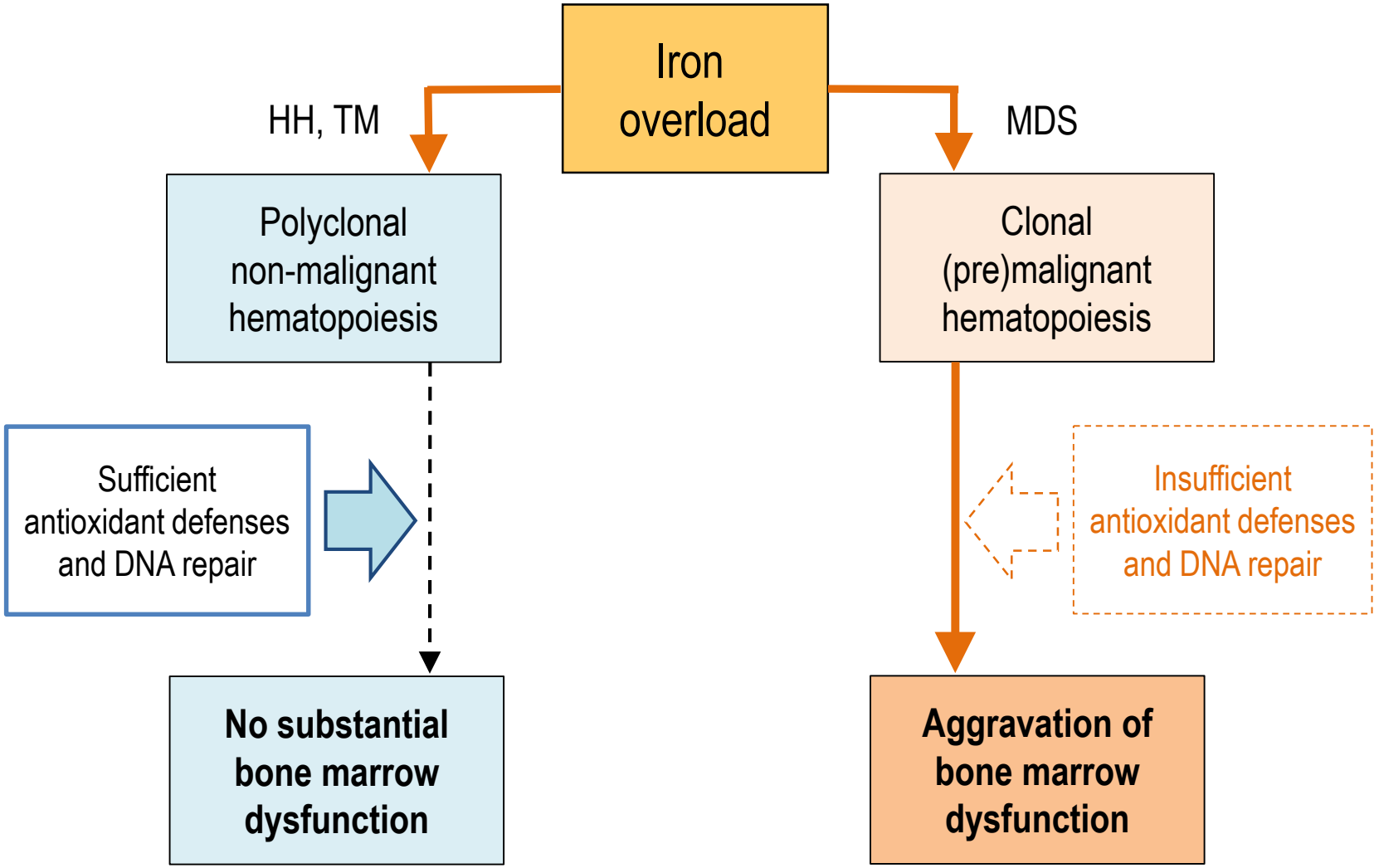


Clinical relevance?

- Hereditary hemochromatosis is **not** notorious for causing bone marrow dysfunction
- Patients with β-thalassemia major and transfusional iron overload are **not** at risk of developing MDS or AML

Is iron overload irrelevant for bone marrow function ?

Iron overload: two different scenarios in the bone marrow



Increased oxidative stress in MDS


EUROPEAN HEMATOLOGY ASSOCIATION

haematologica

Journal of the European Hematology Association
Owned & published by the Ferrata Storti Foundation

Antioxidant Enzyme Expression In Myelodysplastic And Acute Myeloid Leukemia Bone Marrow: Further Evidence Of A Pathogenetic Role For Oxidative Stress?

D Bowen, L Wang, M Frew, R Kerr, M Groves

Haematologica January 2003 88: 1070-1072; **Doi:**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Available online at www.sciencedirect.com

ScienceDirect

Leukemia Research 33 (2009) 340–343

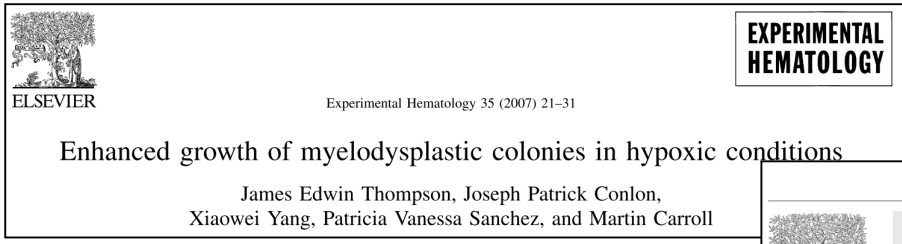
Leukemia Research

www.elsevier.com/locate/leukres

Brief communication

Oxidative DNA damage in bone marrow cells of patients with low-risk myelodysplastic syndrome

Bozena Novotna[a,*], Yana Bagryantseva[a], Magda Siskova[b], Radana Neuwirtova[b]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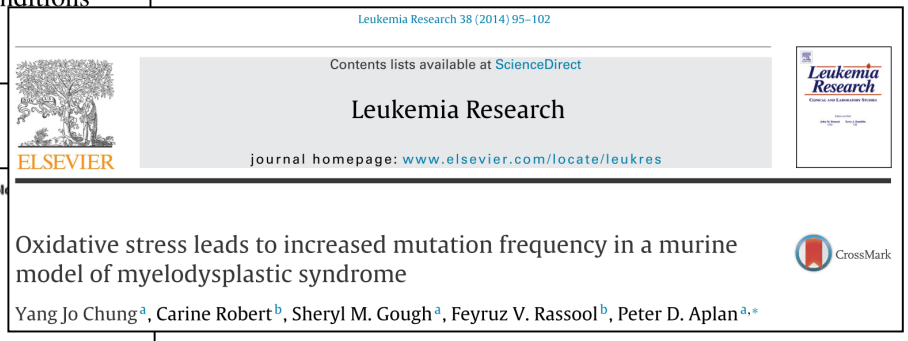
EXPERIMENTAL HEMATOLOGY

Experimental Hematology 35 (2007) 21–31

Enhanced growth of myelodysplastic colonies in hypoxic conditions

James Edwin Thompson, Joseph Patrick Conlon, Xiaowei Yang, Patricia Vanessa Sanchez, and Martin Carroll


Leukemia Research 38 (2014) 95–102

Contents lists available at ScienceDirect

Leukemia Research

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

ELSEVIER

Oxidative stress leads to increased mutation frequency in a murine model of myelodysplastic syndrome

CrossMark

Yang Jo Chung[a], Carine Robert[b], Sheryl M. Gough[a], Feyruz V. Rassool[b], Peter D. Aplan[a,*]


European Journal of Haematol

ORIGINAL ARTICLE

Oxidative stress in red blood cells, platelets and polymorphonuclear leukocytes from patients with myelodysplastic syndrome

Hussam Ghoti[1]*, Johnny Amer[2]*, Asher Winder[1], Eliezer Rachmilewitz[1], Eitan Fibach[2]

Bowen D, et al. Haematologica. 2003;88:1070-2
Chung JY, et al. Leuk Res. 2014;38:95-102
Ghoti H, et al. Eur J Haematol. 2007;79:463-7
Novotna B, et al. Leuk Res. 2009;33:340-3
Thompson JE, et al. Exp Hematol. 2007;35:21-31

Oxidative stress in the bone marrow is aggravated by iron overload, with detrimental effects on hematopoietic progenitors and the stroma

The Journal of International Medical Research
2011; 39: 1941 – 1945

Oxidative Stress Levels in Myelodysplastic Syndrome Patients: their Relationship to Serum Ferritin and Haemoglobin Values

K Saigo[1], M Takenokuchi[1], Y Hiramatsu[2], H Tada[2], T Hishita[3], M Takata[4], M Misawa[5], S Imoto[6] and S Imashuku[7]

European Journal of Haematology 91 (249–261)

ORIGINAL ARTICLE

Free iron catalyzes oxidative damage to hematopoietic cells/mesenchymal stem cells *in vitro* and suppresses hematopoiesis in iron overload patients

Wenyi Lu[1], Mingfeng Zhao[1], Sajin Rajbhandary[1], Fang Xie[1], Xiao Chai[1], Juan Mu[1], Juanxia Meng[1], Yongjun Liu[2], Yan Jiang[1], Xinnv Xu[3], Aimin Meng[4]

Journal of Clinical Pathology
J Clin Pathol 2013;**66**:996-998 doi:10.1136/jclinpath-2012-201288

PostScript

Correspondence

Increased parameters of oxidative stress and its relation to transfusion iron overload in patients with myelodysplastic syndromes

Geane Felix de Souza[1], Maritza Cavalcante Barbosa[2], Talyta Ellen de Jesus Santos[2], Teresa Maria de Jesus Ponte Carvalho[2], Rivelilson Mendes de Freitas[3], Manoel Ricardo Alves Martins[4], Romélia Pinheiro Gonçalves[2], Ronald Feitosa Pinheiro[4], Silvia Maria Meira Magalhães[4]

European Journal of Haematology 93 (118–128)

ORIGINAL ARTICLE

The bone marrow hematopoietic microenvironment is impaired in iron-overloaded mice

Hiroshi Okabe, Takahiro Suzuki, Eisuke Uehara, Masuzu Ueda, Tadashi Nagai, Keiya Ozawa

Leukemia Research 37 (2013) 327–332

Contents lists available at SciVerse ScienceDirect

Leukemia Research

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

Iron overload impairs proliferation of erythroid progenitors cells (BFU-E) from patients with myelodysplastic syndromes☆

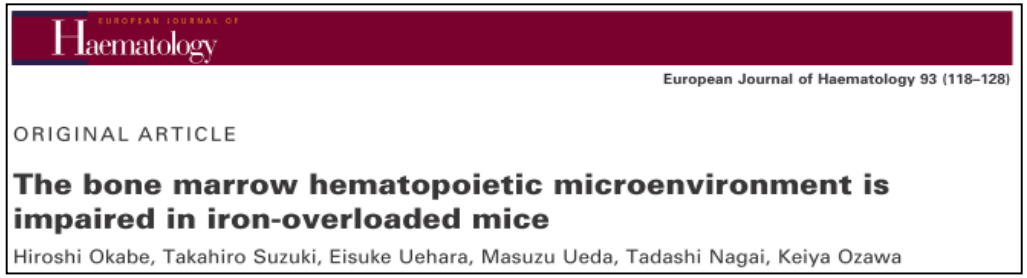
Julia Hartmann[a,b,1], Friederike Braulke[a,*,1], Ursula Sinzig[a], Gerald Wulf[a], Jens Holger Maas[c], Frank Konietschke[d], Detlef Haase[a]

De Souza GF, et al. J Clin Pathol. 2013;66:996-8
Hartmann J, et al. Leuk Res. 2013;37:327-32
Lu W, et al. Eur J Haematol. 2013;91:249-61
Okabe H, et al. Eur J Hematol. 2014;93:118-28
Saigo K, et al. J Int Med Res. 2011;39:1941-5

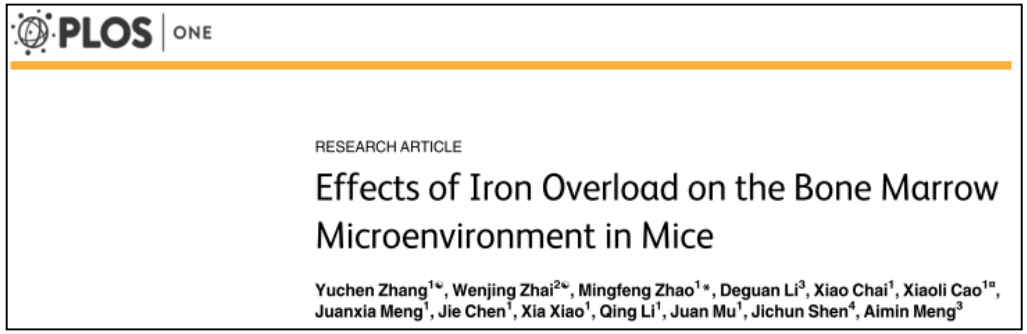
Contribution of IOL to bone marrow dysfunction in MDS

- Iron overload by itself is apparently not leukemogenic
- In the context of pre-existing genomic instability of the MDS clone, iron overload may accelerate mutagenesis and clonal evolution
- Iron overload may impair proliferation and maintenance of (residual) normal HSPCs
- Erythropoiesis appears to be particularly vulnerable to IOL
- **IOL als perturbs the bone marrow stroma**

Iron overload damages the bone marrow stroma



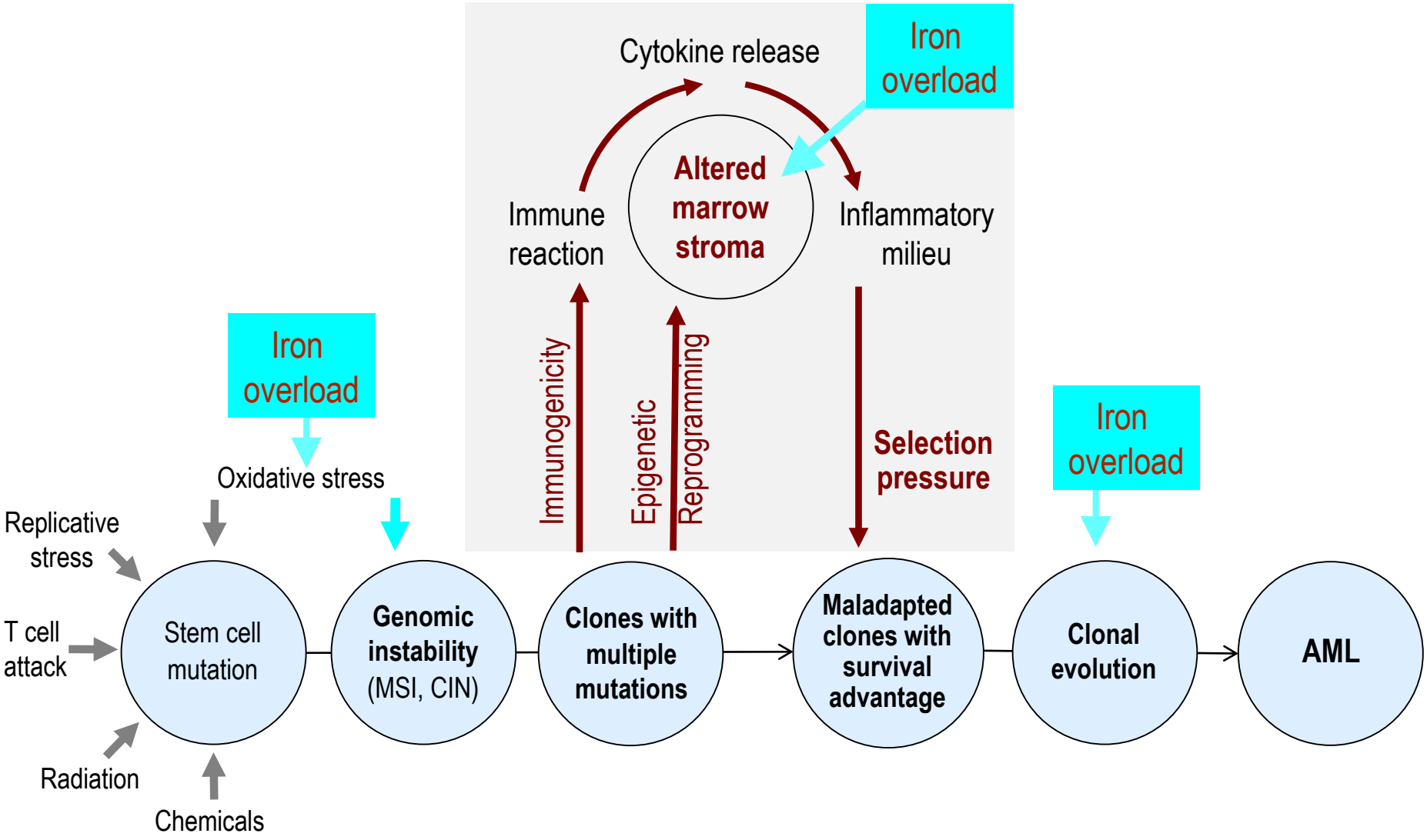
- BM transplantation from normal donors to recipients with IOL showed delayed haemopoietic reconstitution, indicating that excess iron negatively impacts the haemopoietic microenvironment
- MSC showed markedly reduced expression of surface molecules known to be involved in stem cell homing



- IOL impairs the proliferation of mouse BM mesenchymal cells
- Free iron catalyzes in vitro oxidative damage to mesenchymal cells attenuating haemopoiesis

Okabe H, et al. Eur J Haematol. 2014;93:118-28.
Zhang Y, et al. PLoS One. 2015;10:e0120219.

Where does iron overload contribute to MDS pathology?



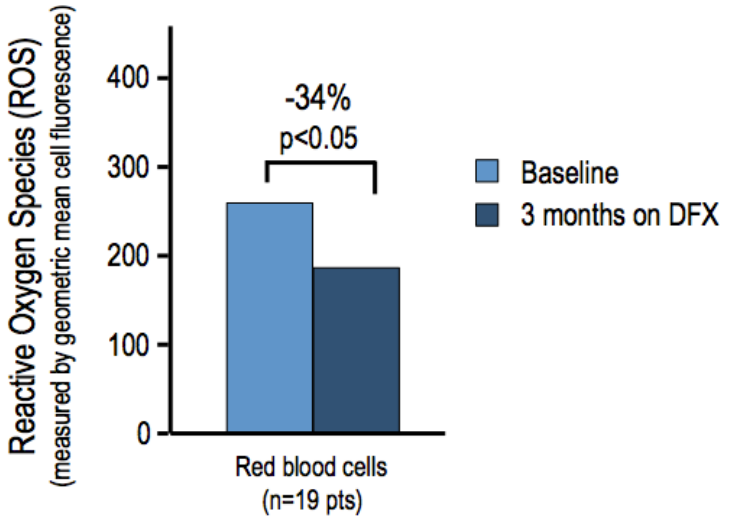
Beneficial effect of **chelation with DFX** on oxidative stress in MDS:

decreased ROS production, decreased lipid peroxidation, improved colony growth, and diminished iron-mediated oxidative DNA damage

- Ghoti H, Fibach E, Merkel LD, Perez-Avraham G, Grisariu S, Rachmilewitz E (2010)

  Changes in parameters of oxidative stress and free iron biomarkers during treatment with deferasirox is iron-overloaded patients with myelodysplastic syndromes.

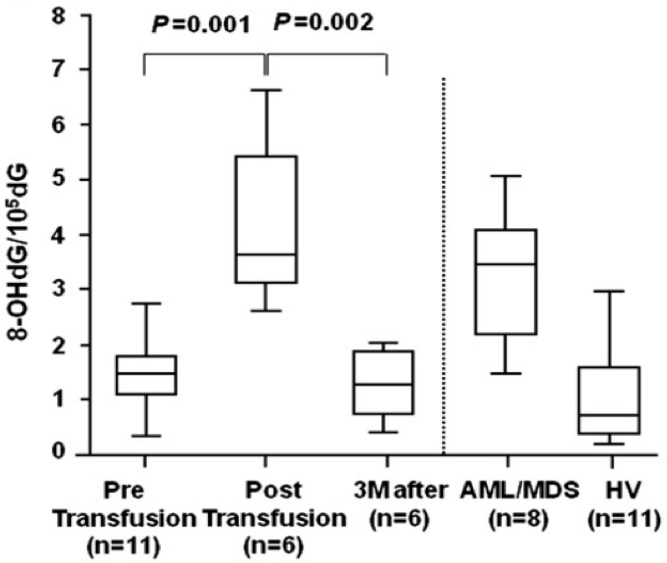
  Haematologica 95:1433-1434



- Kikuchi S, Kobune M, Iyama S, Sato T, Murase K, Kawano Y, et al. (2012)

  Improvement of iron-mediated oxidative DNA damage in patients with transfusion-dependent myelodysplastic syndrome by treatment with deferasirox.

  Free Radical Bio Med 53:643-648



Deferasirox can improve hematopoiesis in MDS

Study	Risk IPSS	RBC response	Neutrophil response	PLT response
List A et al. J Clin Oncol. 2012; 30:2134-9	Low/Int-1	**15%** (n=173)	15% (n=52)	22% (n=77)
Gattermann N et al. Haematologica 2012; 97:1364-71	Low/Int-1	**21.5%** (n=247)	22% (n=50)	13% (n=100)
Nolte F et al. Ann Hematol. 2013; 92:191-8	Low/Int-1	**11%** (n=50)	NR	NR
Angelucci E et al. Eur J Hematol 2014; 92:527-36	Low/Int-1	Transfusion independence in **15.5%** (n=152)	NR	NR
Meunier M et al. Oncotarget 2017; 8:105510-105524	Low/Int-1	Transfusion independence in **100%** (n=6)	NR	NR

Potential benefits of iron chelation in MDS

- Lower incidence of cardiac events, diabetes, and hepatic impairment
- Fewer infectious complications
- Improved hematopoietic function
- Lower risk of leukemic transformation
- Improved outcome of allogeneic SCT

→ Improved overall survival?

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
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
de Witte T 2012	1,000	Prospective, registry	Adjusted HR	1	0.51 (0.19-1.32)	NS
Delforge 2014	127	Retrospective	Median OS in Low/Int-1	3.1 yrs	10.2 yrs	< 0.001
Lyons 2014	600	Prospective, registry	Median OS from diagnosis	47.8 mo	All 88.0 mo ICT > 6 mo 100.0 mo	< 0.0001
Remacha 2015	263	Retrospective	Median OS	105 mo	133 mo	<0.001

Delforge M, et al. Leuk Res 2014;38:557-63 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. Ann Hematol 2015;94:779-87. 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.

The main problem with studies on the survival impact of iron chelation in MDS patients

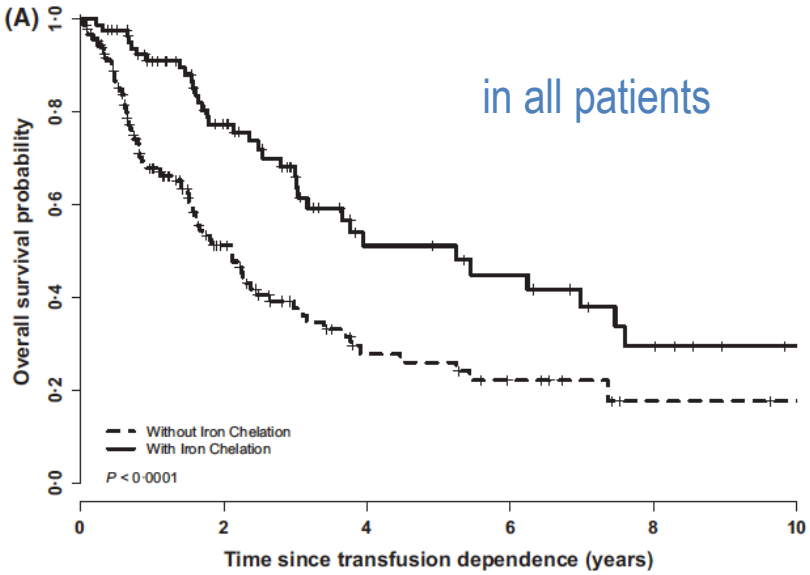
- Patient populations are usually well characterized regarding **disease-related** parameters and risk factors.
- Patient populations are usually **not** characterized and **not** stratified according to overall **performance status** and **comorbidities.**
- Possible bias:

  Patients with better overall performance status may have been more likely to be started on iron chelation therapy.

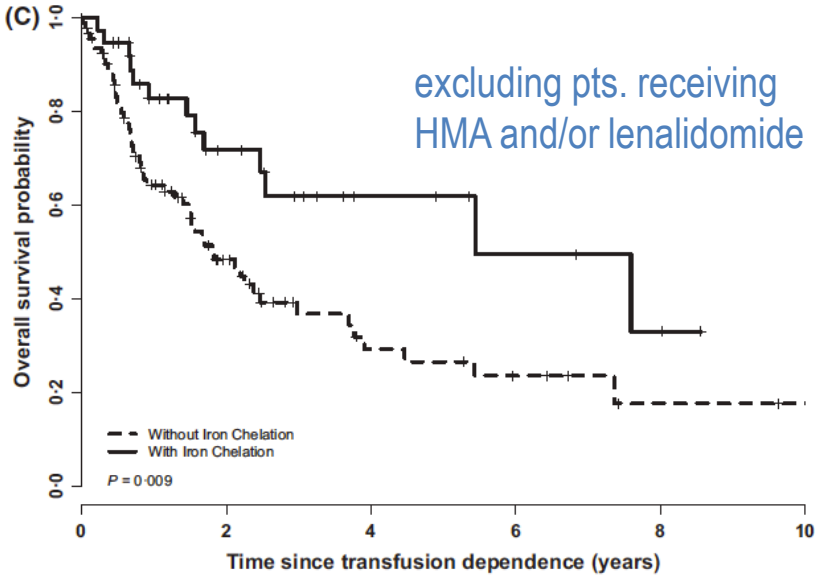
  This may have had an impact on clinical outcome.

Overall survival with and without ICT

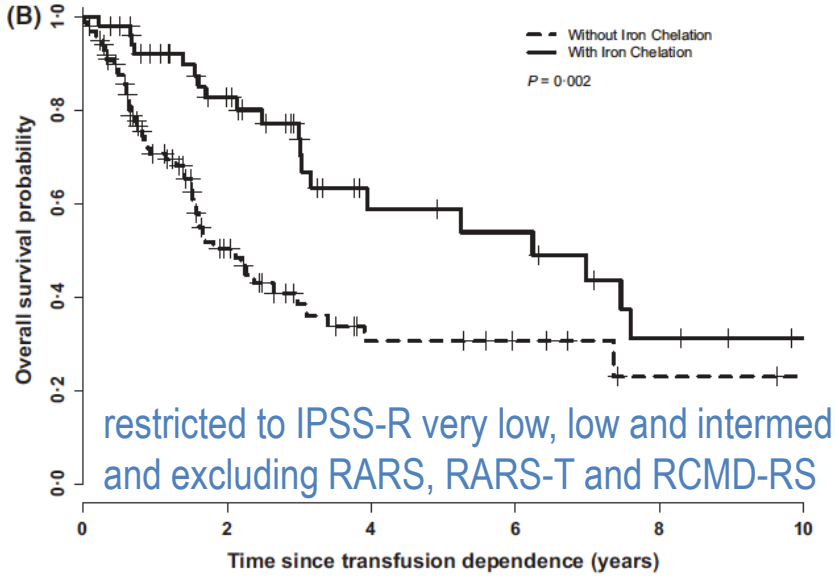
OS measured from start of transfusion dependence



in all patients



excluding pts. receiving HMA and/or lenalidomide



restricted to IPSS-R very low, low and intermediate, and excluding RARS, RARS-T and RCMD-RS

bjh research paper

Overall survival in lower IPSS risk MDS by receipt of iron chelation therapy, adjusting for patient-related factors and measuring from time of first red blood cell transfusion dependence: an MDS-CAN analysis

Leitch HA et al., Br J Haematol. 2017; 179:83-97

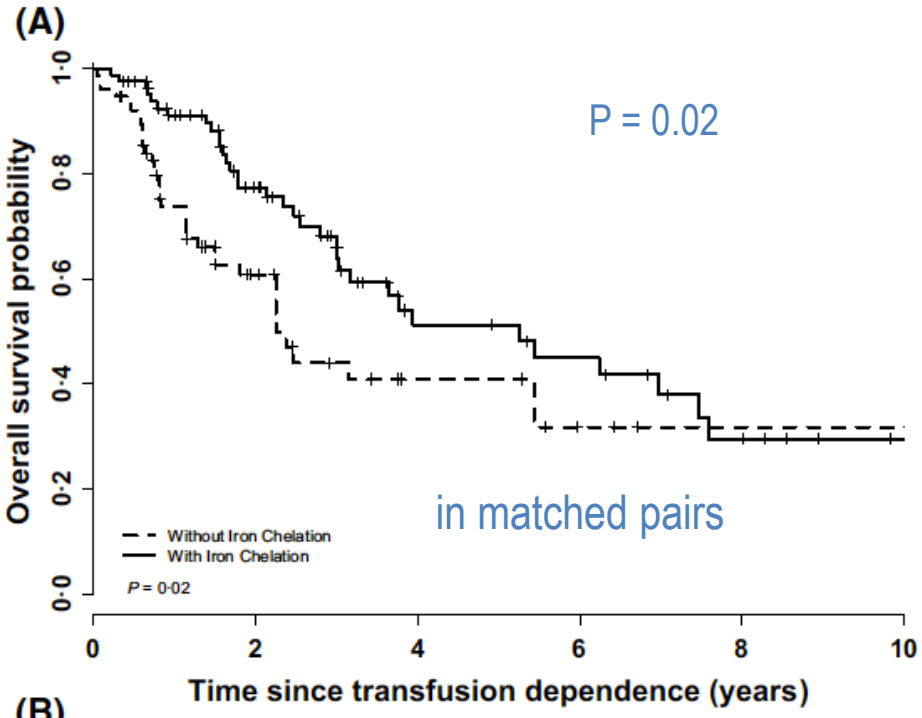
Overall survival with and without ICT **in matched pairs**

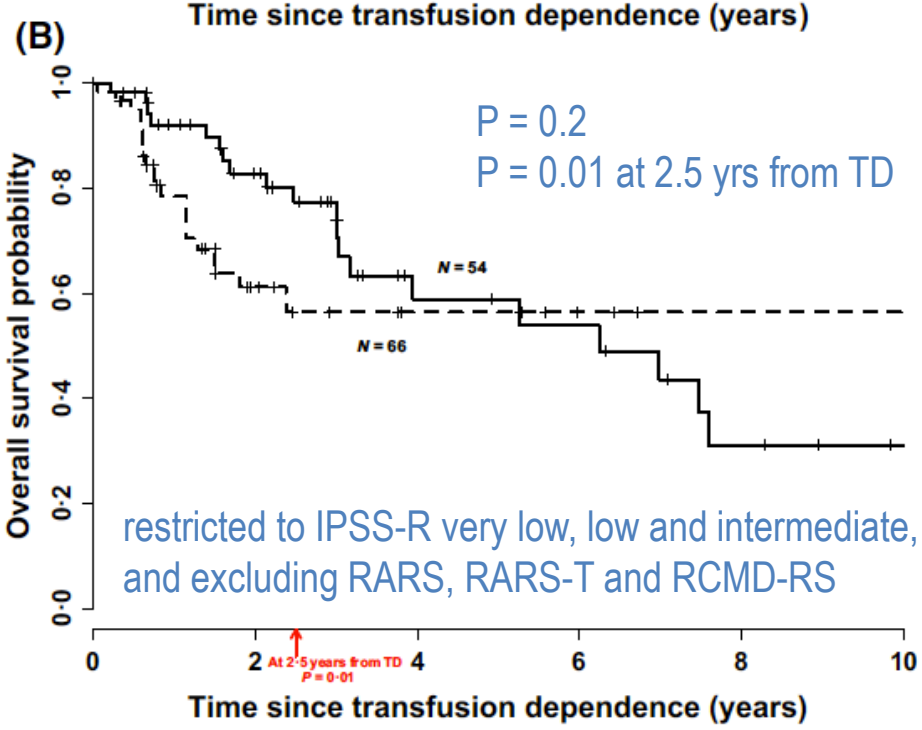
In order to further adjust for differences in baseline characteristics between groups, a **matched pair analysis** (at the time of transfusion dependence) was performed, including 83 ICT and 83 non-ICT pts.

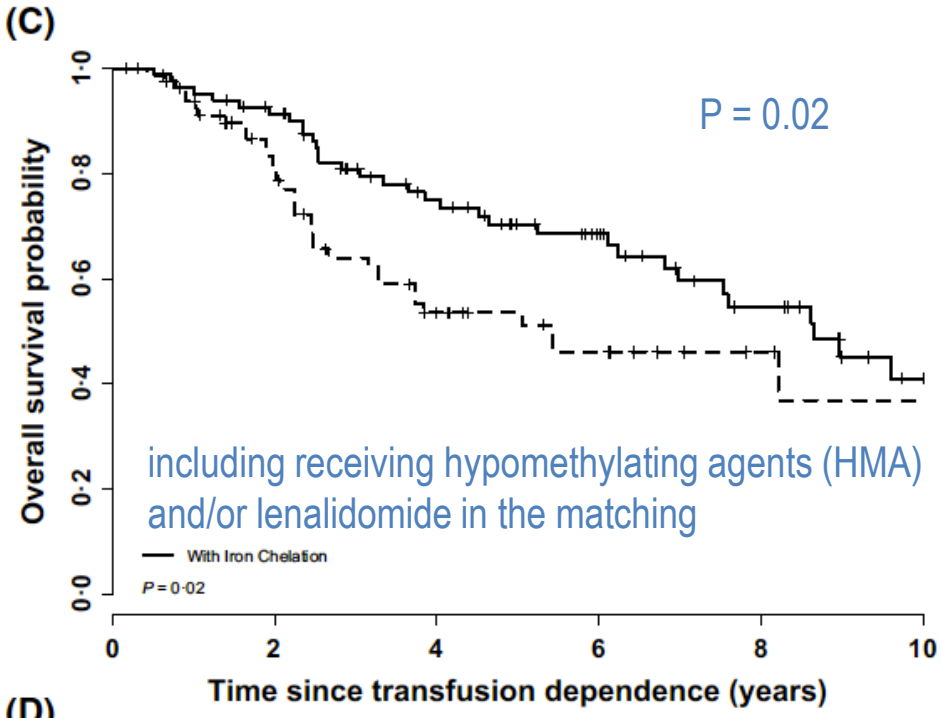
Matching criteria:

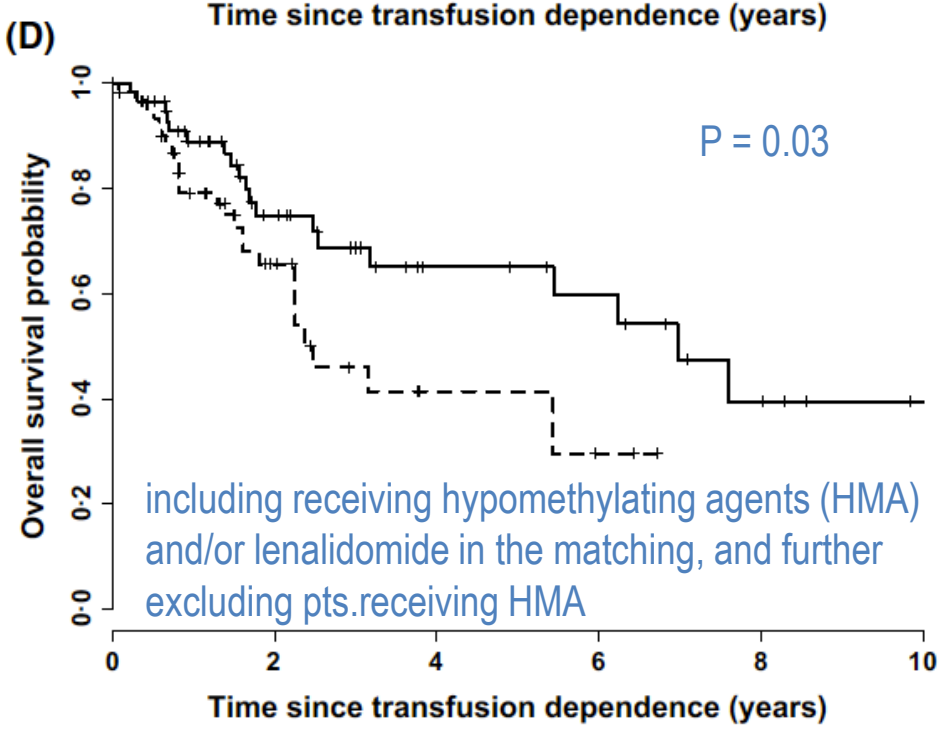
- **Age**
- **IPSS-R**
- **Number of RBC units transfused per month**
- **Time from MDS diagnosis until RBC transfusion dependence**

Leitch HA et al., Br J Haematol. 2017; 179:83-97

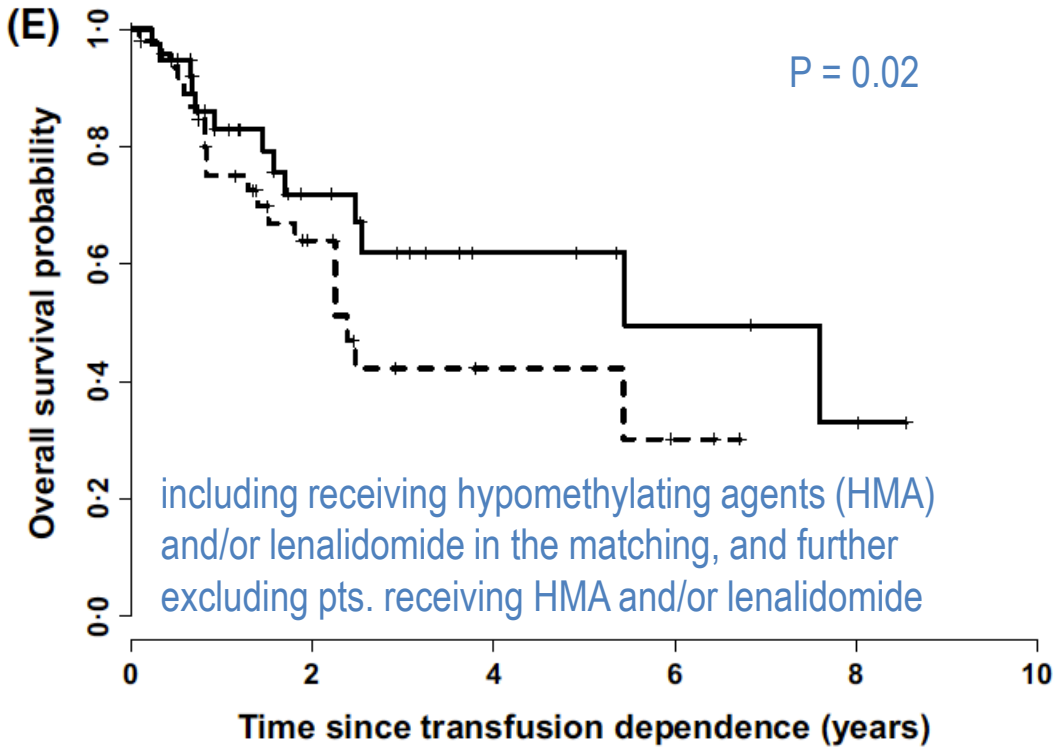

(A)
P = 0.02
in matched pairs
Without Iron Chelation
With Iron Chelation
P = 0·02
Overall survival probability
Time since transfusion dependence (years)


(B)
P = 0.2
P = 0.01 at 2.5 yrs from TD
N = 54
N = 66
restricted to IPSS-R very low, low and intermediate, and excluding RARS, RARS-T and RCMD-RS
At 2·5 years from TD
P = 0·01
Overall survival probability
Time since transfusion dependence (years)


(C)
P = 0.02
including receiving hypomethylating agents (HMA) and/or lenalidomide in the matching
With Iron Chelation
P = 0·02
Overall survival probability
Time since transfusion dependence (years)


(D)
P = 0.03
including receiving hypomethylating agents (HMA) and/or lenalidomide in the matching, and further excluding pts.receiving HMA
Overall survival probability
Time since transfusion dependence (years)

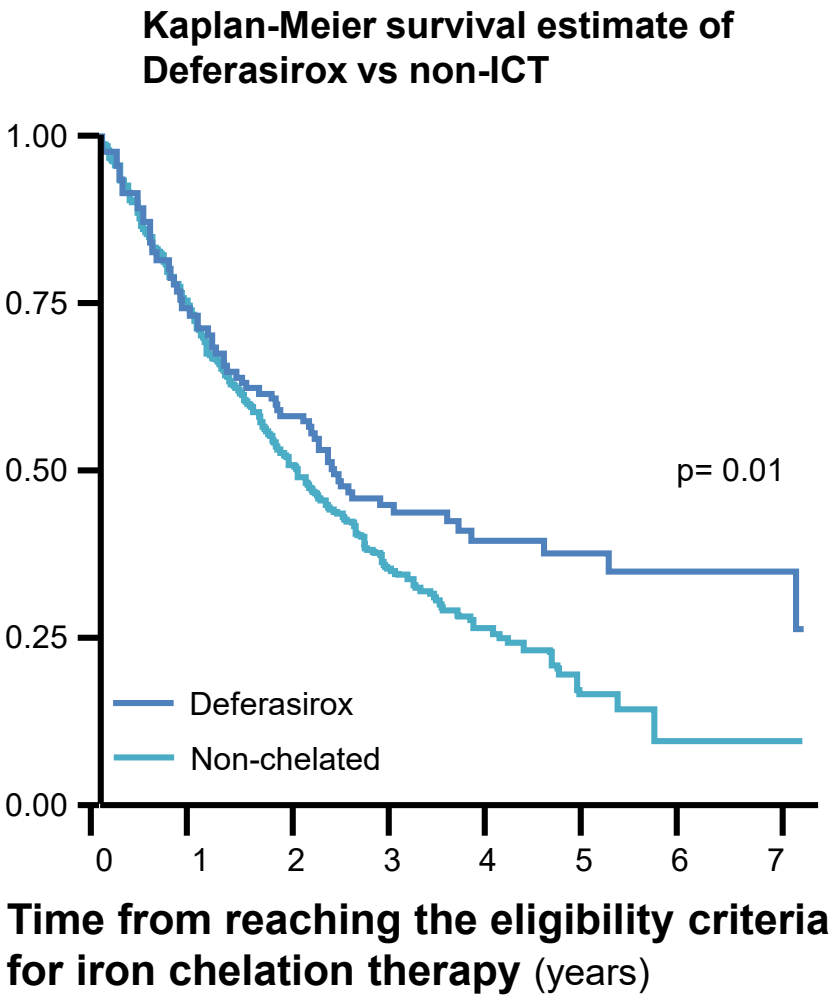
Overall survival with and without ICT **in matched pairs**



In this prospective, nonrandomized analysis, receiving ICT was associated with superior OS in lower IPSS risk MDS, adjusting for age, frailty, comorbidity, disability, revised IPSS, TD severity, time to TD and receiving disease-modifying agents. This provides additional evidence that ICT may confer clinical benefit.

Leitch HA et al., Br J Haematol. 2017; 179:83-97

Impact of treatment with iron chelators in lower-risk MDS patients participating in the European Leukemia Net MDS (EUMDS) Registry



Adjusted Overall Survival

OS of 192 chelated patients was significantly better when compared with a large control group of 573 patients, even after adjustment for all relevant prognostic factors, i.e.

- age
- sex
- comorbidity
- performance status
- number of RBC units transfused prior to start of chelation

Langemeijer S, et al. ASH Annual Meeting 2016; Abstract 3186

425 Impact of Treatment with Iron Chelation Therapy in Lower-Risk MDS Patients Participating in the European Leukemianet MDS (EUMDS) Registry

Hoeks M, et al.

Table 2 Data of three chelated subgroups and control group at time of reaching the eligibility criteria

	Unchelated		Chelated		Deferasirox		Deferoxamine		Deferiprone	
Total	657		205		154		39		12	
No. of countries with chelated patients	17 / 17		17 / 17		14 / 17		10 / 17		6 / 17	
Mean age at eligible (sd)	75	(10)	70	(9)	69	(9)	72	(8)	69	(11)
Time from diagnosis (months)										
Inclusion, median (p10-p90)	0	(0 - 27)	0	(0 - 21)	6	(0 - 26)	0	(0 - 19)	0	(0 - 7)
Chelation median (p10-p90)			15	(4 - 44)	17	(4 - 46)	13	(2 - 39)	22	(5 - 51)
Transfused prior to being chelated										
No	0	0%	6	3%	4	3%	2	5%	0	0%
Yes	657	100%	199	97%	150	97%	37	95%	12	100%
Total number of units, median (range)	15	(1 - 210)	13	(2 - 91)	12	(2 - 75)	11	(2 - 75)	25	(2 - 91)
Ferritin (ug/L)										
Median (range)	393	(5315)	665	(3087)	658	(3087)	668	(1941)	530	(913)
Comorbidity (MDSCI)										
Low risk	395	60%	153	75%	120	78%	26	67%	7	58%
Intermediate risk	225	34%	44	22%	29	19%	11	28%	4	33%
High risk	35	5%	7	3%	4	3%	2	5%	1	8%
Performance status										
Unable to care for self	12	2%	0	0%	0	0%	0	0%	0	0%
Unable to work	161	29%	34	18%	20	15%	12	31%	2	18%
Able to work and normal activity	376	68%	152	82%	116	85%	27	69%	9	82%
Duration of treatment with chelation (months)										
Median (p10-p90)			13	(3 - 42)	16	(3 - 43)	9	(1 - 34)	14	(6 - 30)
Overall Survival (OS)*										
Unadjusted	1		0.66	(0.52 - 0.85)	1		1.77	(1.02 - 3.05)	0.43	(0.10 - 1.77)
Adjusted**	1		0.75	(0.50 - 1.15)	1		1.95	(0.85 - 4.50)	0.38	(0.04 - 4.06)

* HRs and 95% CI were estimated using receipt of chelation as a time-varying covariate.

** adjusted by age at eligibility criteria, sex, comorbidity, performance status, and number of units transfused

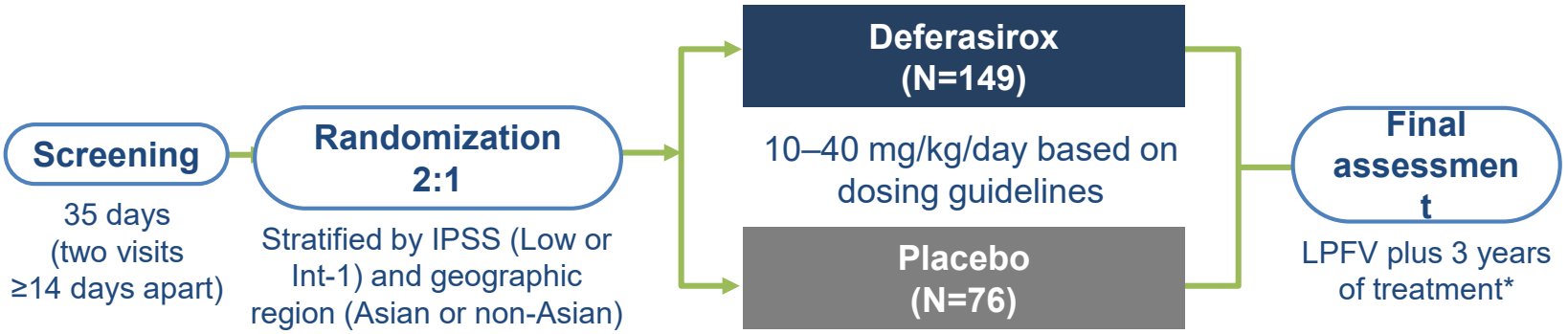
ASH Annual Meeting 2018

Safety and Efficacy, Including Event-free Survival, of Deferasirox Versus Placebo in Iron-Overloaded Patients with Low- and Int-1-Risk Myelodysplastic Syndromes (MDS): Outcomes from the Randomized, Double-Blind TELESTO Study

Emanuele Angelucci,[1] Junmin Li,[2] Peter Greenberg,[3] Depei Wu,[4] Ming Hou,[5] Efreen Horacio Montaño Figueroa,[6] Maria Guadalupe Rodriguez,[7] Xunwei Dong,[8] Jagannath Ghosh,[8] Miguel Izquierdo,[9] and Guillermo Garcia-Manero[10]

[1]Hematology and Transplant Center, IRCCS Ospedale Policlinico San Martino, Genova, Italy; [2]Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [3]Stanford University Medical Center, Stanford, CA, USA; [4]Jiangsu Institute of Hematology, First Affiliated Hospital of Soochow University, Suzhou, China; [5]Department of Hematology, Qilu Hospital, Shandong University, Jinan, China; [6]Department of Hematology, Hospital General de México, Mexico City, Mexico; [7]Department of Hematology, Hospital de Especialidades, Centro Médico Nacional La Raza, IMSS, Mexico City, Mexico; [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [9]Novartis Pharma AG, Basel, Switzerland; [10]MD Anderson Cancer Center, University of Texas, Houston, TX, USA

TELESTO – a Phase II, randomized, double-blind study



*Patients who experienced a non-fatal event were discontinued and followed up for 28 days; patients were then followed up every 3–6 months (for evaluation or survival)

Key inclusion criteria:

- Hematologically stable IPSS Low or Int-1-risk MDS, confirmed by bone marrow within 6 months prior to study entry
- Serum ferritin >1000 ng/mL
- History of transfusion of 15–75 pRBC units
- No history of hospitalization due to congestive heart failure and LVEF ≥50% by echocardiography
- ALT or AST ≤3.5×ULN, total bilirubin ≤1.5×ULN, no previous diagnosis of liver cirrhosis; CrCl ≥40 mL/min
- ECOG performance status ≤2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; LPFV, last patient first visit; LVEF, left ventricular ejection fraction; pRBC, packed red blood cell; ULN, upper limit of normal

TELESTO study design

Designed as a **Phase III trial**
with a target enrolment of **630** patients

Because of low enrolment, the target sample size was reduced,
based on the feasibility of enrolling patients
and consultations with the health authorities

Changed to a **Phase II trial**
with target enrolment of **210** patients
Trial was therefore not designed to make statistical comparisons

TELESTO – study objectives

Primary

To evaluate event-free survival (composite endpoint)

- Defined as the time from randomization to first documented non-fatal event (worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, transformation to AML), based on review and confirmation by an **independent adjudication committee**, or death, whichever occurred first

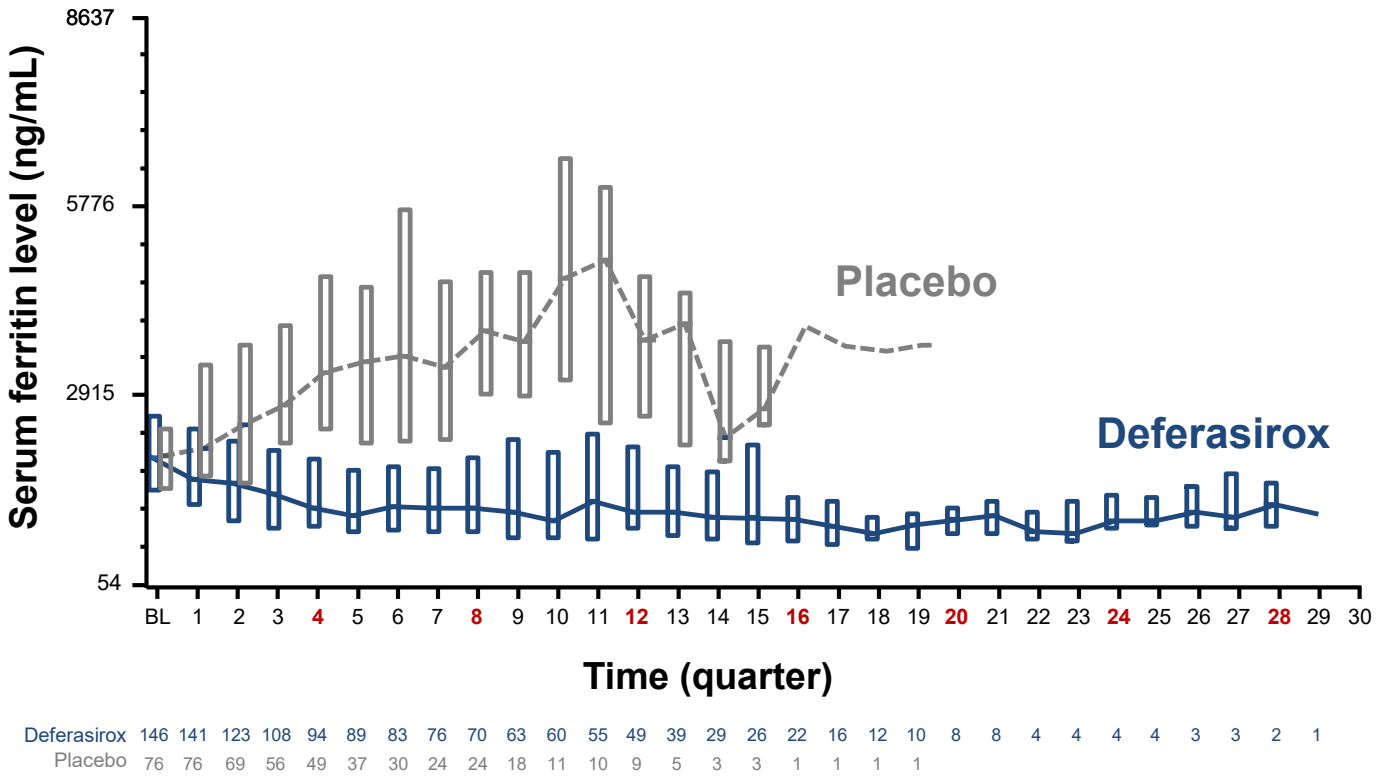
Key secondary

To assess:

- Overall survival
- Change in serum ferritin level
- Hematologic improvement in terms of erythroid response (based on International MDS Working Group criteria[1])
- Change in endocrine function (thyroid and glycemic control)
- Safety

1. Cheson BD *et al. Blood* 2006;108:419–425

Serum ferritin trends



Boxes show lower and upper quartiles, horizontal line shows the median

Primary endpoint EFS:
Stratified log-rank test and Cox regression model

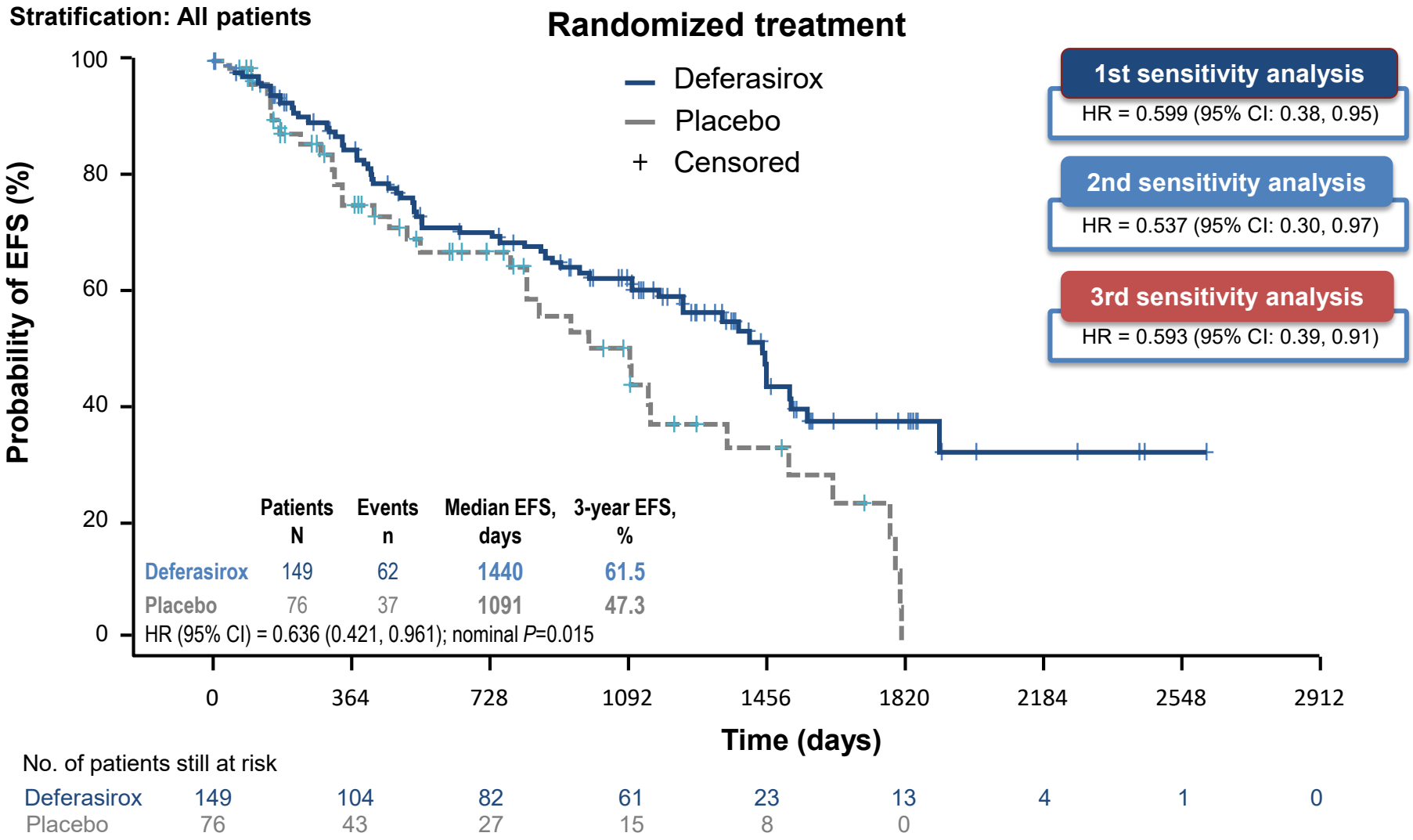
All patients*	Log-rank test			Cox model
	Event / % (N)	**Median time to event** (95% CI), days†	***P* value‡**	**HR** (95% CI)§
Deferasirox	**41.6** (62/149)	**1440** (1167, 1559)	0.015	0.636 (0.42, 0.96)
Placebo	**48.7** (37/76)	**1091** (820, 1348)		

*Both the log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model

A **36.4%** risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm
(HR: 0.636; 95% CI: 0.42, 0.96; nominal *P*=0.015)

CI, confidence interval; HR, hazard ratio

Kaplan–Meier plot of EFS



EFS events (non-fatal events or deaths) that occurred first as confirmed by the EAC (adjudication rate 44%)

Parameter	Patients with events†		
	Deferasirox N=149 n (%)	**Placebo** N=76 n (%)	**All patients** N=225 n (%)
Non-fatal events confirmed by EAC*	14 (9.4)	12 (15.8)	26 (11.6)
Progression to AML	10 (6.7)	6 (7.9)	16 (7.1)
Hospitalization for CHF	1 (0.7)	3 (3.9)	4 (1.8)
Liver cirrhosis	0	0	0
Liver function impairment	1 (0.7)	1 (1.3)	2 (0.9)
Worsening of cardiac function	2 (1.3)	2 (2.6)	4 (1.8)
Deaths during treatment	48 (32.2)	25 (32.9)	73 (32.4)

*Investigators were asked to report any event that was even remotely possible to be an event to the EAC; only events confirmed by the EAC are included; †A patient with multiple occurrences of the same event is counted only once in the component category

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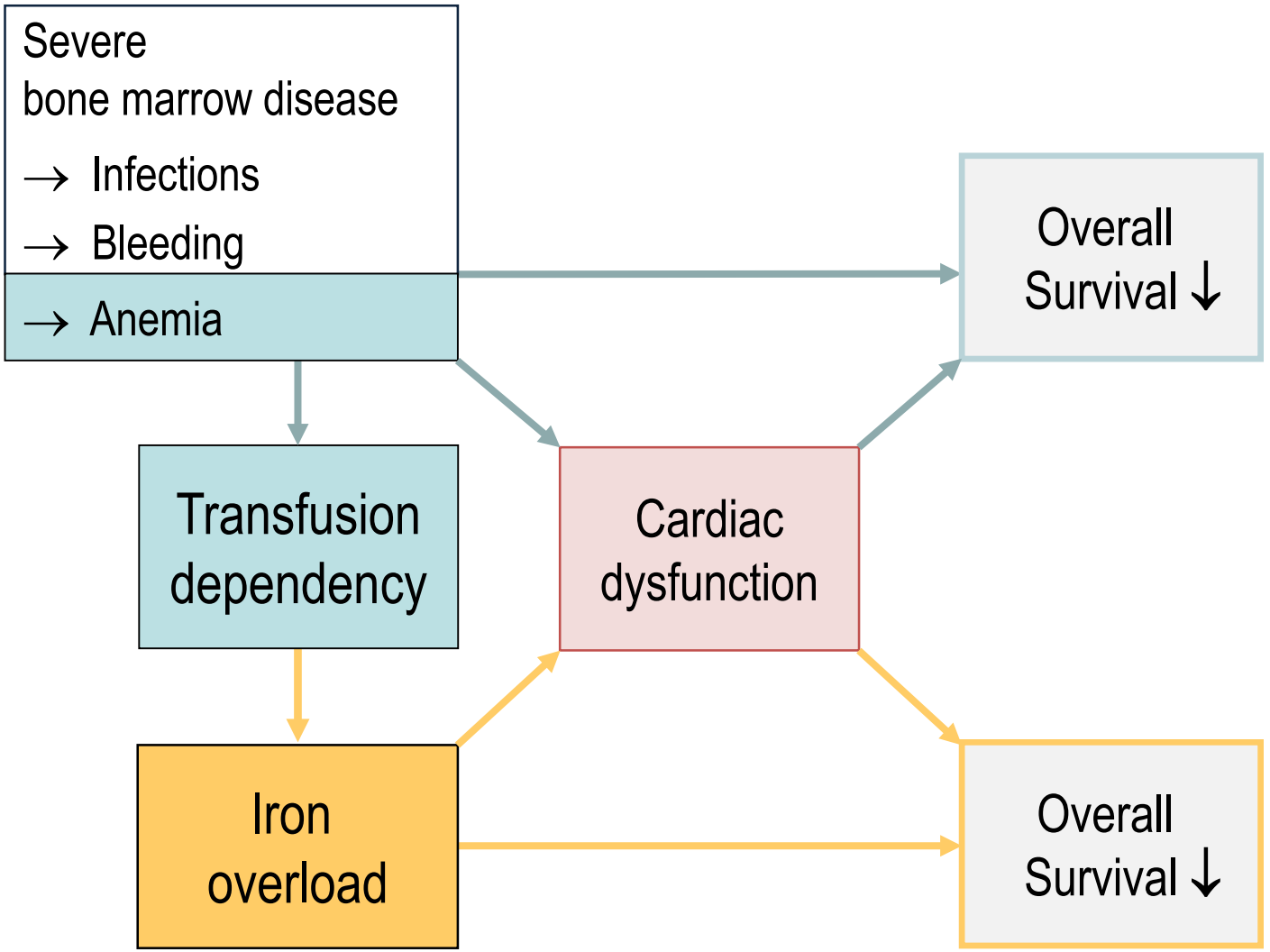
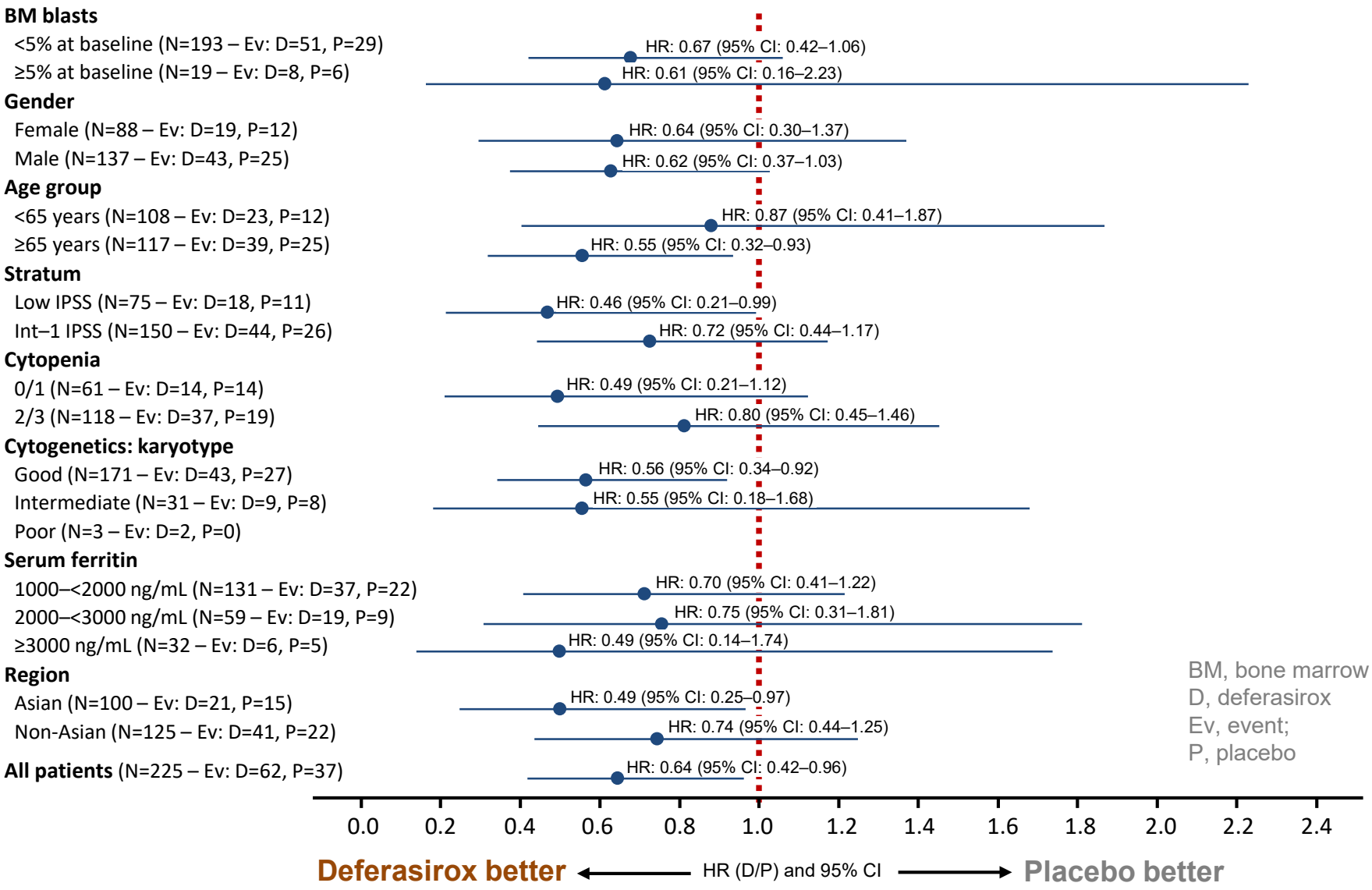
TELESTO was not powered to detect differences between deferasirox and placebo for single-event categories of the composite primary endpoint for EFS

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



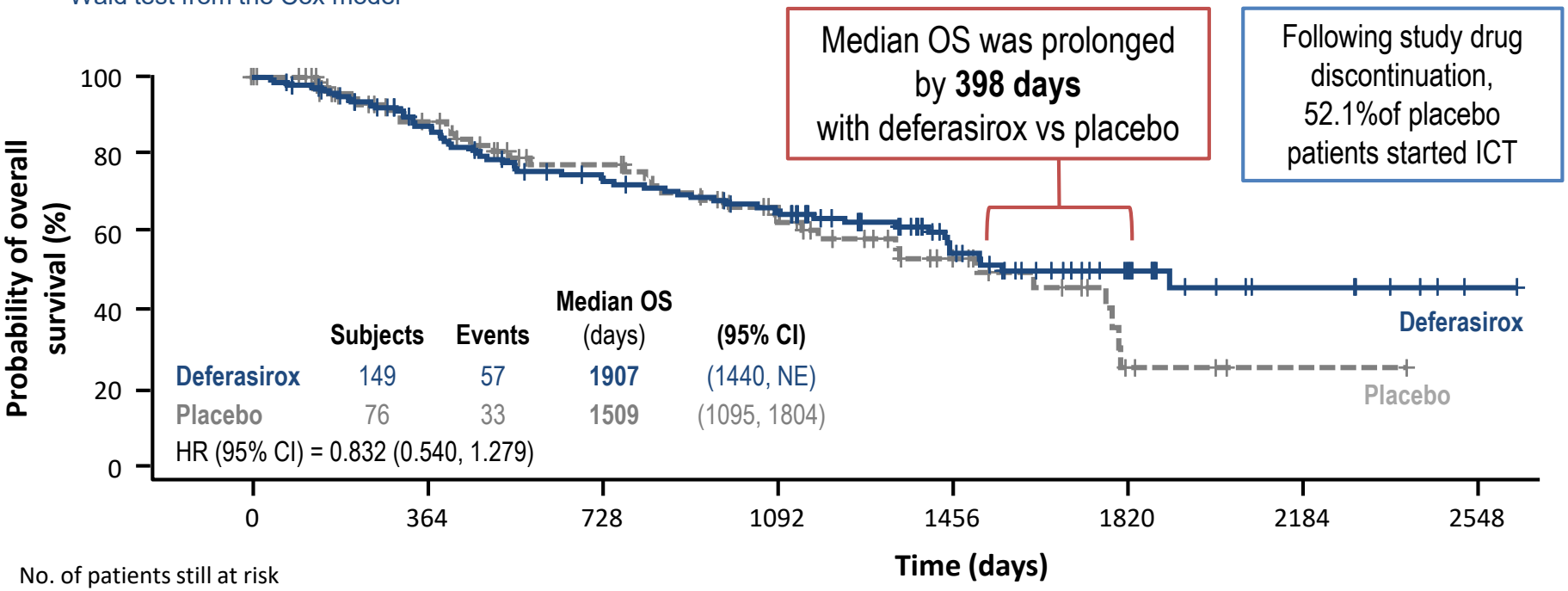
Forest plot for EFS



Summary of overall survival

All patients*	Log-rank test		Cox model	
	Event/N (%)	Median time (95% CI), days†	*P* value‡	Hazard ratio (95% CI)§
Deferasirox	57/149 (38.3)	**1907** (1440, NE)	0.200	0.832 (0.54, 1.28)
Placebo	33/76 (43.4)	**1509** (1095, 1804)		

*Both log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one-tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model



No. of patients still at risk

Deferasirox	149	113	91	76	40	20	7	1
Placebo	76	60	45	33	18	4	1	0

Summary of Telesto study

- TELESTO is the first prospective, randomized study of ICT in patients with Low-/Int-1-risk MDS and iron overload
- Treatment with deferasirox led to longer EFS compared with placebo
- Exposure-adjusted AEs were similar in the two arms with the exception of non-severe increases in serum creatinine, with no new safety signals
- Considering the current treatment landscape, it is unlikely that a similar randomized trial will be performed

TELESTO provides evidence on the clinical benefit of ICT in lower risk MDS patients with iron overload

Conclusions

- There is no reason to believe that iron overload is less toxic in elderly MDS patients than young thalassemia patients
- Cardiovascular problems seem to be the most relevant sequelae of IOL in elderly MDS patients
- Age-related cardiac comorbidities may lead to increased vulnerability to the toxic effects of IOL
- The impact of IOL is difficult to prove in elderly MDS patients, due to overlap with age-related clinical problems
- In recent years, well-conducted registry studies have consistently shown a survival benefit of ICT in patients with lower-risk MDS
- These results are now corroborated by the improved EFS demonstrated by the Telesto study