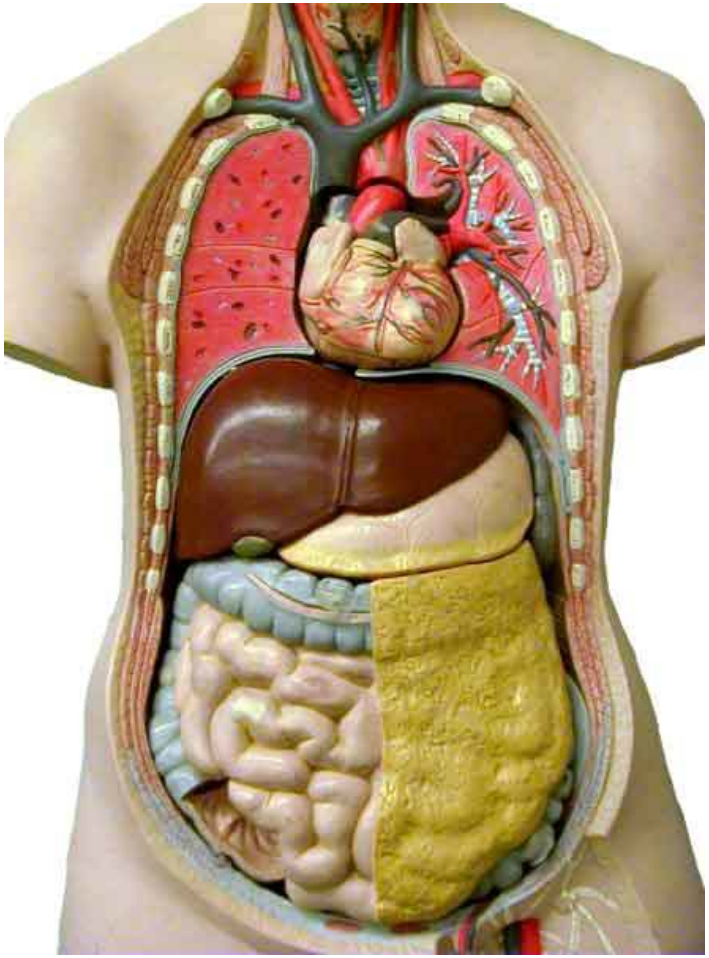
CARENZA ED ECCESSO DI FERRO: nuove conoscenze ed approccio terapeutico

Ore 15,50-16,10

Esperienze della chelazione nelle mielodisplasie e politrasfusi

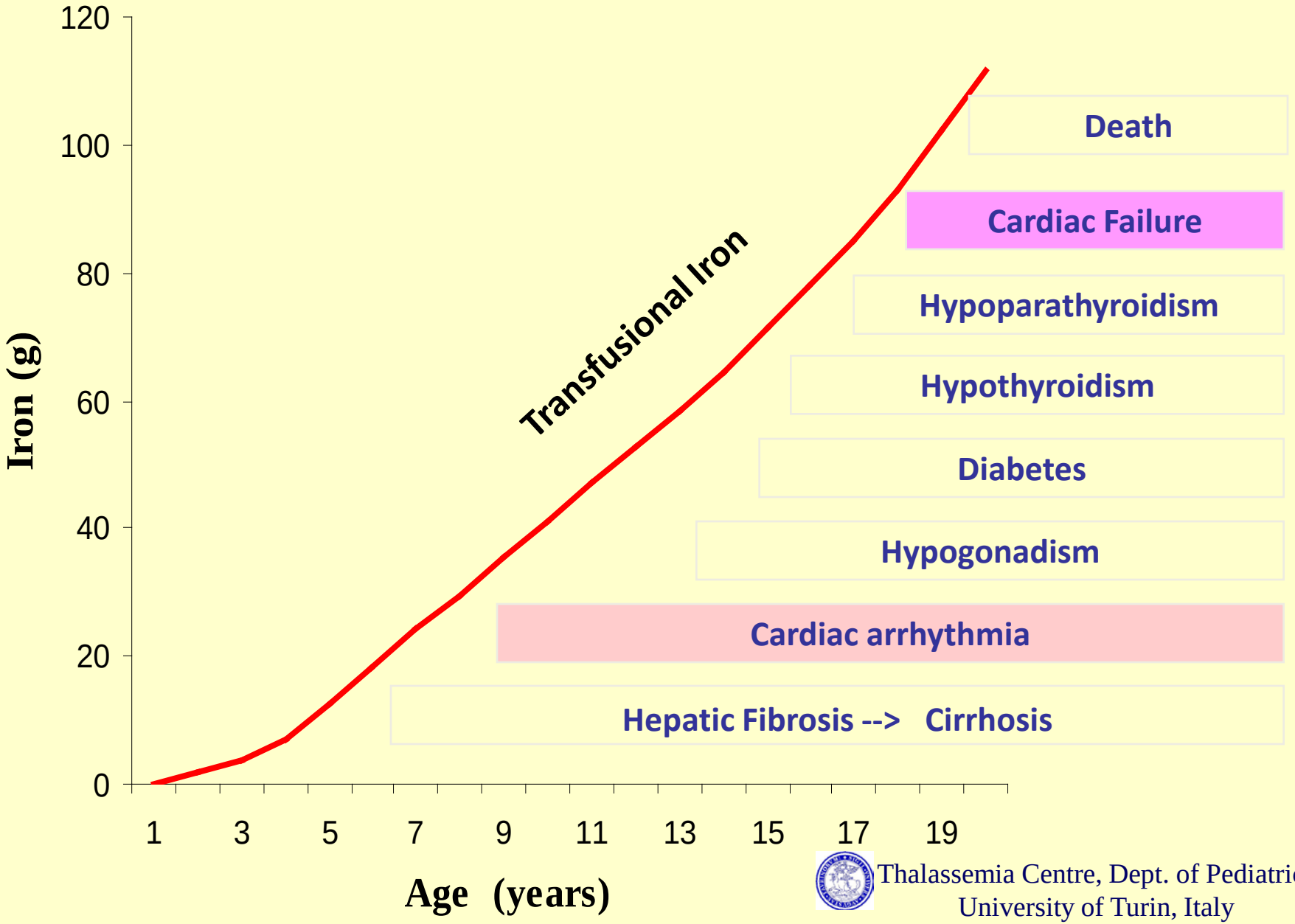
E. Angelucci- Genova

Organ systems susceptible to iron overload



Clinical sequelae of iron overload	
Hypophyse	impaired growth hypogonadism hypothyroidism
Thyroid	hypothyroidism
Heart	cardiac failure arrythmias
Liver	hepatic cirrhosis, cancer
Pancreas	Diabetes mellitus
Bone	osteoporosis

Iron overload progressively affects organ functions



Thalassemia Centre, Dept. of Pediatrics
University of Turin, Italy

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Hypophyse	impaired growth hypogonadism hypothyroidism
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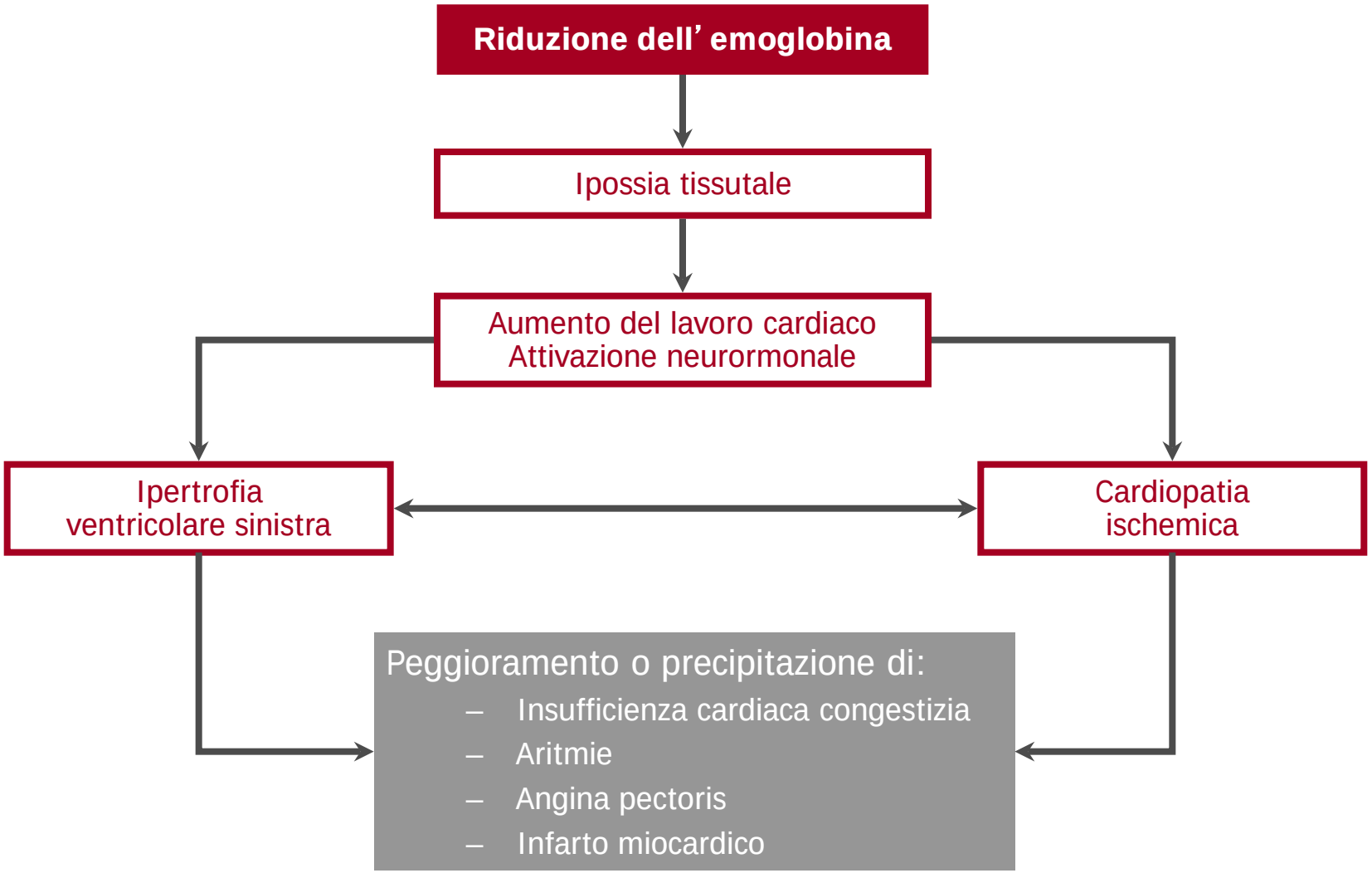
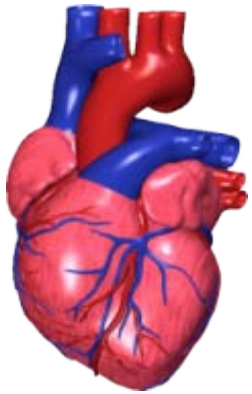
Anemia and cardiac disease in adults



Modificata da National Anemia Action Council. Anemia: A Hidden Epidemic. Los Angeles, CA: HealthVizion Communications, Inc., 2002

Heart and kidney strongly interact in regulating blood volume homeostasis and systemic blood pressure

Acute or chronic dysfunction in either the heart or kidneys can induce dysfunction in the other organ. → cardiorenal syndromes



Anemia; Inflammation

Sympathetic and RAA activation; humoral signalling

Hypertension; Dyslipidemia

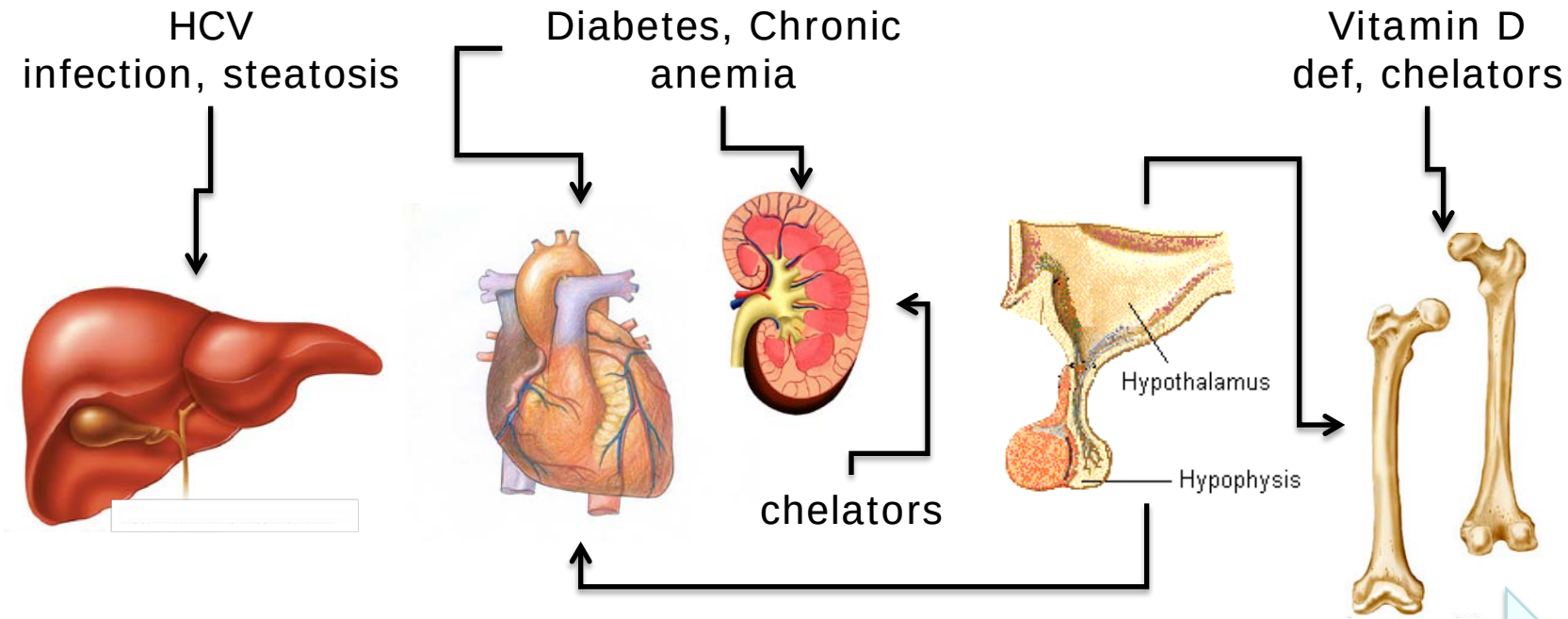
Low cardiac output

Acute/chronic renal hypoperfusion and/or renal congestion

Subclinical inflammation
Endotelial disfunction

Shamseddin & Parfrey. Nature Review Nephrology 2009; Ronco et al JACC 2008

One cause, different comorbidities



Iron overload – Iron toxicity

rate of iron accumulation, amount and duration of iron overload

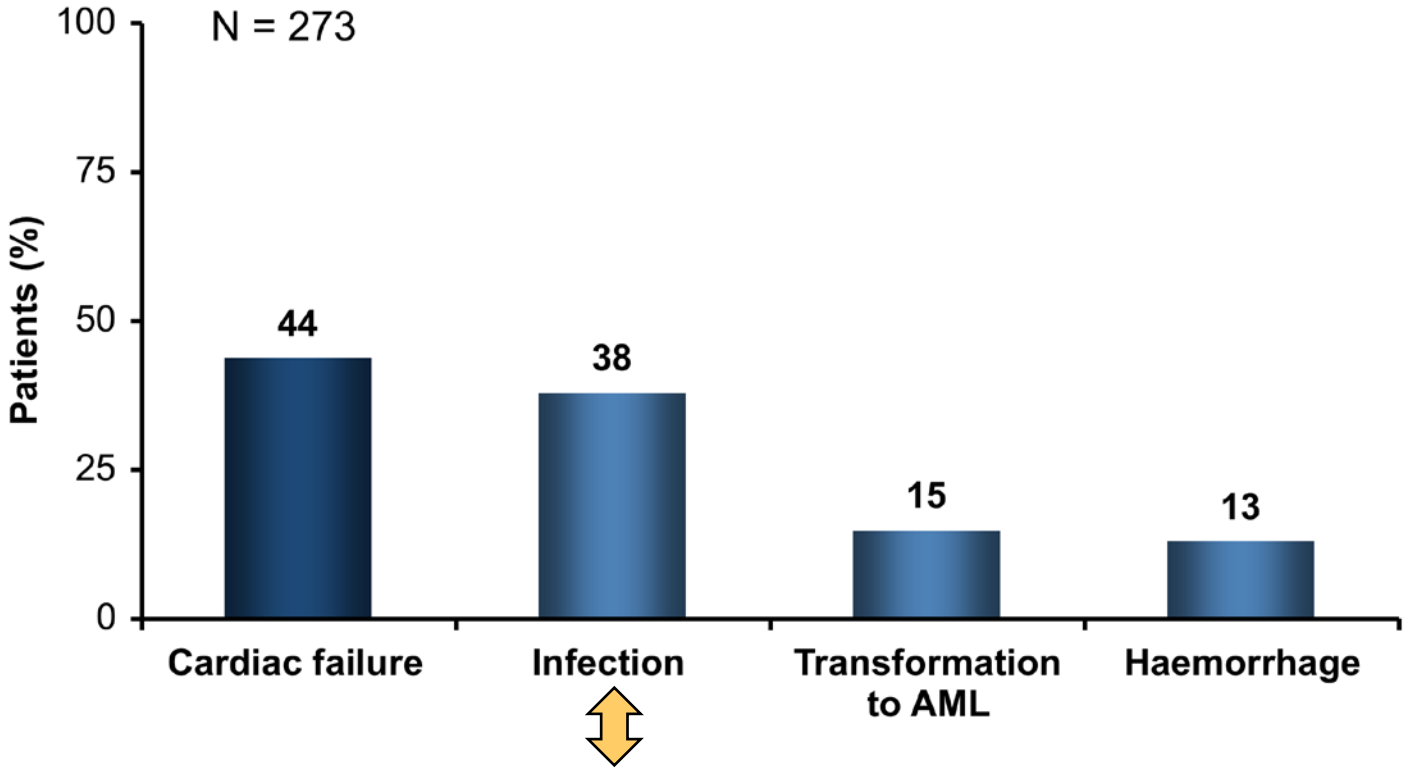
cortesia P.Cianciulli, modificata

Fe Toxicity tissue =

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

Coates TD. Free Radic Biol Med 2014

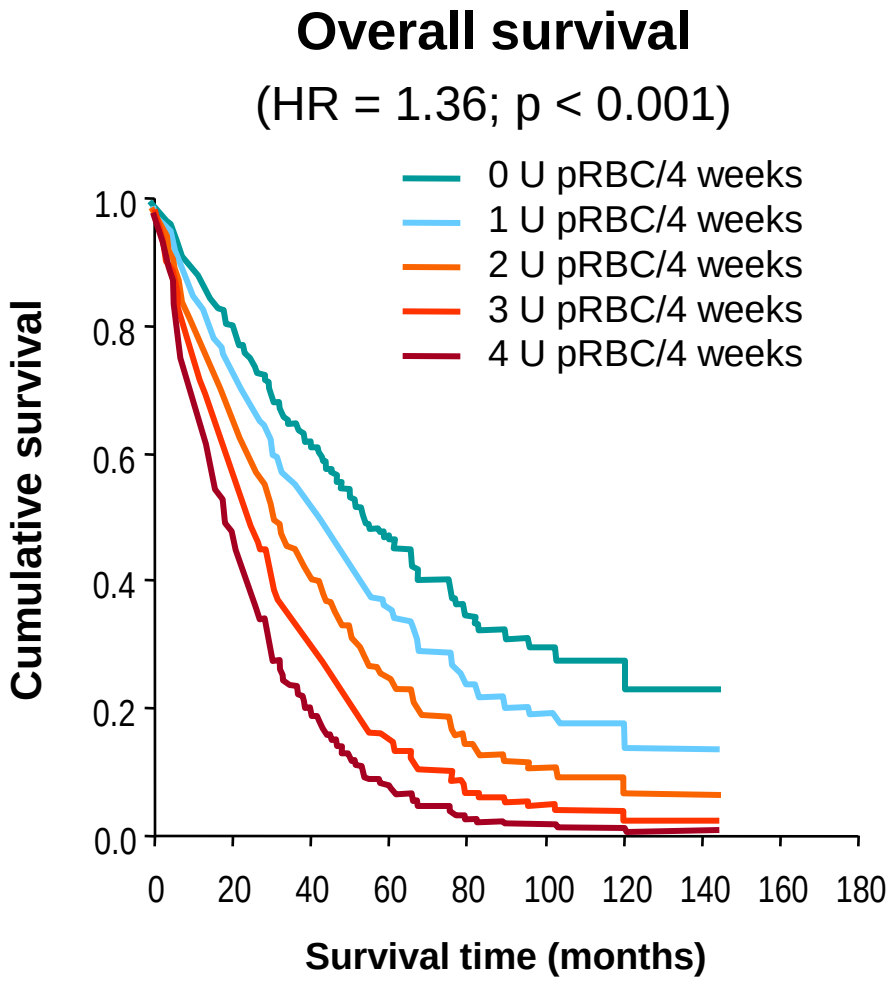
Causes of Death in Lower-risk MDS[1]

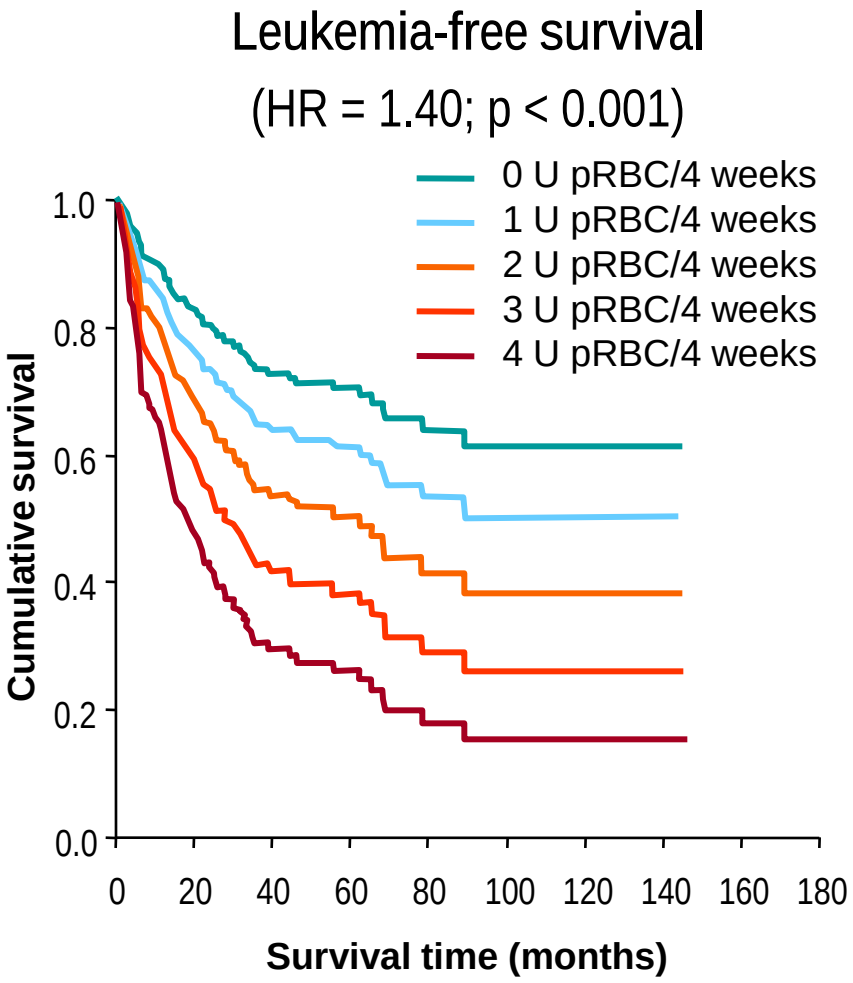


Increased availability of iron in iron-overloaded states provides a nutrient for bacterial and fungal growth, increasing the risk of infections[2]

[1] Dayyani F, *et al. Cancer.* 2010;116:2174-9. [2] Bullen JJ, *et al. J Med Microbiol*. 2006;55:251-8.

Survival of MDS Patients according to Transfusion Requirements

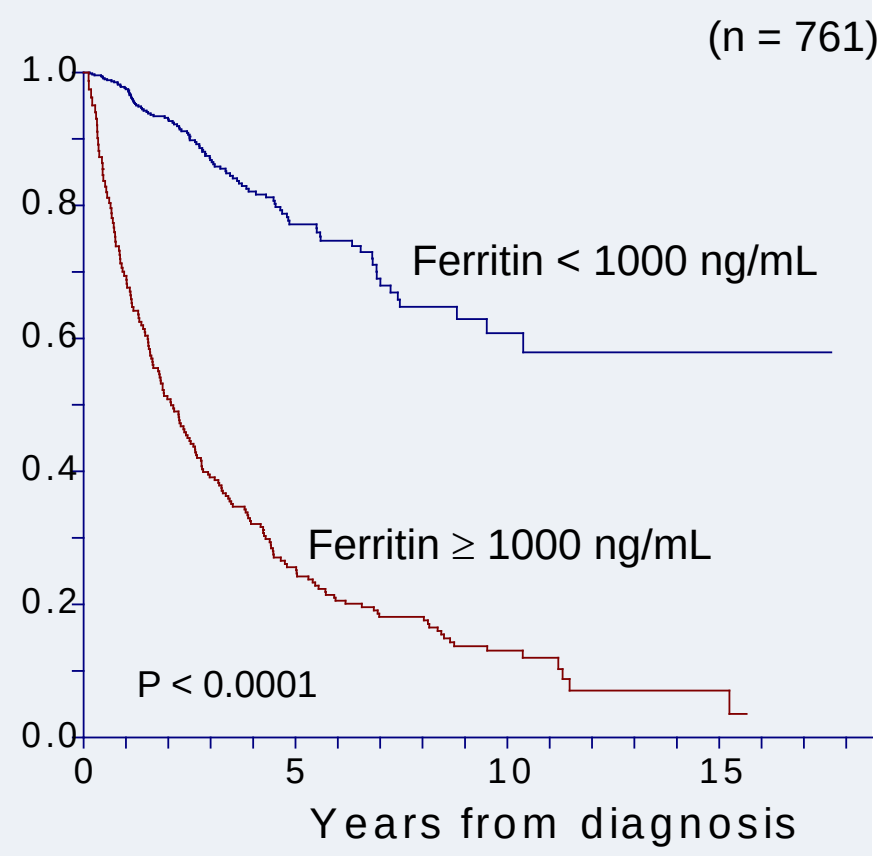




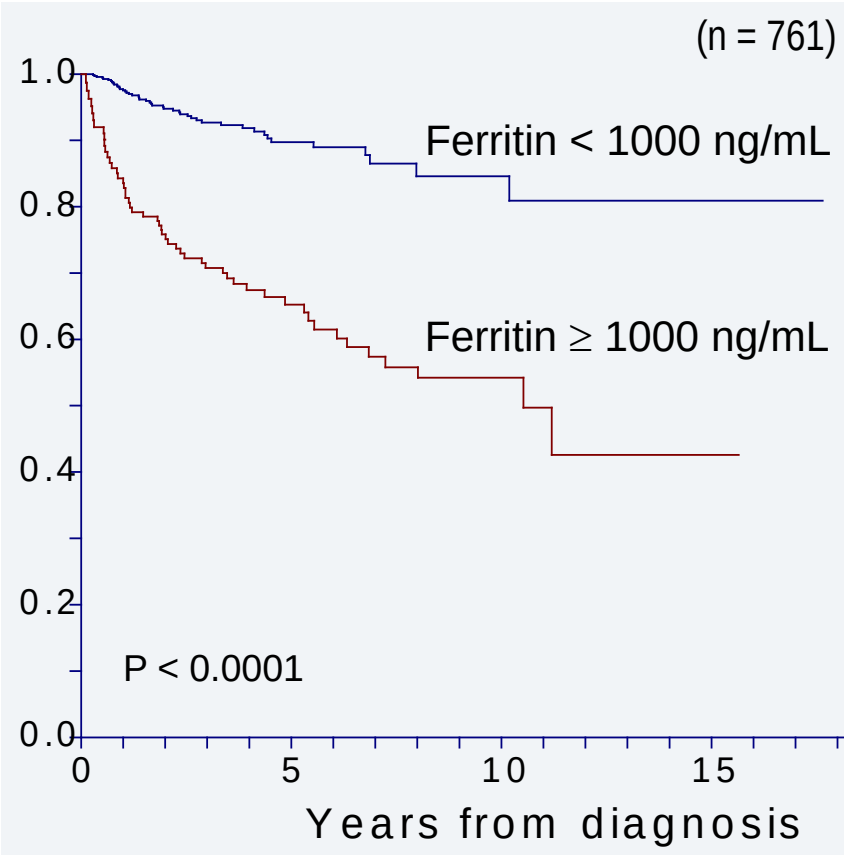
Malcovati L, *et al. Haematologica.* 2006;91:1588-90.

Survival by Serum Ferritin Level

Overall survival

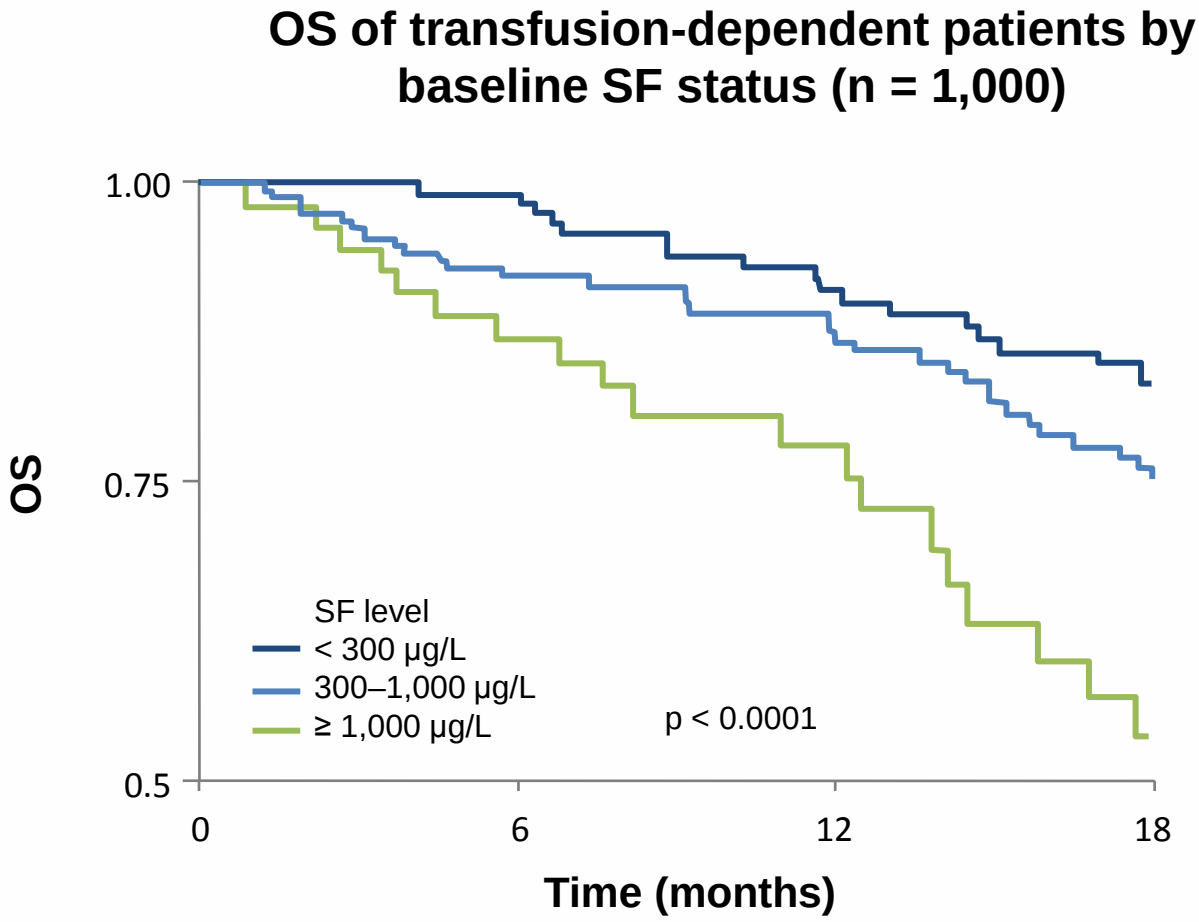


Leukemia-free survival



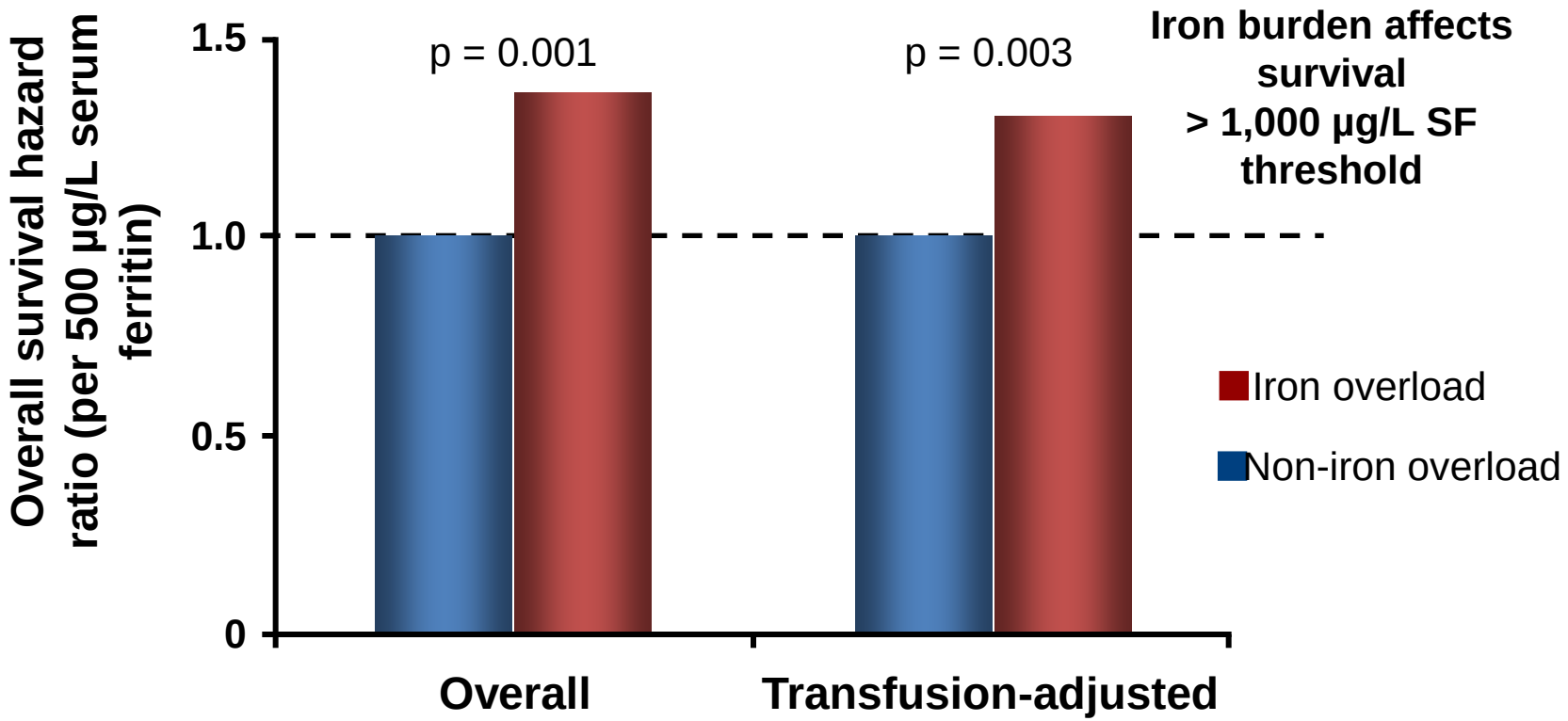
Sanz *et al.*, *Blood* 2008; 112(11) ASH abstract #640.

LeukemiaNet prospective registry: SF has independent impact on OS



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

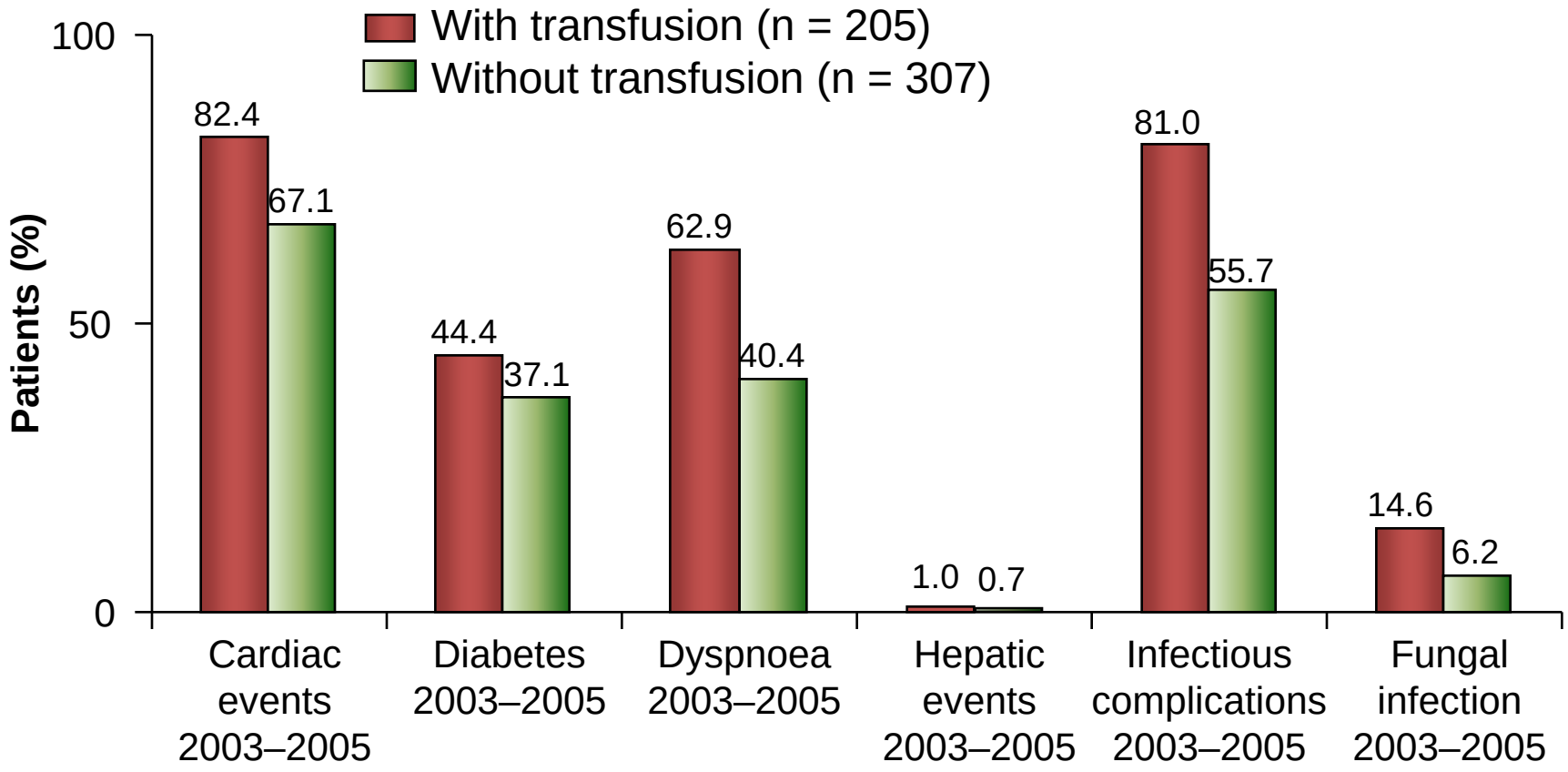
Serum Ferritin is an Independent Prognostic Factor in MDS



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.

Prevalence of Comorbidities in Transfusion-Dependent MDS

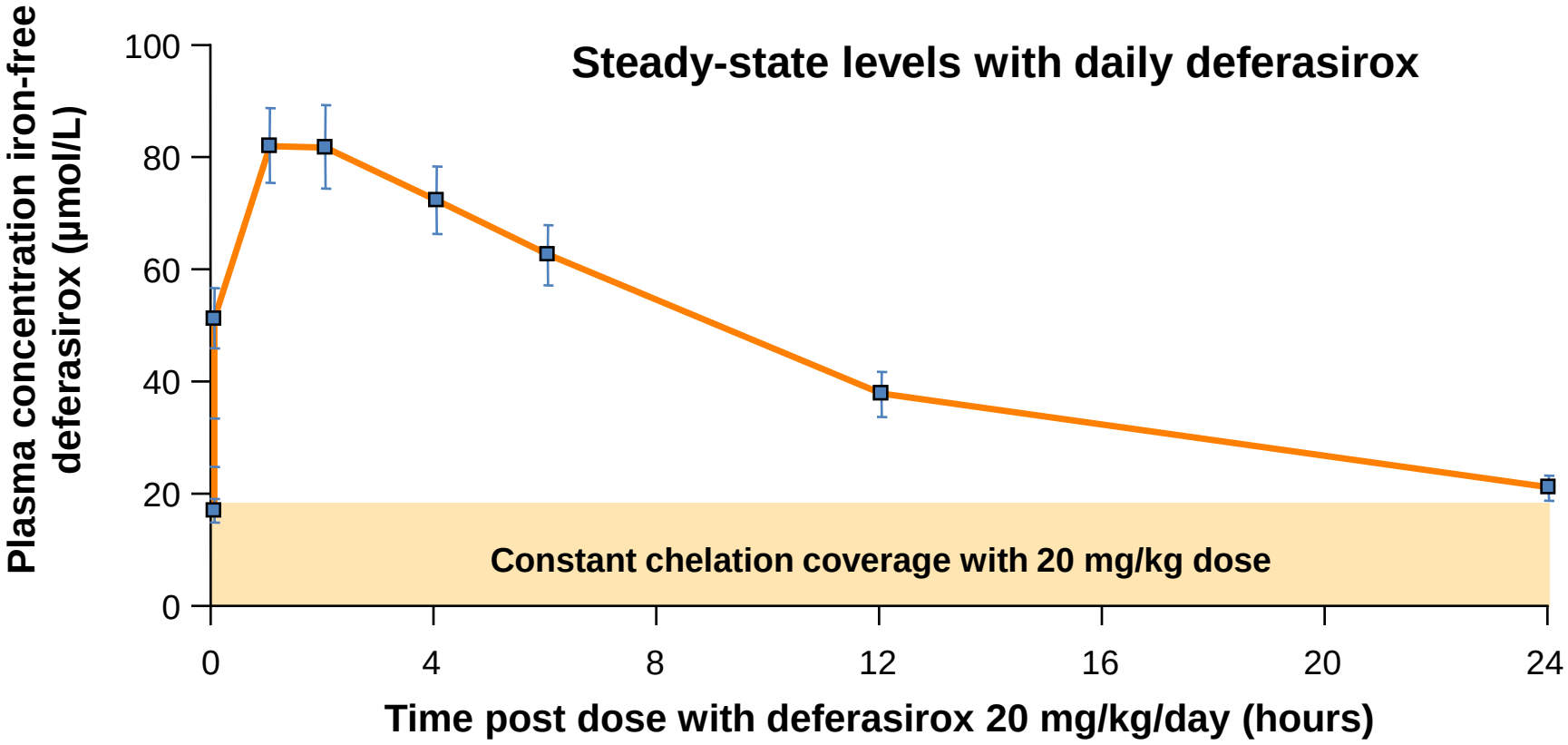


Transfused MDS patients have a higher prevalence of cardiac events, diabetes mellitus, dyspnoea, and hepatic and infectious diseases than non-transfused MDS patients

Goldberg SL, *et al. J Clin Oncol*. 2010;28:2847-52.

24-hour Chelation Coverage After Repeated Daily Deferasirox Dosing

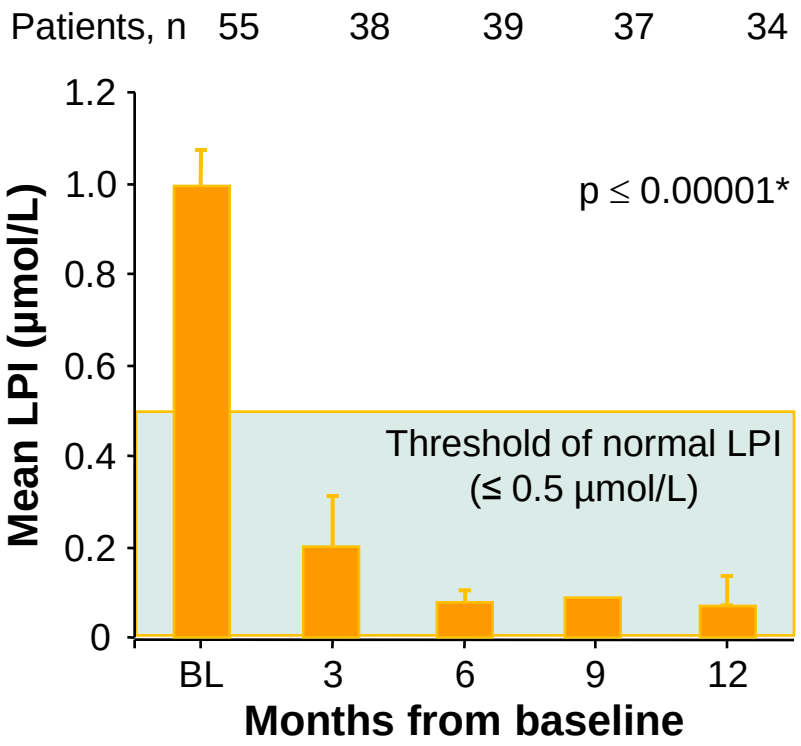
Mean values of measurements taken on weeks 2, 4, 8, and 12 are presented



Piga *et al. Haematologica*. 2006;91:873-80.

Deferasirox Normalizes LPI in Patients With MDS

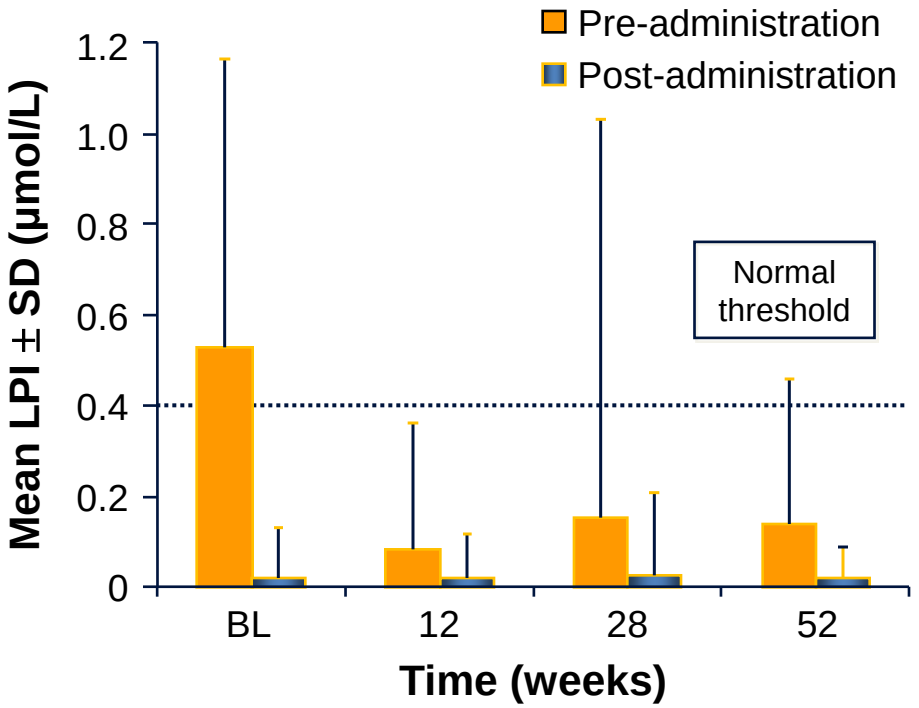
US03 study[1]



Patients with baseline LPI ≥ 0.5 µmol/L = 41%

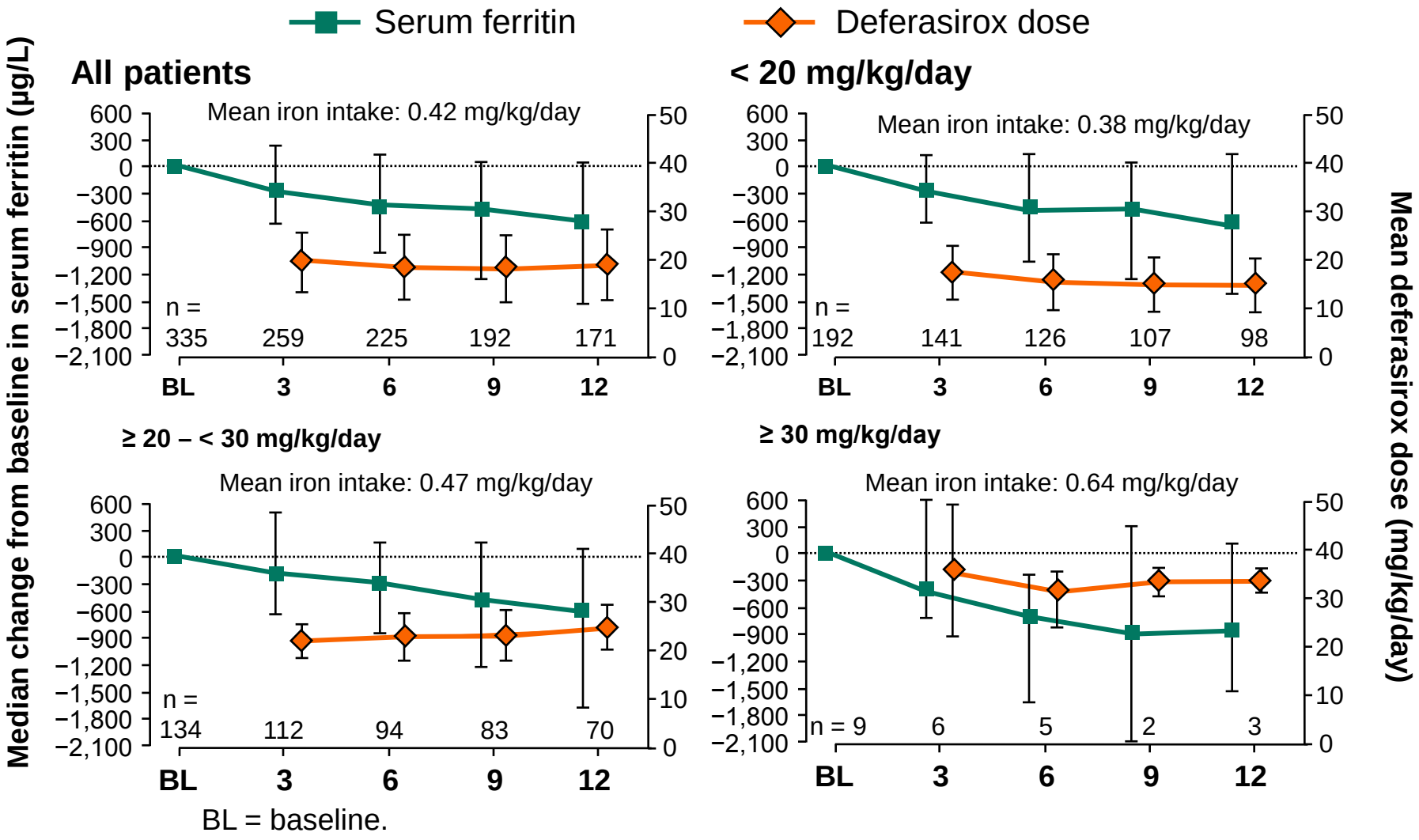
*Comparison of baseline LPI vs each treatment time point

EPIC study – MDS cohort[2]



[1]List *et al. Blood.* 2008;112:[abstract 634] [2]Gattermann *et al. Leuk Res.* 2010; 34:1143-50.

EPIC Study: Dose-optimized Deferasirox Therapy is Associated with Decreased Serum Ferritin Levels



BL = baseline.

Gattermann *et al. Leuk Res.* 2010;34:1143-50

Patients

Patients (#)	**152**
Male / Female	56/96
Low /Intermediate 1 risk	61/89
Centers	37
Accrual duration	July 10, 2007- March 03, 2010

Patients' characteristics

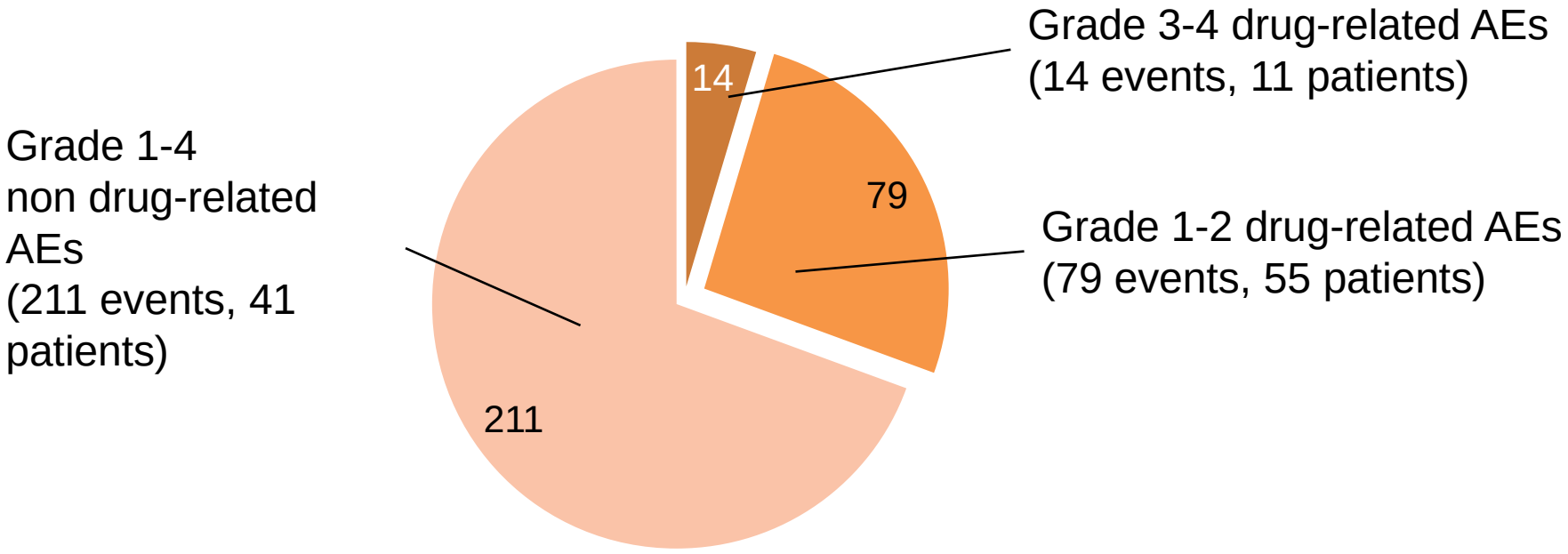
	Median (interquartile range)
Age (years)	72 (66-77)
Diagnosis–therapy (mo)	32 (17-54)
First transfusion–therapy (mo)	21 (10-36)
PRBC Units received	37 (22-63)
Serum Ferritin (ng/ml)	1966 (1416 -2998)

Results
Adverse Events (AEs)

AEs	Patients	%
302	107	70

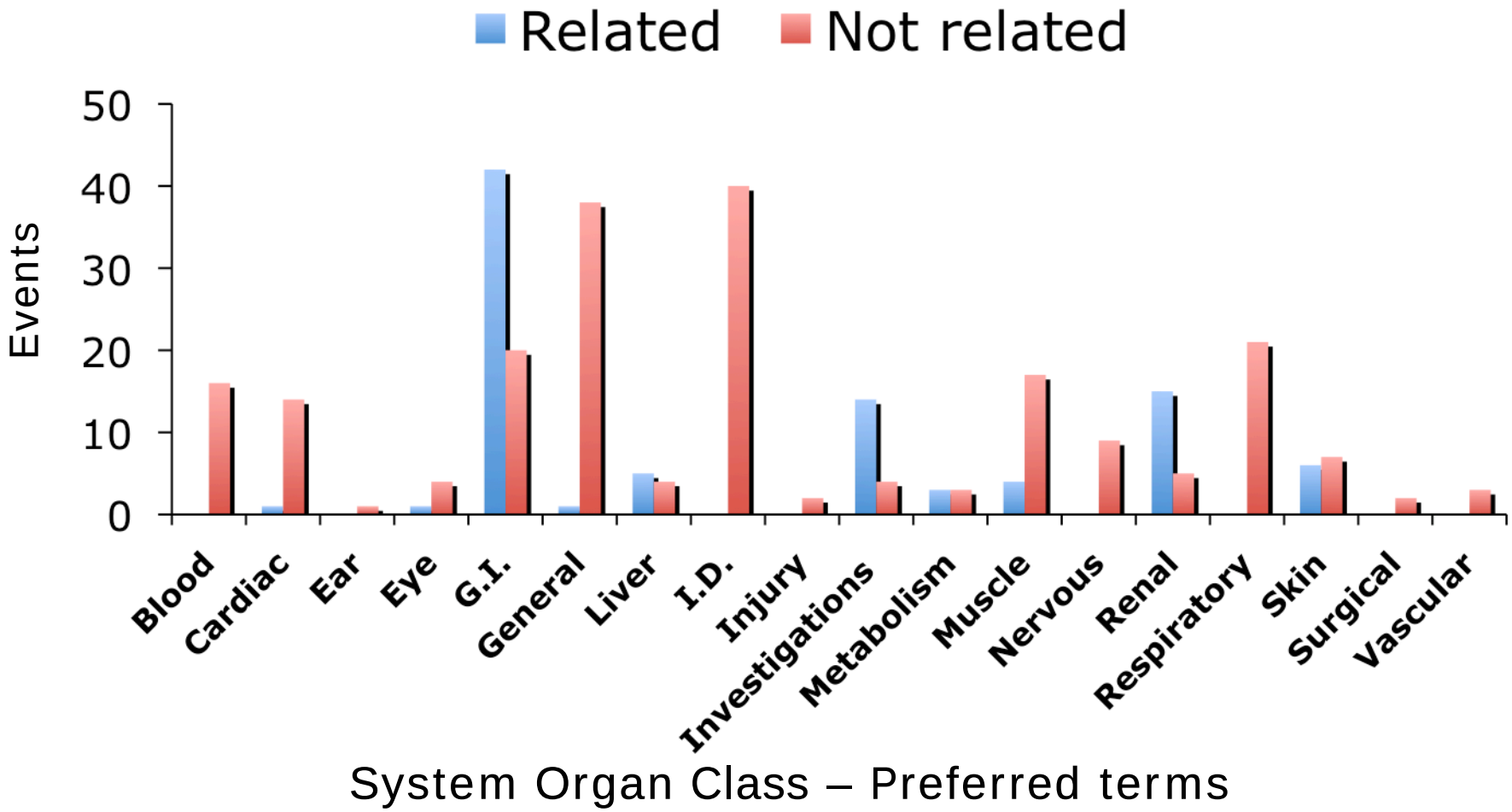
GIMEMA Prospective Trial: 69% of AEs are Disease-related

- >50% of patients were unable to complete 1 year due to drop out and progression despite limited number of >2 grade AEs
- >69% of AEs were not drug related, indicating a basic vulnerability of this population



Angelucci et al., ASH 2012, abstract 425

Adverse Events.
System Organ Class classification of related and not related AEs



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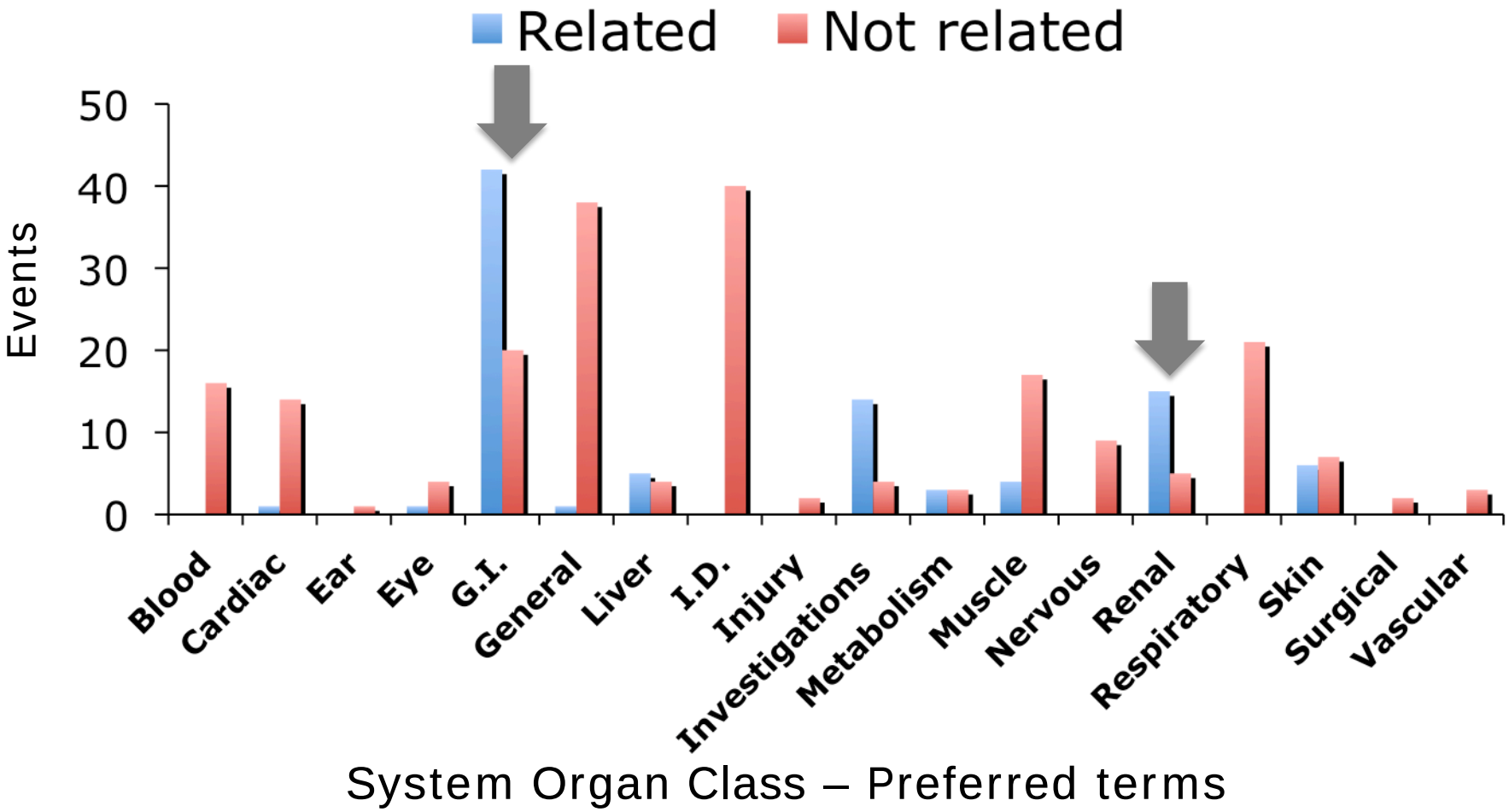


Deferasirox in MDS: Side Effects

Adverse event	Number (%)
Diarrhoea	111 (32.6)
Nausea	45 (13.2)
Vomiting	26 (7.6)
Abdominal pain	26 (7.6)
Upper abdominal pain	25 (7.3)
Rash	23 (6.7)
Constipation	21 (6.2)
Total number	341

Gattermann *et al. Leuk Res* (2010) 34, 1143-1150.

Prevention of Deferasirox GI Side Effects

Time of administration

- Intake at least 30 min before breakfast or dinner
- No intake with food

Starting dose and escalation

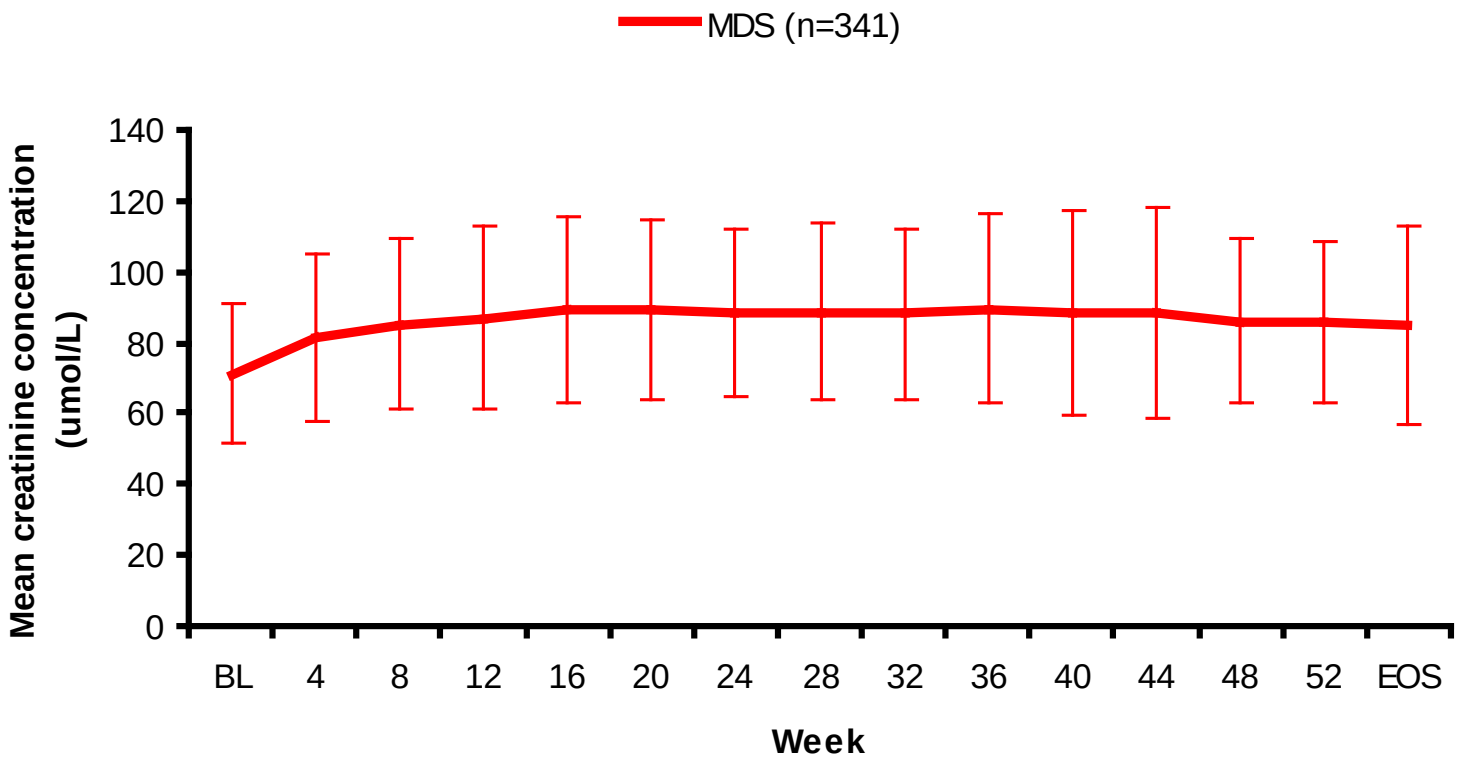
- Anecdotal reports suggest reduction of the frequency and severity of GI disturbances with BID dosing

Use of prophylactics

- Treatment with anti-acids in prophylaxis not recommended

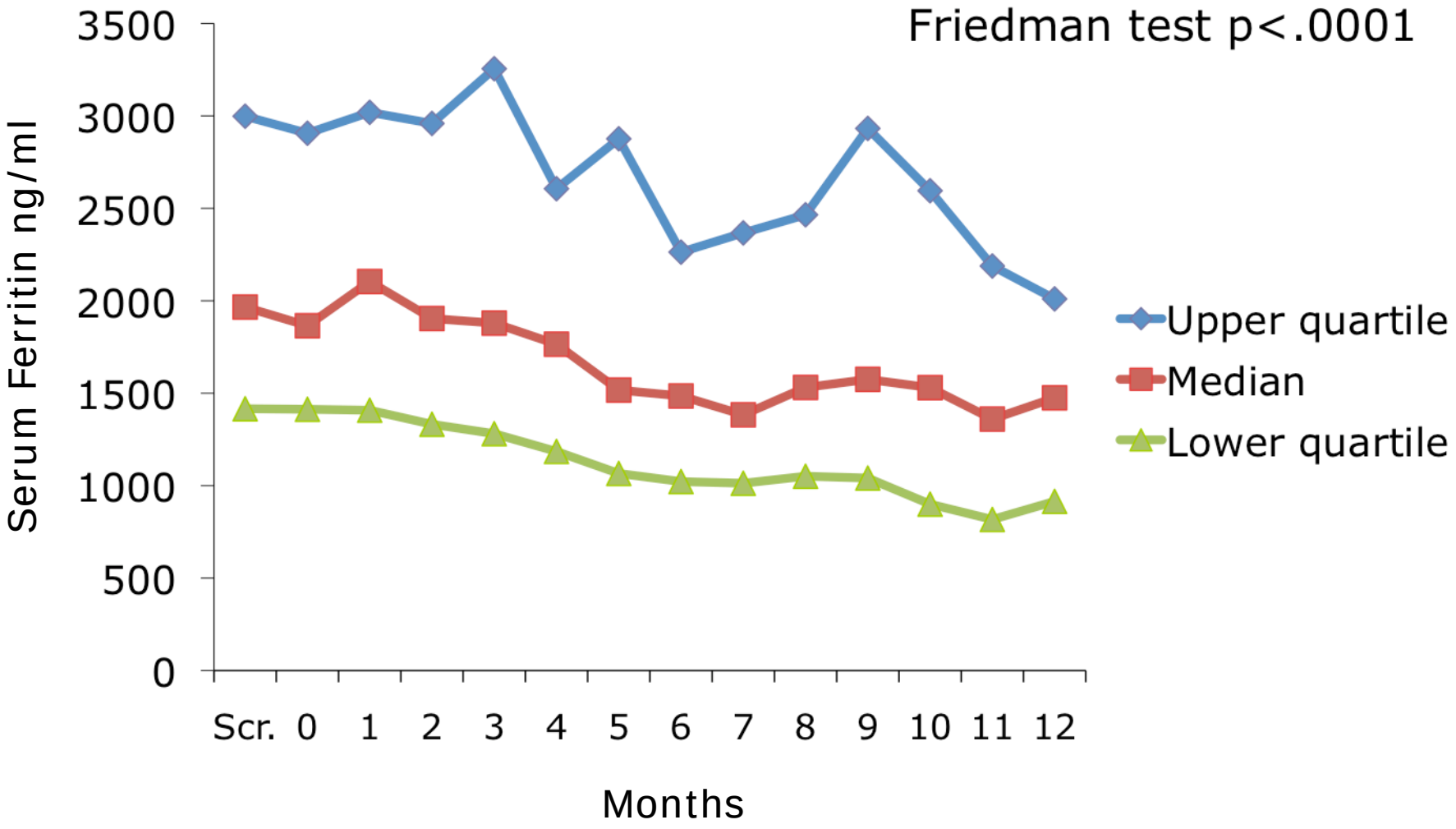
Nolte *et al. Leuk Res* (2011) 49, 528-533.

Deferasirox and Serum Creatinine in MDS-Patients



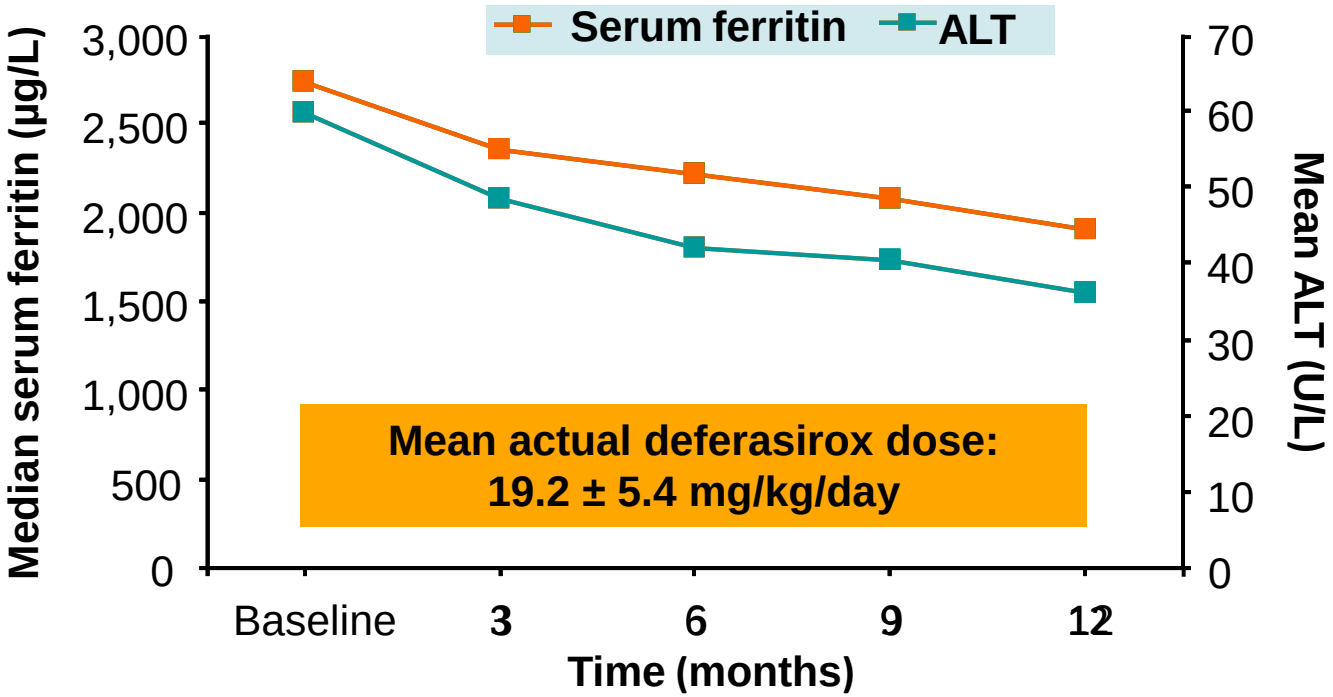
Gattermann *et al. Blood* (2009) 114, [abstract 633].

Activity – Serum ferritin



EPIC: Reduction in Serum Ferritin is Associated with Improvement in ALT in MDS

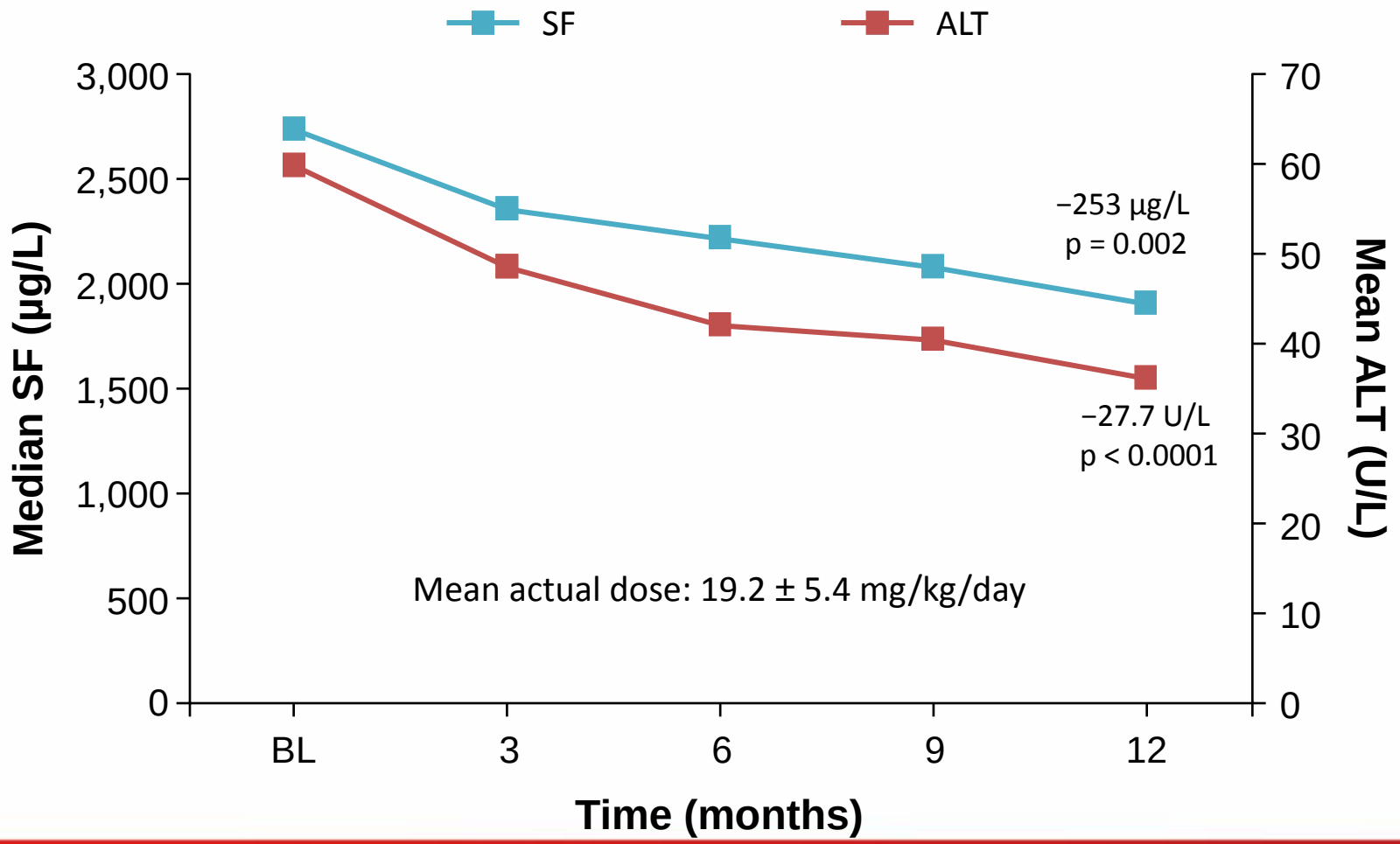
- At 12 months, there were significant reductions in
  - median serum ferritin (−253 µg/L; p=0.002)
  - mean ALT (−27.7 ± 37.4 U/L; p<0.0001)



ALT = alanine transaminase;
EPIC = European Prospective Investigation into Cancer and Nutrition.

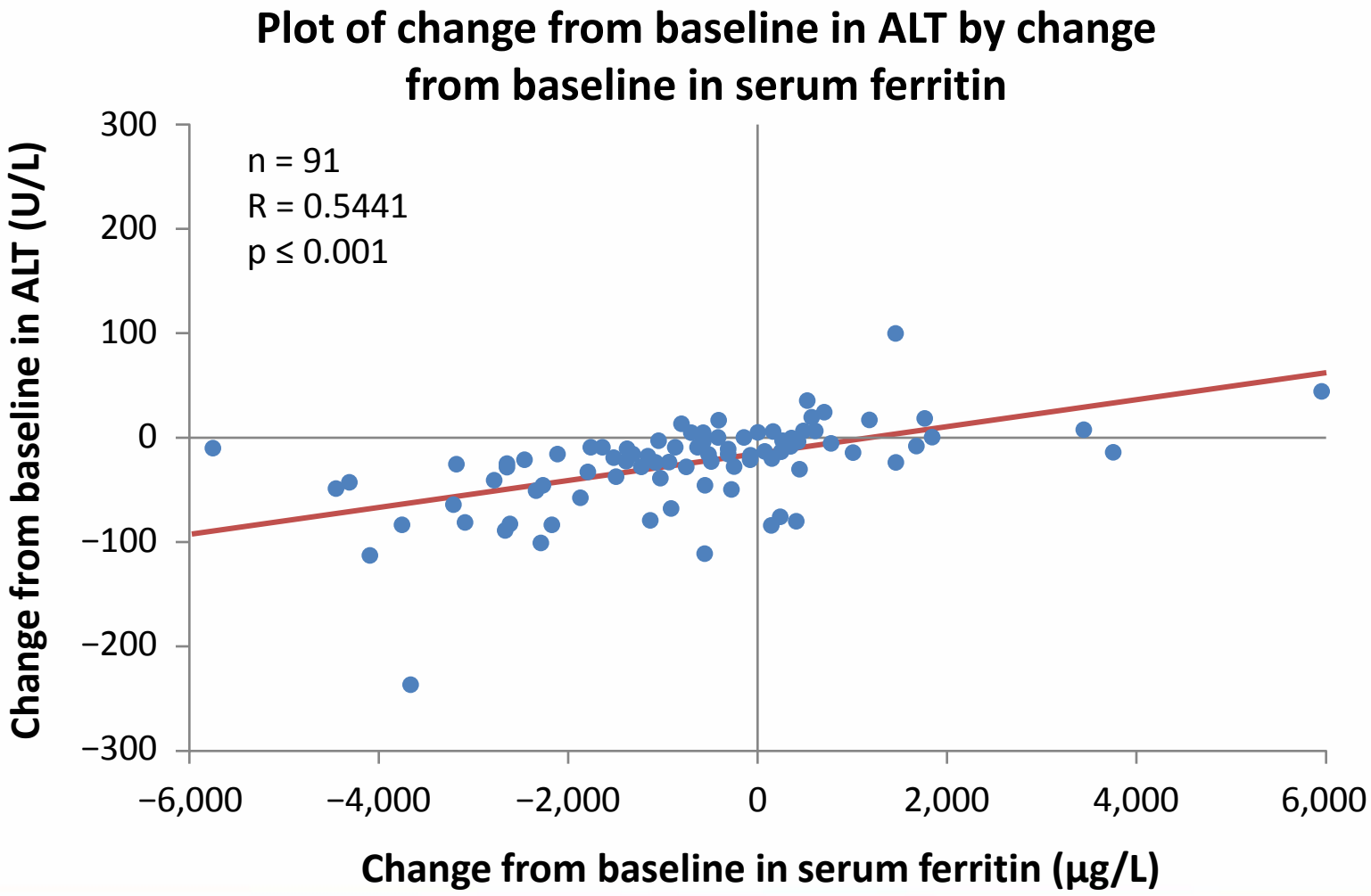
Gattermann *et al. Leuk Res.* 2010 Sep;34(9):1143-50.

EPIC study: improvement in liver function during treatment with deferasirox



Gattermann N, et al. Blood. 2009;114:abstract 3803.
Gattermann N, et al. Leuk Res. 2010;34:1143-50.

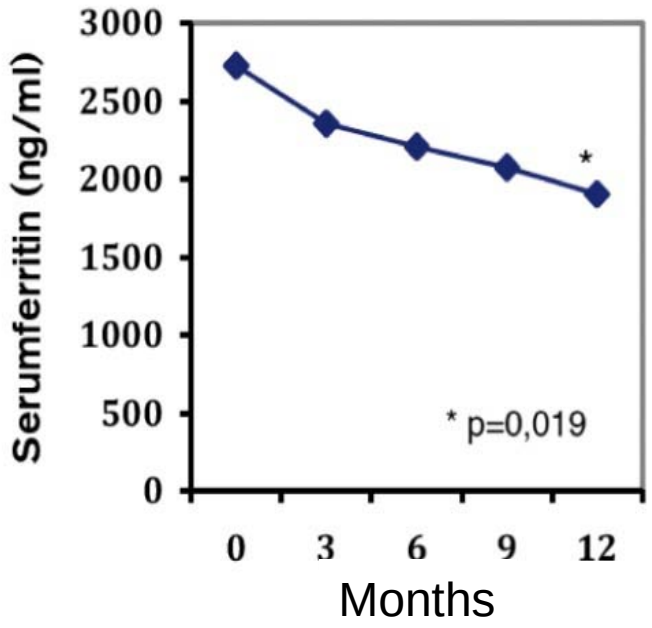
Decline in SF with deferasirox therapy correlates with improvement in liver damage markers in MDS

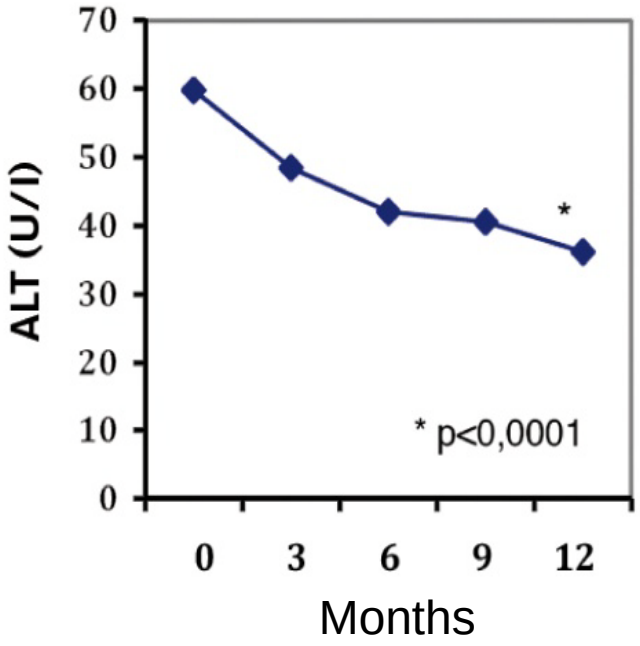


List AF, et al. J Clin Oncol. 2012;30:2134-9.

Iron Chelation and Liver Toxicity in MDS

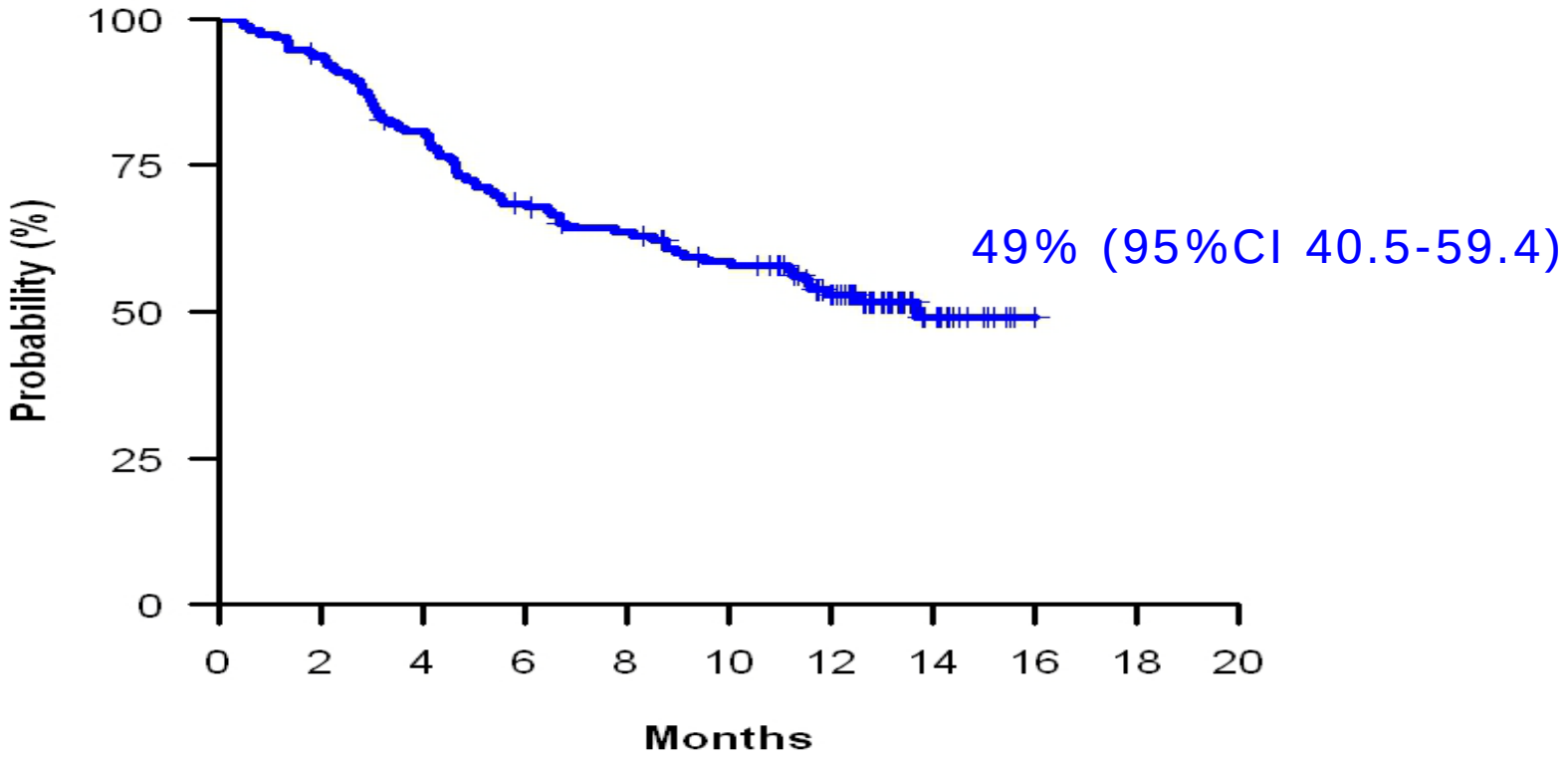
- Increased ALT in polytransfused MDS-patients as a marker for enhanced liver toxicity?
- Significant reduction of serum ALT (corresponding to reduction of serum ferritin) after 1 year of treatment with Deferasirox in patients with MDS





Gattermann *et al. Blood* (2009) 114, [abstract 3803].

K-M probability of continuing therapy

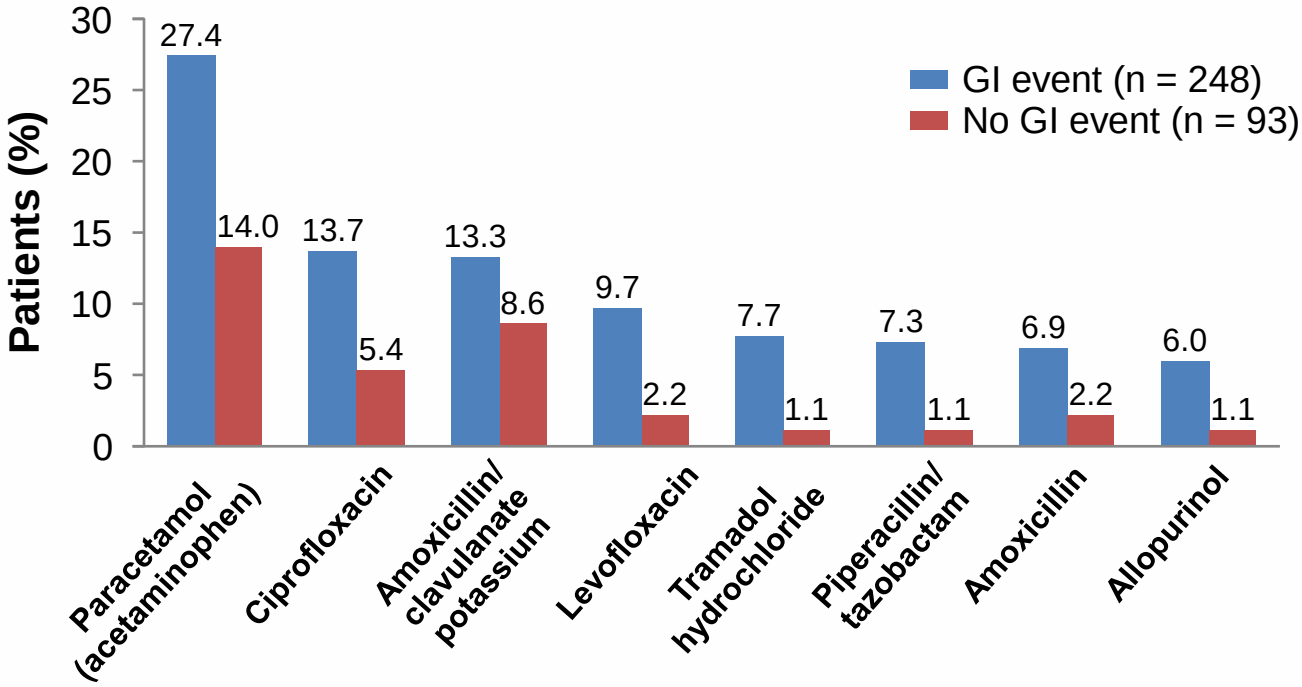


Causes of therapy discontinuation

Cause	Patients	%	
Adverse Event	28	33.3	33%
Death	22	26.2	36%
Disease progression	8	9.5	
Consent withdrawal	9	10.7	31%
Lost at follow up	8	9.5	
No response	2	2.4	
Serum ferritin < 500 ng/ml (no PRBC)	2	2.4	
Medical decision	5	6.0	
Total	84	100	

Concomitant medications are a risk factor for poor compliance and might impact on GI events

MDS patients receiving deferasirox who reported a GI event used a larger number of concomitant medicines



Rational drug use may improve compliance:
choose your drug carefully; discontinue the unnecessary drugs

Cappellini MD, et al. Blood. 2012;120:abstract 5182.

Hematological response – Methods

International Working Group 2006 criteria. Blood 2006; 108: 419-25
What are RBC-transfusion-dependence and -independence? Leuk Res 2011; 35: 8-11

	Inclusion criteria	Criteria	Minimal duration
Erythroid	≥ 6 units last 12 weeks	Transfusion independence	3 months
Platelets	Baseline platelets count $<100 \times 10^9/L$	Platelets $\geq 30 \times 10^9/L$ for patients with $>20 \times 10^9/L$ platelets at baseline or increase from $<20 \times 10^9/L$ to $>20 \times 10^9/L$ and by 100%	3 months
Myeloid	Baseline neutrophil count $<1 \times 10^9/L$	≥100% increase and an absolute increase $>0.5 \times 10^9/L$	3 months

Patients receiving concurrent MDS medication (rHuEpo, 5 Azacitidine, Lenalidomide, GCSF ….) were excluded.

Hematological response – Methods

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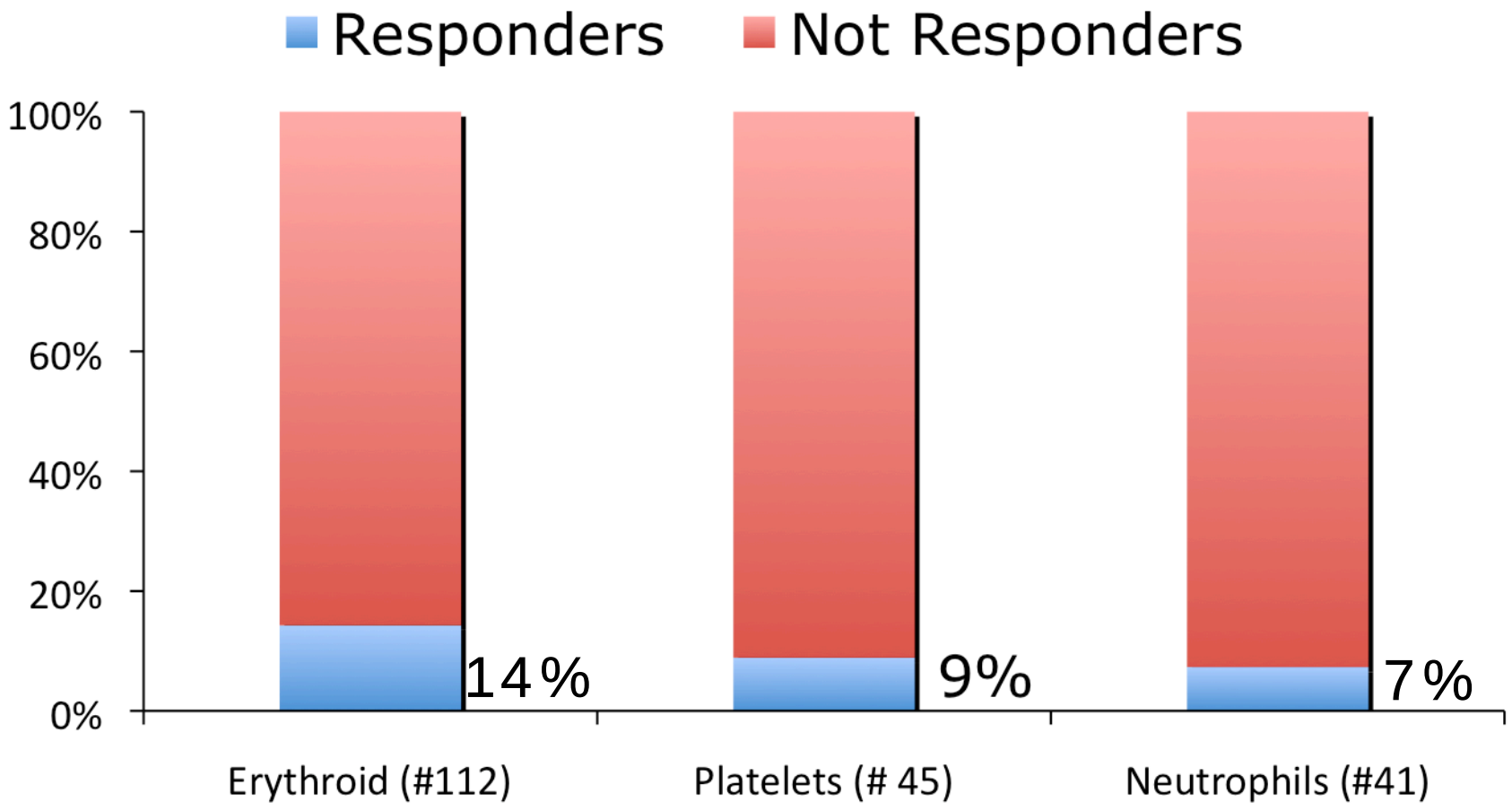
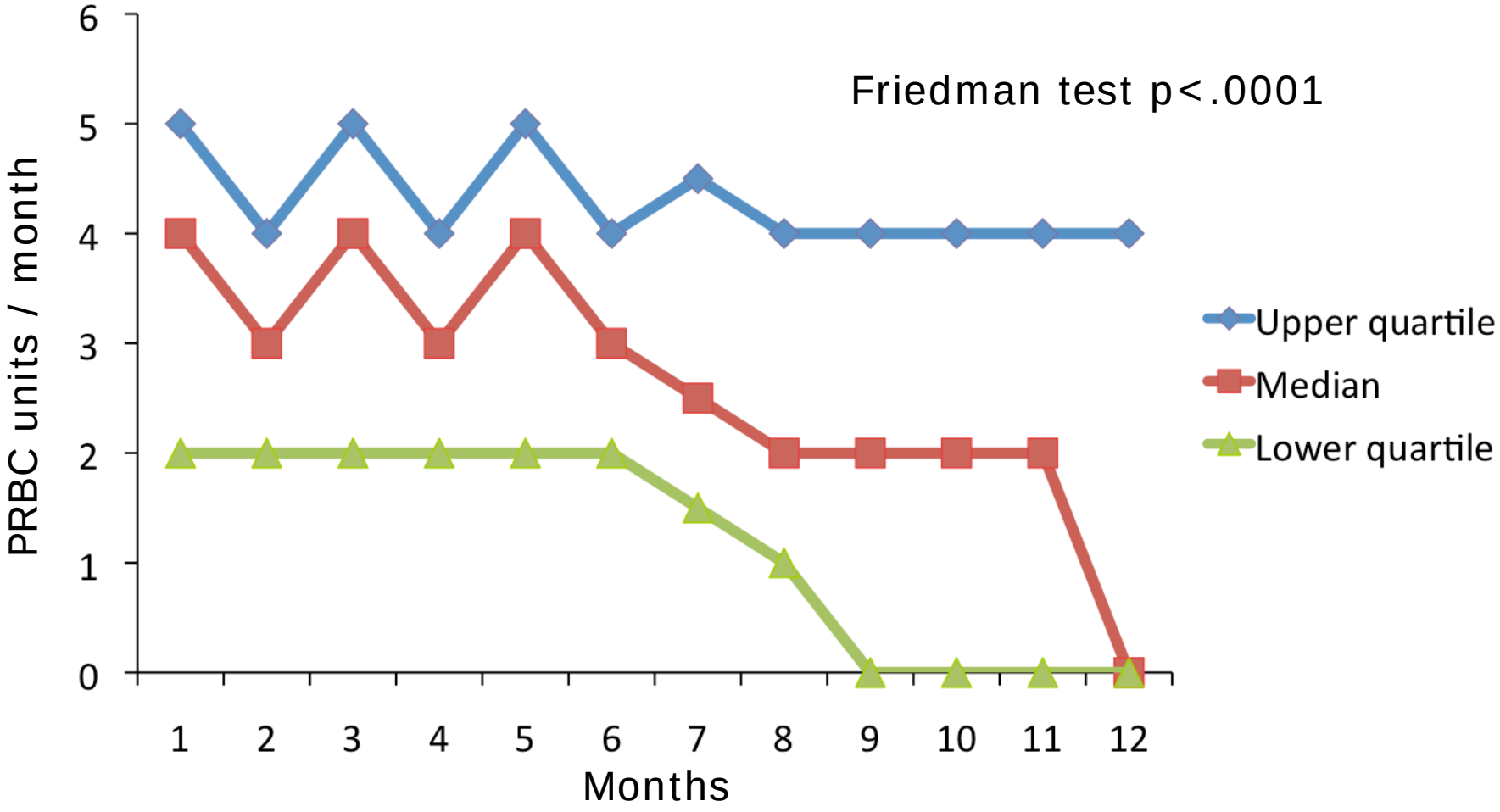
	Inclusion criteria	Criteria	Minimal duration
Erythroid	≥ 6 units last 12 weeks	Transfusion independence	3 months
Platelets	Baseline platelets count <100 x 10^9/L	Platelets ≥30 x 10^9/L for patients with >20 x 10^9/L platelets at baseline or increase from <20x10^9/L to >20x10^9/L and by 100%	3 months
Myeloid	Baseline neutrophil count <1 x 10^9/L	≥100% increase and an absolute increase >0.5x10^9/L	3 months

Patients receiving concurrent MDS medication (rHuEpo, 5 Azacitidine, Lenalidomide, GCSF ….) were excluded.

Hematologic response

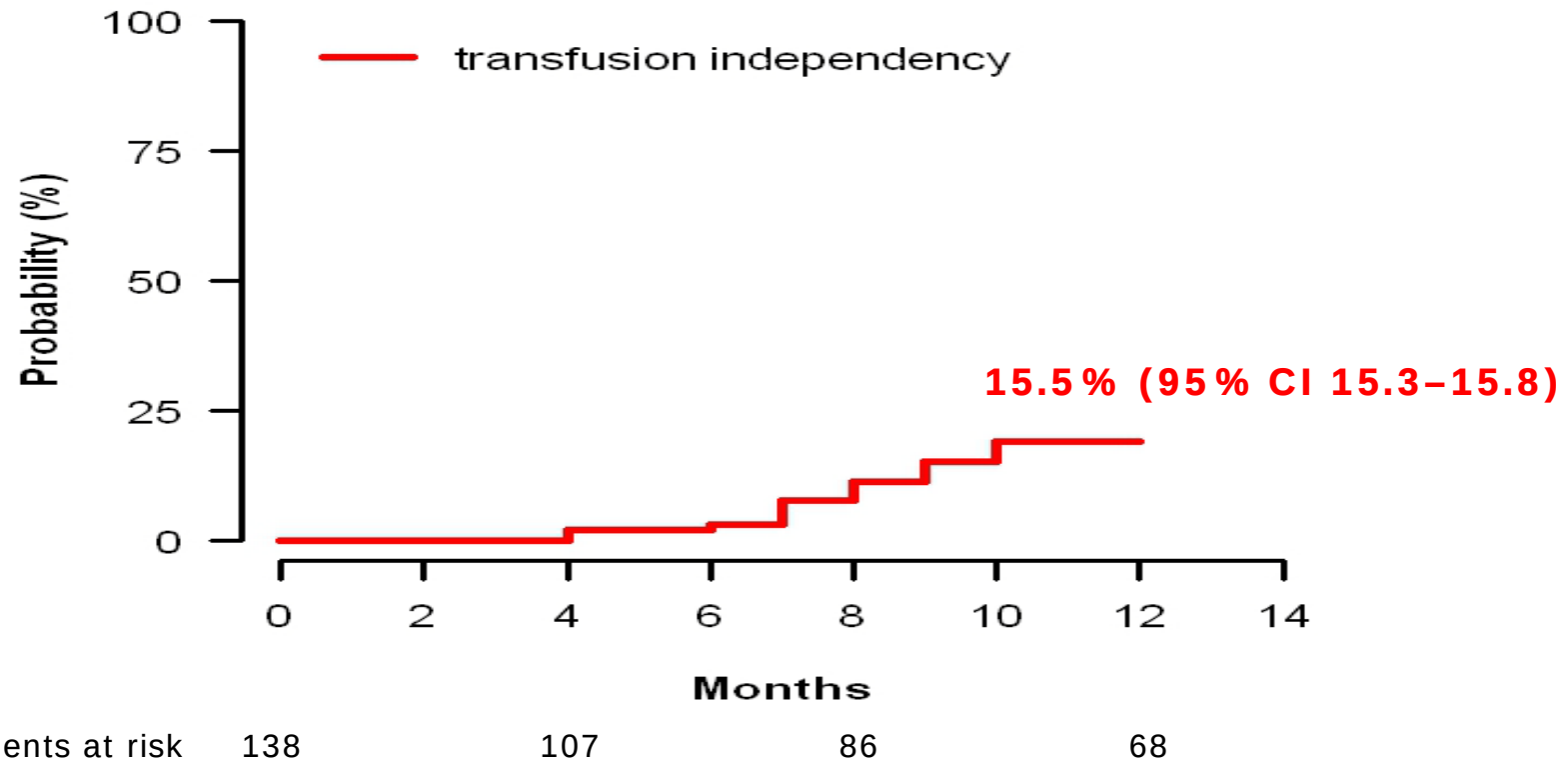


Erythroid response
PRBC units requirement



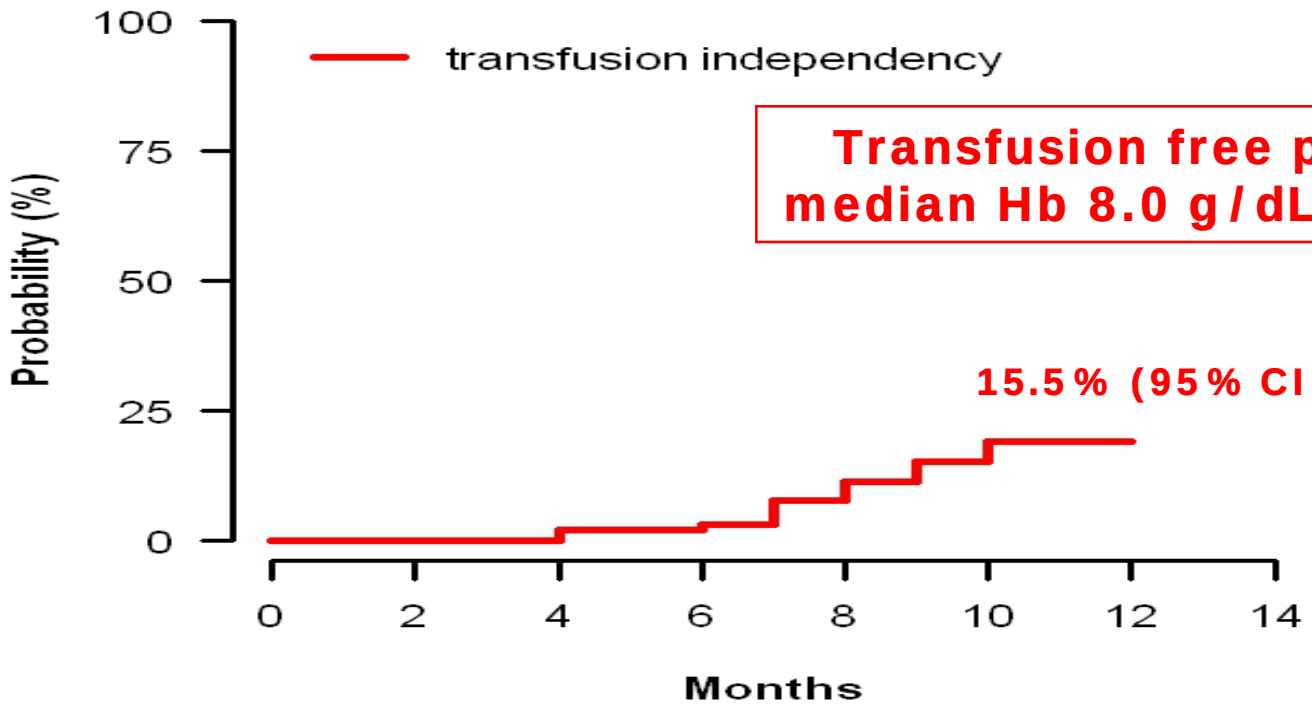
Patients receiving concurrent MDS medication (rHuEpo, 5 Azacitidine, Lenalidomide) were excluded.

Probability of acquiring transfusion independency



Non parametric cumulative incidence estimator.
Drop out, progression and death were considered competitive risks

Probability of acquiring transfusion independency



Transfusion free patients: median Hb 8.0 g/dL (7.3-8.6)

15.5% (95% CI 15.3–15.8)

Non parametric cumulative incidence estimator.
Drop out, progression and death were considered competitive risks

Deferasirox can improve haemopoiesis in MDS

Study	n	IPSS risk	RBC response	Neutrophil response	Platelet response
Breccia M, et al. 2010[1]	1	Low	Major	NR	NA
Capalbo S, et al. 2009[2]	1	Low	Major	NA	NA
Messa E, et al. 2008[3]	4	Int-1 Int-1 High	Minor Major Major	NA NA Major	NA NA NR
Okabe H, et al. 2009[4]	1	NR	Major	Major	NR
Oliva EN, et al. 2010[5]	1	Low	Major	NA	NA
Guariglia R, et al. 2011[6]	1	Int-1	Major	Major	NA
List AF, et al. 2009[7]	6	Low/Int-1	2 Major 1 Minor[a]	1 Major 1 Major[b]	1 Major 1 Major[b]
Badawi MA, et al. 2010[8]	1	Int-1	Major[c]	NA	NA
Nishiuchi T, et al. 2010[9]	1	Int-1	Major[d]	Major[d]	NA
Molteni A, et al. 2010[10]	6	NR	5 Minor	1 Major	NA

RBC, platelet, and neutrophil responses were assessed according to IWG 2000 criteria.

[a] The patient also received darbopoietin treatment. [b] The patient also received G-CSF and decitabine treatment.

[c] Response duration was 38 months; cutaneous leukaemic infiltration was observed. [d] Response duration was more than 12 months.

IPSS, International Prognostic Scoring System; G-CSF, granulocyte colony-stimulating factor; NA, not applicable; NR, not reported.

1. Breccia M, et al. Acta Haematol. 2010;124:46-8. 2. Capalbo S, et al. Acta Haematol. 2009;121:19-20. 3. Messa E, et al. Acta Haematol. 2008;120:70-4. 4. Okabe H, et al. Rinsho Ketsueki. 2009;50:1626-9. 5. Oliva EN, et al. Transfusion. 2010;50:1568-70. 6. Guariglia R, et al. Leuk Res. 2011;35:566-70. 7. List AF, et al. Blood. 2009;114:abstract 3829. 8. Badawi MA, et al. Adv Hematol. 2010; 2010:164045. 9. Nishiuchi T, et al. Int J Hematol. 2010;91:333-5. 10. Molteni A, et al. Haematologica. 2010;95 Suppl 2:abstract 1410.

Deferasirox can improve haemopoiesis in MDS: recent data

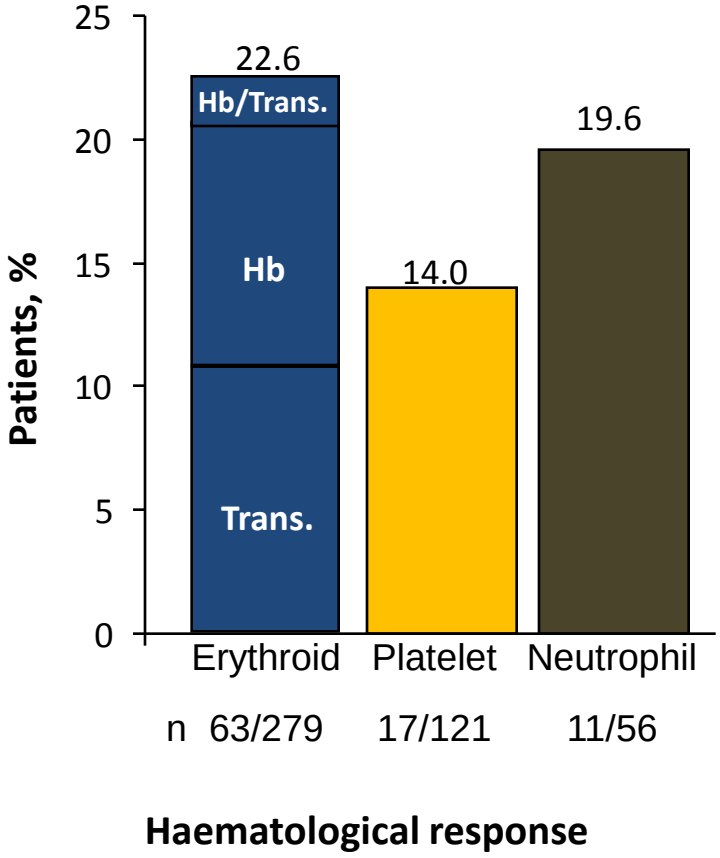
Study	n	IPSS risk	RBC response	Neutrophil response	Platelet response
Cilloni D, et al. 2011[1]	57	Low/Int-1	45.6%	NR	NR
List A, et al. 2012[2]	173 52 77	Low/Int-1	15%	15%	22%
Gattermann N, et al. 2012[3]	247 50 100	Low/Int-1	21.5%	22%	13%
Nolte F, et al. 2012[4]	50	Low/Int-1	11%	NR	NR
Angelucci E, et al. 2012[5]	152	Low/Int-1	Transfusion independence in 14.5%	NR	NR

RBC, platelet, and neutrophil responses are assessed according to IWG 2006 criteria (1-3); NR, not reported

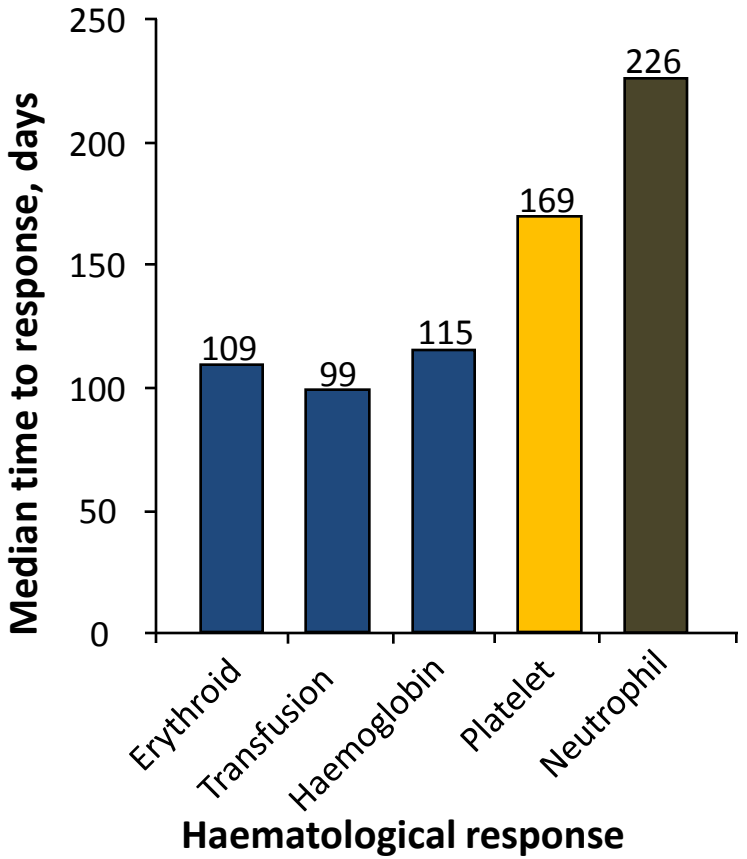
1. Cilloni D, et al. Blood. 2011;118:abstract 611. 2. List A, et al. J Clin Oncol. 2012;30:2134-9. 3. Gattermann N, et al. Haematologica. 2012;97:1364-71. 4. Nolte F, et al. Ann Hematol. 2013;92:191-8. 5. Angelucci E, et al. Blood. 2012;118:abstract 425.

Haematological responses in MDS patients treated with deferasirox

Percentage of patients with haematological response



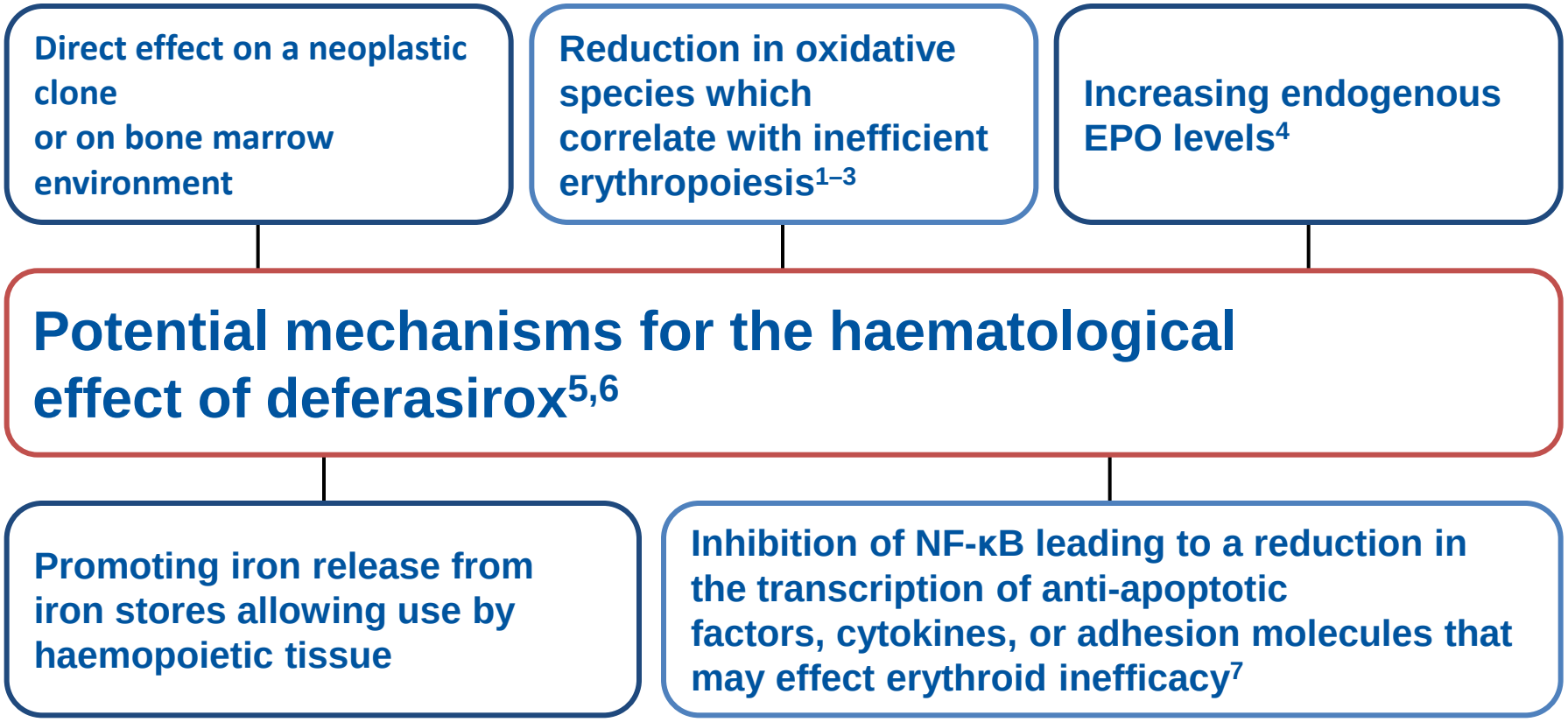
Time to haematological response



Trans. = transfusion.

Gattermann N, et al. Blood. 2010;116:abstract 2912.

Potential mechanisms for the haematological effect of deferasirox

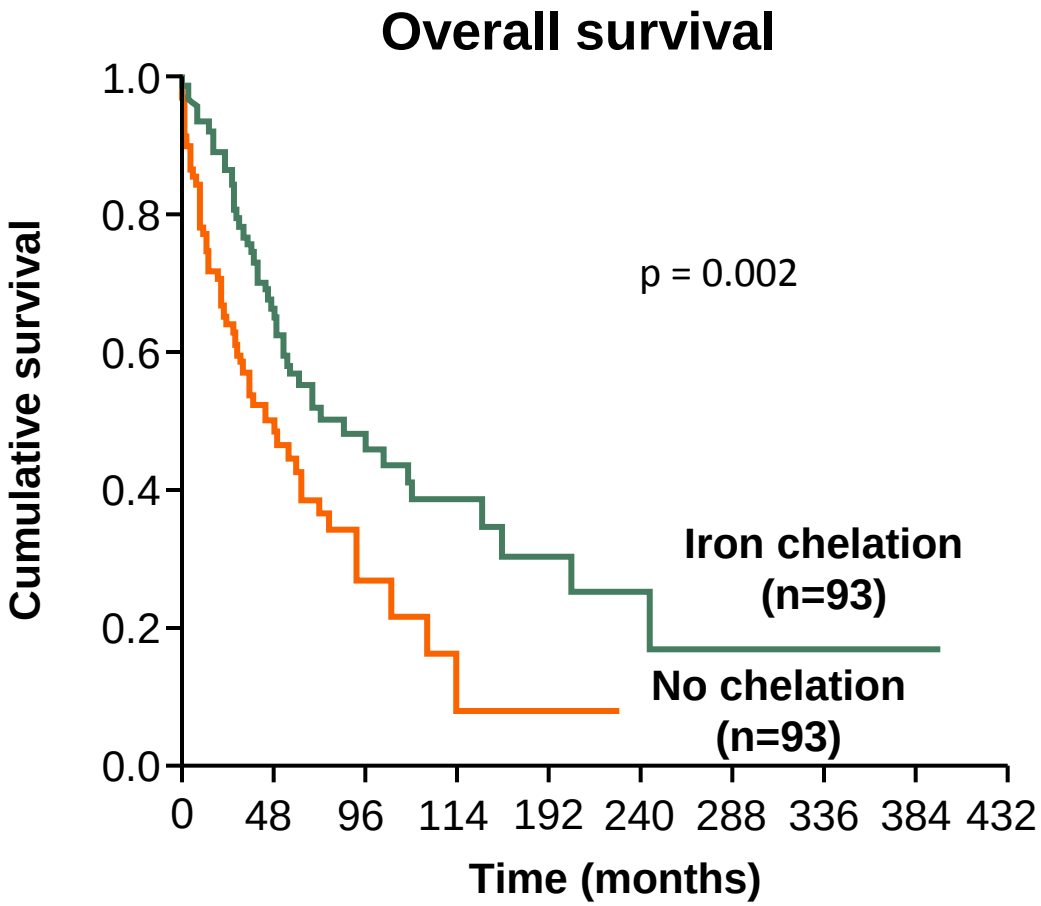


NF-κB, nuclear factor kappa B.

1. Ghoti H, et al. Eur J Haematol. 2007;79:463-7. 2. Hartmann J, et al. Blood. 2008;112:abstract 2694. 3. Chan LSA, et al. Blood. 2008;112:abstract 2685. 4. Ren X, et al. J Appl Physiol. 2000;89:680-6. 5. Breccia M, et al. Acta Haematol. 2010;124:46-8.
6. Guariglia R, et al. Leuk Res. 2011;35:566-70. 7. Messa E, et al. Haematologica. 2010;95:1308-16.

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

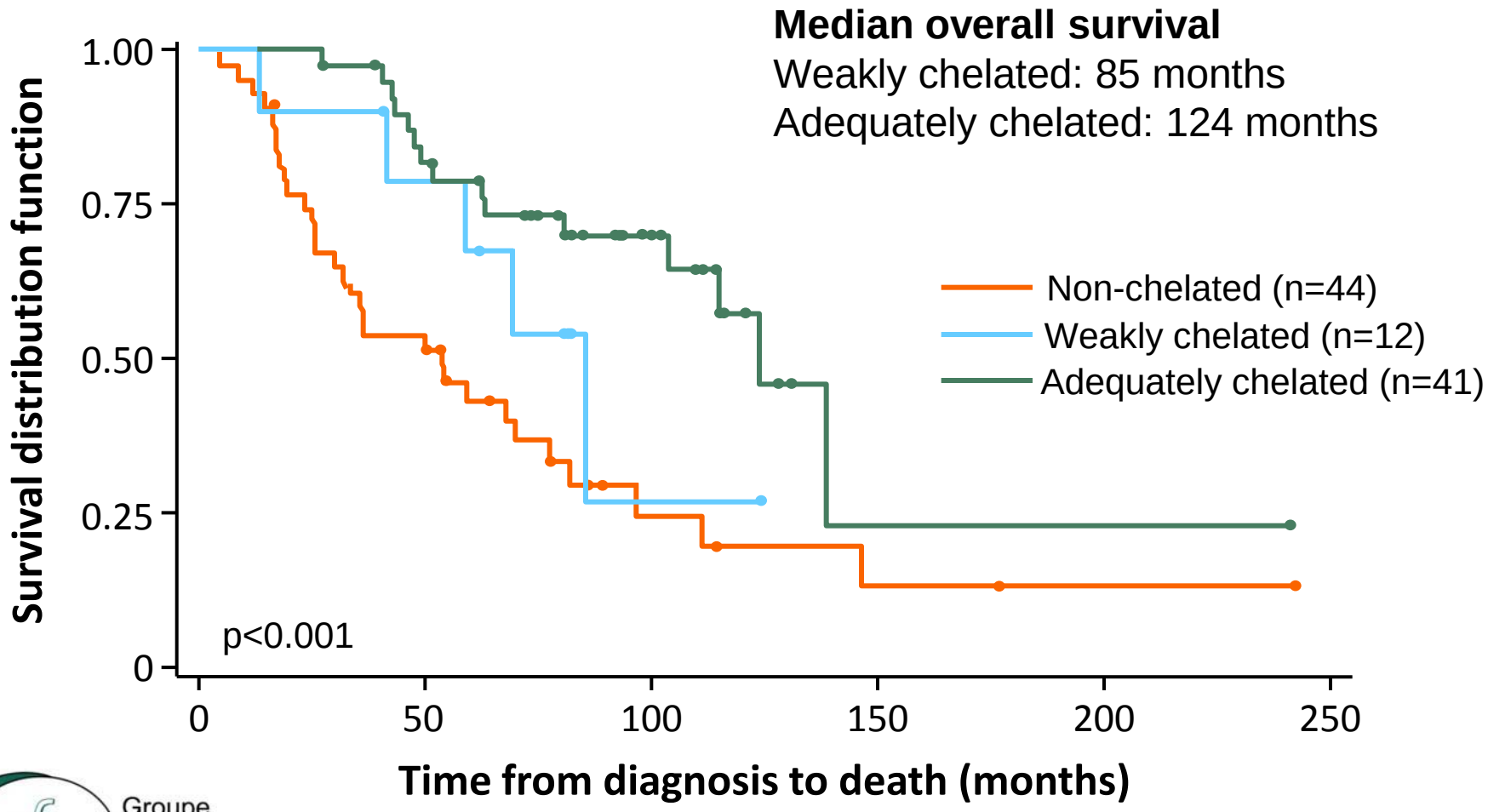
Iron Chelation Therapy improves Survival in MDS Patients: Matched-pair Analysis



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

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

Adequate chelation improves survival more than weak chelation in MDS (GFM analysis)

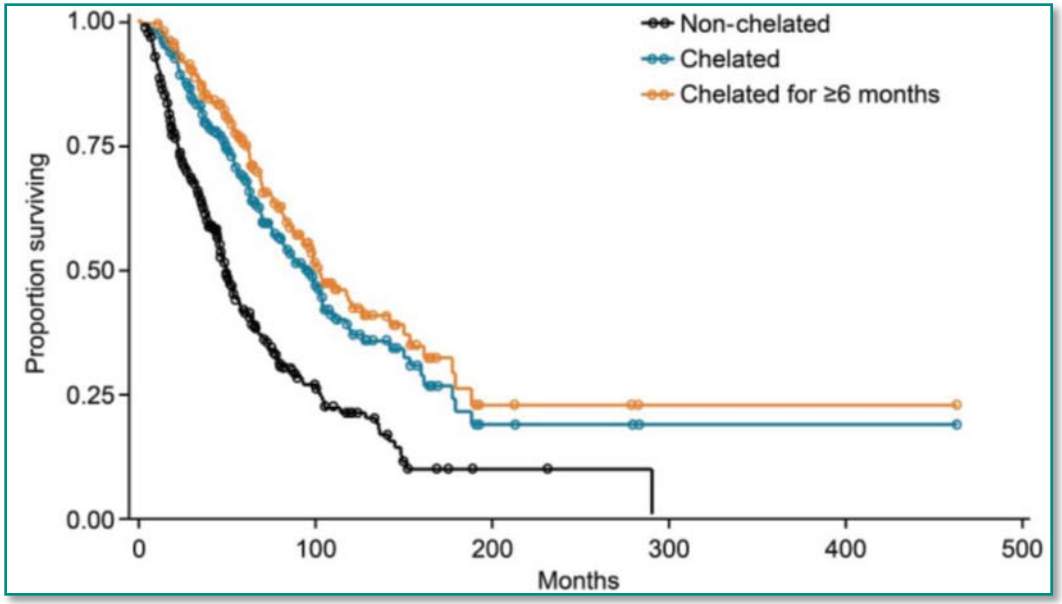


Groupe Francophone des Myélodysplasies

Rose et al. Leuk Res. 2010 Jul;34(7):864-70.

Iron Chelation and overall Survival: ASH2012

- Each incremental week of deferasirox is associated with a decreased risk of death.[1]
- Deferasirox and vitamin D promote cell differentiation and improve overall survival in elderly AML patients after demethylating agent failure.[2]
- Patients on iron chelation therapy show a higher cardiac EFS, OS and LFS compared with those not treated.[3]
- According to the MDS US registry, chelated patients had significantly longer OS and time to AML transformation, as well as significantly fewer deaths.[4]

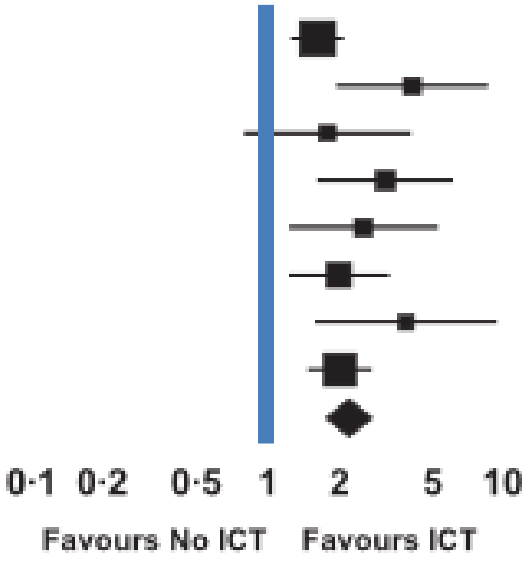


1. Zeidan et al., ASH 2012, abstract 426
2. Paubelle et al., ASH 2012, abstract 3622
3. Remacha et al., ASH 2012, abstract 1723
4. Lyons et al., ASH 2012, abstract 3800

Iron chelation and survival in MDS Meta-analysis

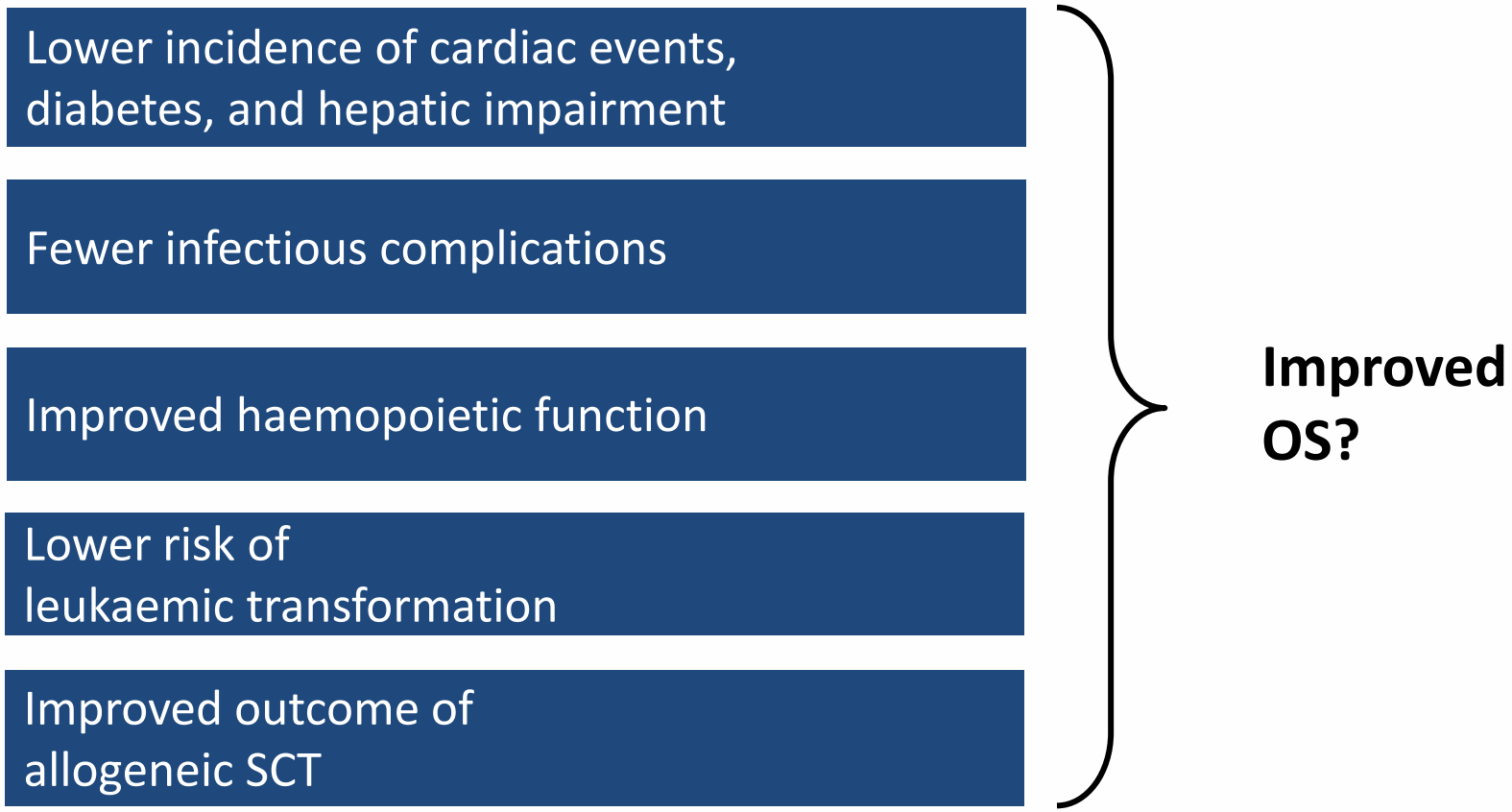
Pooled Difference in Median Overall Survival

Source	Odds ratio	Lower limit	Upper limit	*P*-value
Neukirchen *et al*, (2012)	1·470	1·131	1·911	0·004
Rose *et al*, (2010)	3·719	1·760	7·859	0·001
Raptis *et al*, (2010)	1·626	0·715	3·699	0·246
Delforge *et al*, (2014)	2·864	1·471	5·575	0·002
Komrokji *et al*, (2011)	2·305	1·107	4·799	0·026
Remacha *et al*, (2012)	1·819	1·109	2·983	0·018
Leitch *et al*, (2008)	3·505	1·435	8·564	0·006
Lyons *et al*, (2012)	1·834	1·333	2·525	0·000
	1·984	1·583	2·486	0·000



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 in MDS: what is the anticipated benefit from iron control?



Grazie per la vostra attenzione