Iron Chelation Therapy in Pediatrics Patients

- Assoc Prof **Antonis Kattamis**

  Division of Hematology-Oncology, Head
  First Department of Pediatrics,
  University of Athens, Greece

Goals in Chelation Therapy

Prevent Iron Overload

- Iron accumulates very rapidly

Prevent Iron Toxicity

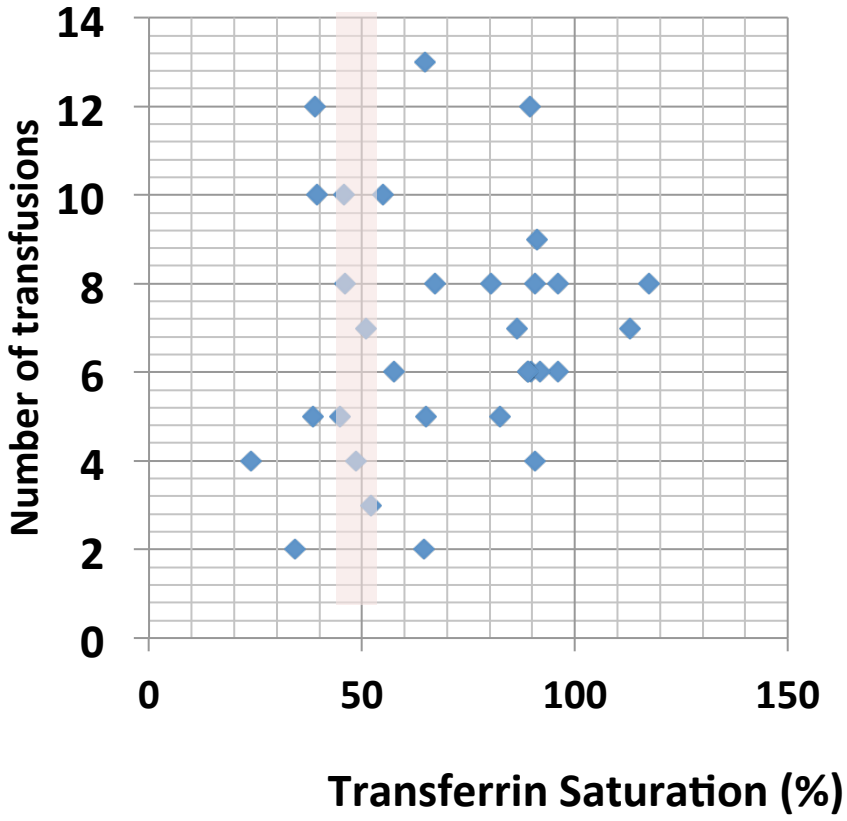
- When does it start?

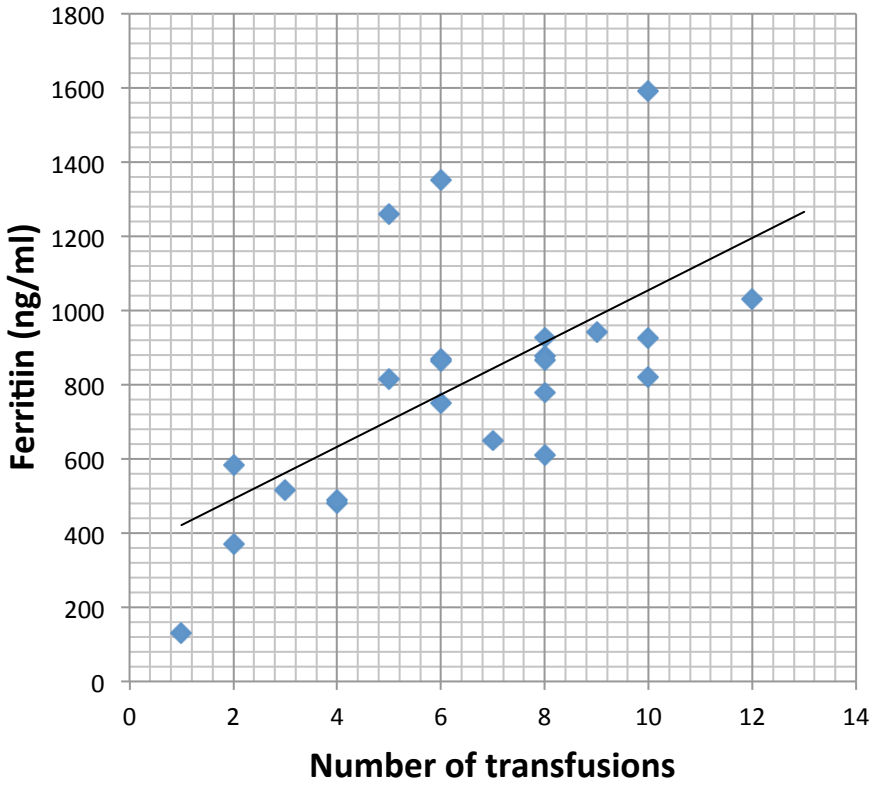
Efficacy and Long-term Safety

- Differences between chelators

Progression of Iron Overload

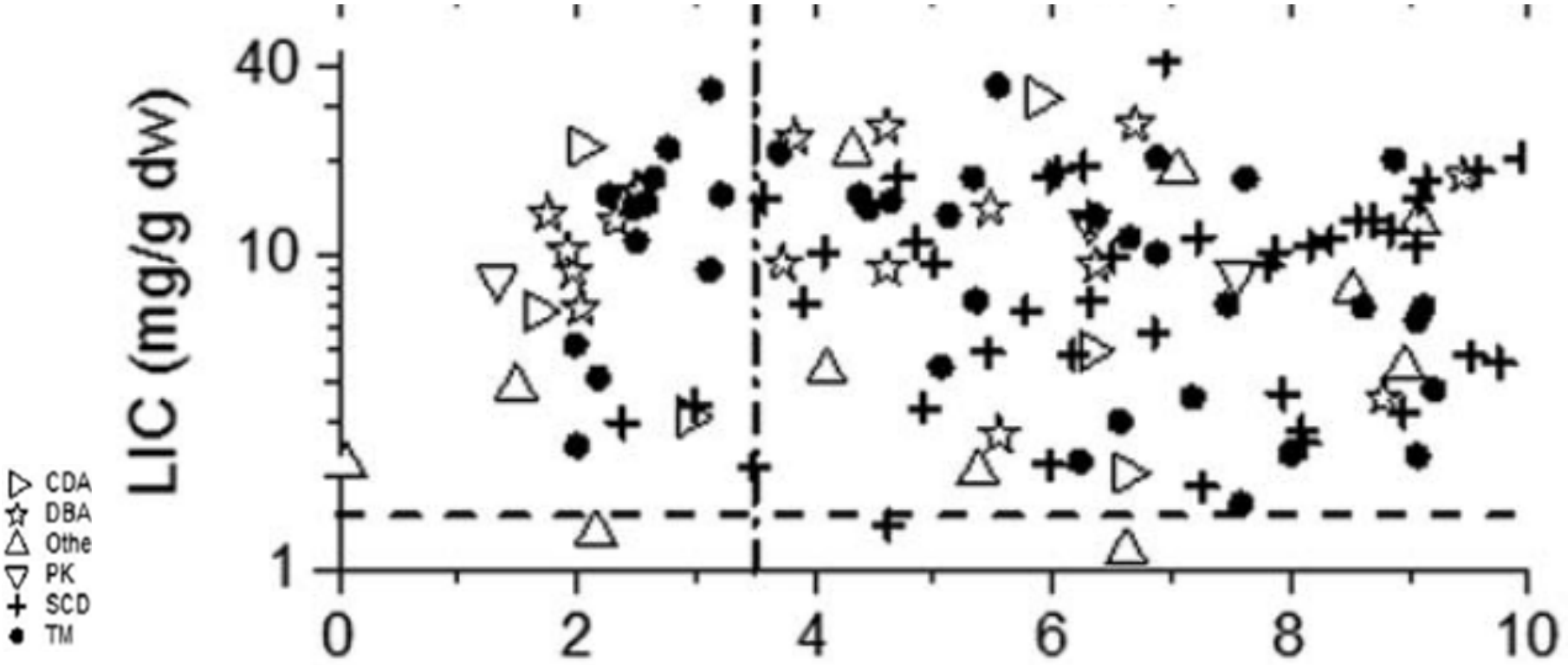
Newly-diagnosed Chelation-naïve Patients with Transfusion-dependent Anemias N=9





Delaporta et al; Blood Suppl 2013

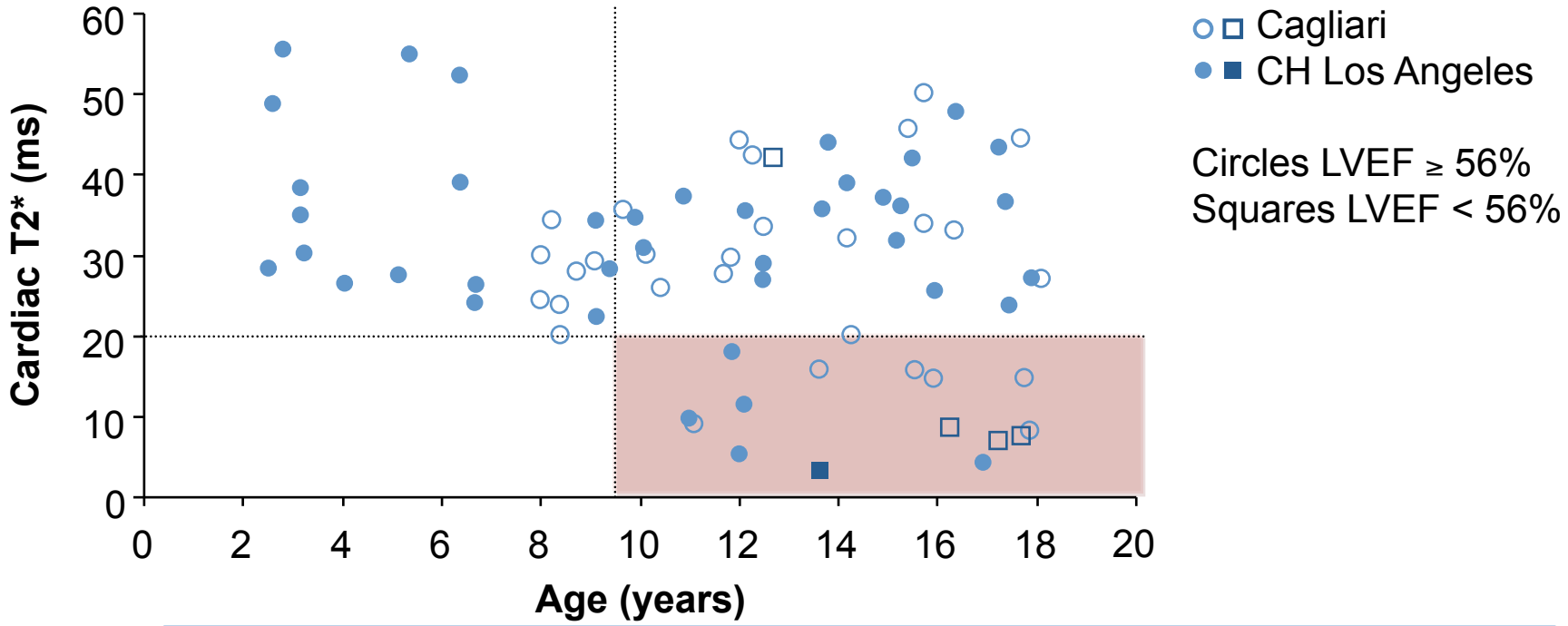
MRI in young patients <10 y.o



Berdoukas V et al, Amer J Hematol; in press 2013

Cardiac iron in β-thalassaemia major

Plot of first cardiac T2* as a function of age in 77 patients from Cagliari and Los Angeles
Circles indicate patients with normal cardiac function (LVEF ≥ 56%) and
squares indicate left-ventricular dysfunction



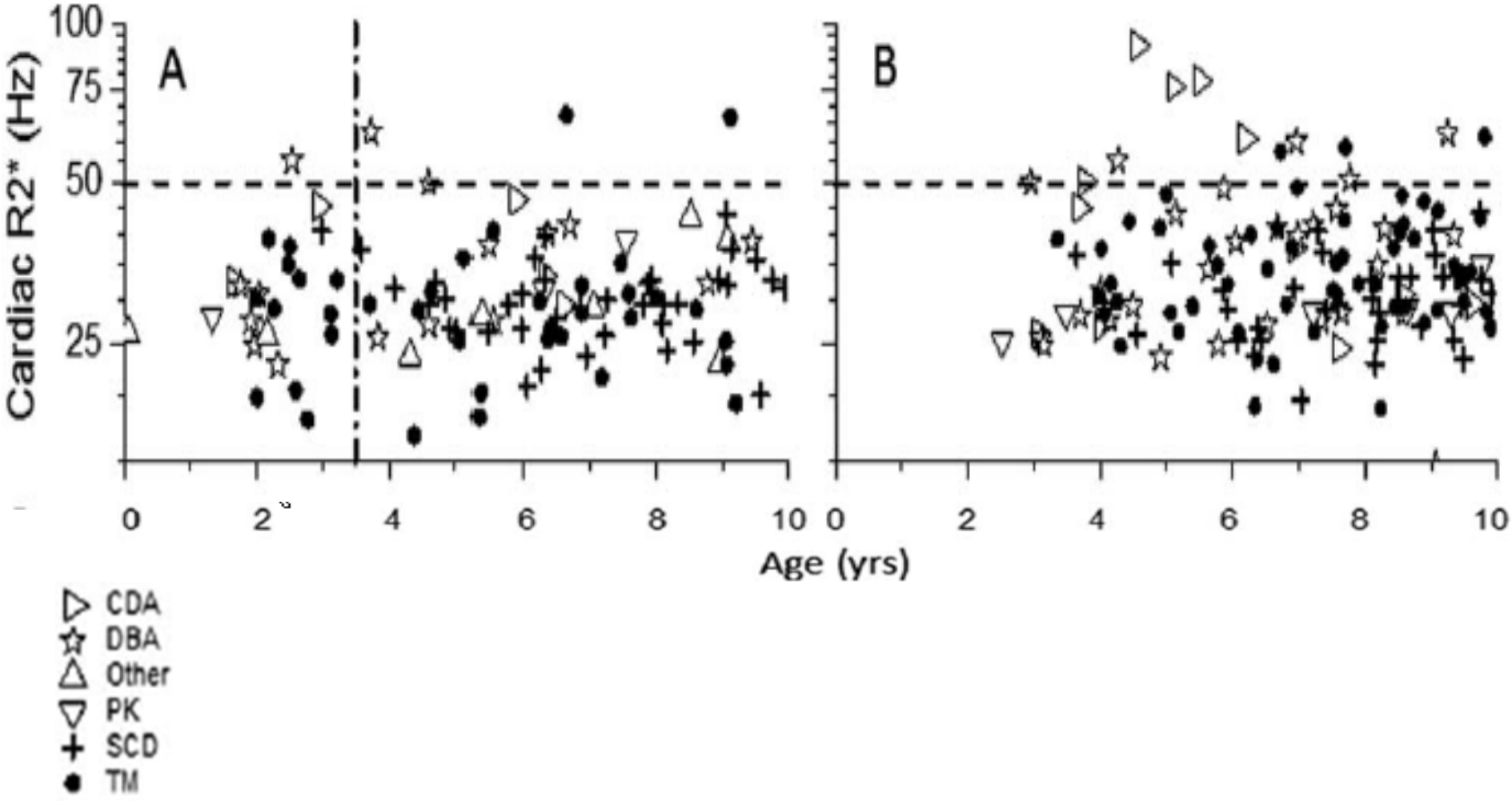
Cardiac T2* is negatively correlated with transfusion duration in patients with β-thalassaemia major

CH = Children's Hospital.

Wood JC, et al. Haematologica. 2008;93:917-20.

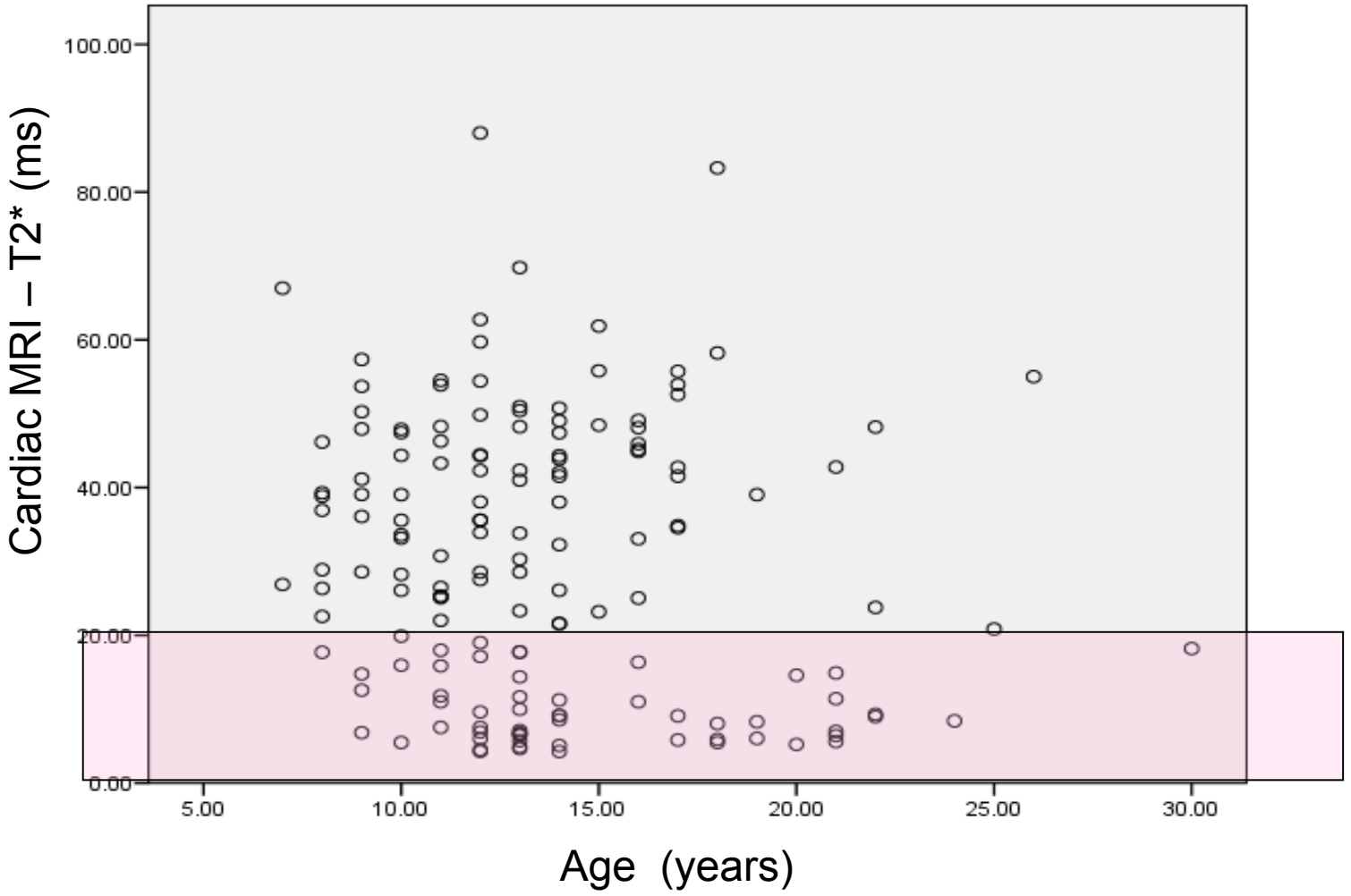
MRI in young patients <10 y.o

CARDIAC IRON (R2*) vs AGE



Berdoukas V et al, Amer J Hematol; in press 2013

Cardiac T2*



Au W et al; Hemoglobin 2013 in press

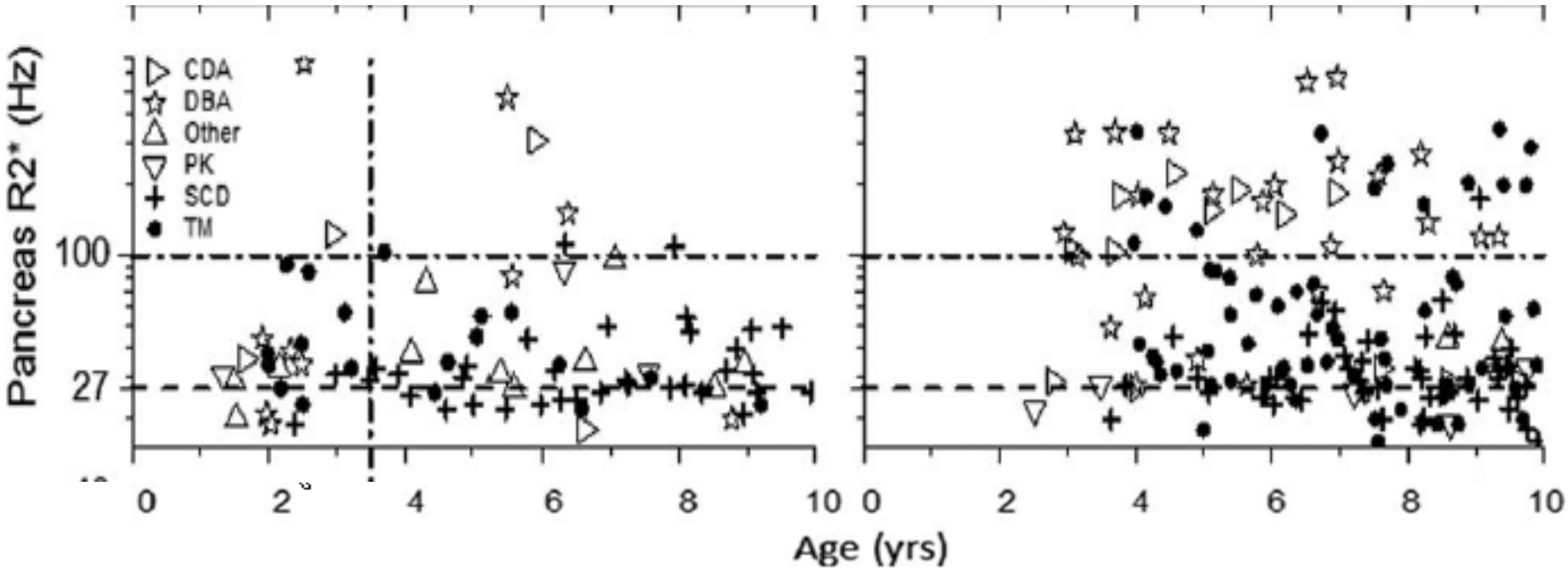
Cardiac T2*
in 23 Transfusion-Dependent patients

Characteristics	Patient 1	Patient 2	Patient 3	All other patients
Age (years)	9.7	7.4	9.8	12.6±3.1
Diagnosis (see text)	TM	TM	Sideroblastic anemia	Varied
Age at start of transfusion therapy (mo)	6	12	1	9.4 (1-18)
Age of initial chelation therapy (years)	1.9	3.3	0.7	1.4 (0.6-3.3)
Serum ferritin range (ng/dL)	2008-2568	1313-2316	1299-3076	957 (340-4211)
Transfusional iron input (mg/kg/y)	143.6	121.5	302.1	133.7 (76-403)
Cardiac T2* (ms)	8.1	6.9	3.2	27.3±6.5
Liver iron concentration (mg/g)	8.4	16.7	12.7	6.4 (1.2-18.9)

Fernandes JL, et al, Haematologica 94(12); 1776, 2009

MRI in young patients <10 y.o

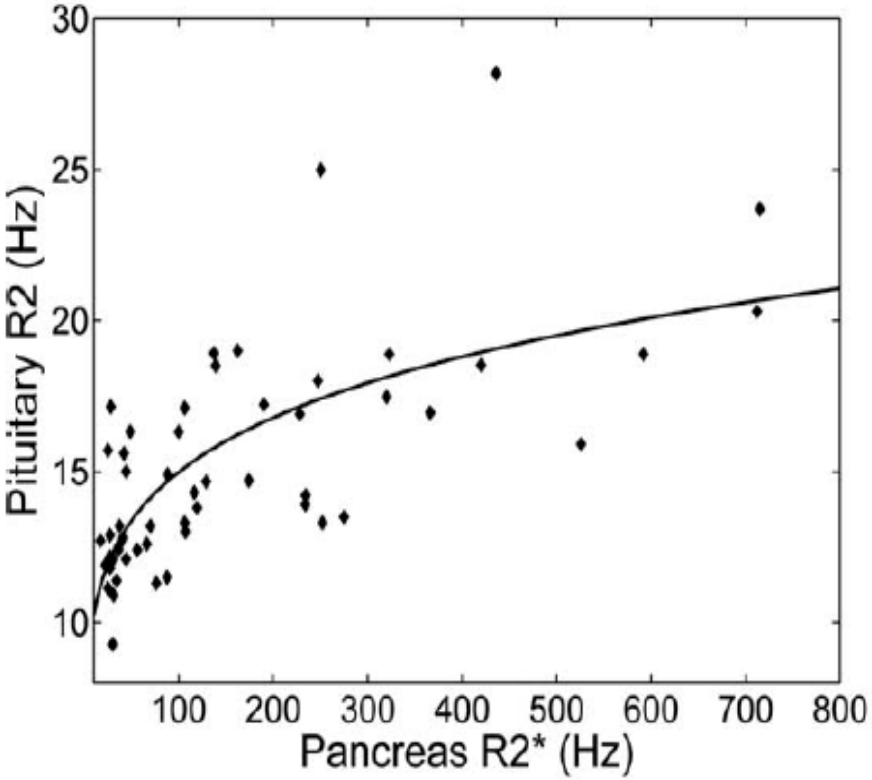
PANCREAS IRON (R2*) vs AGE



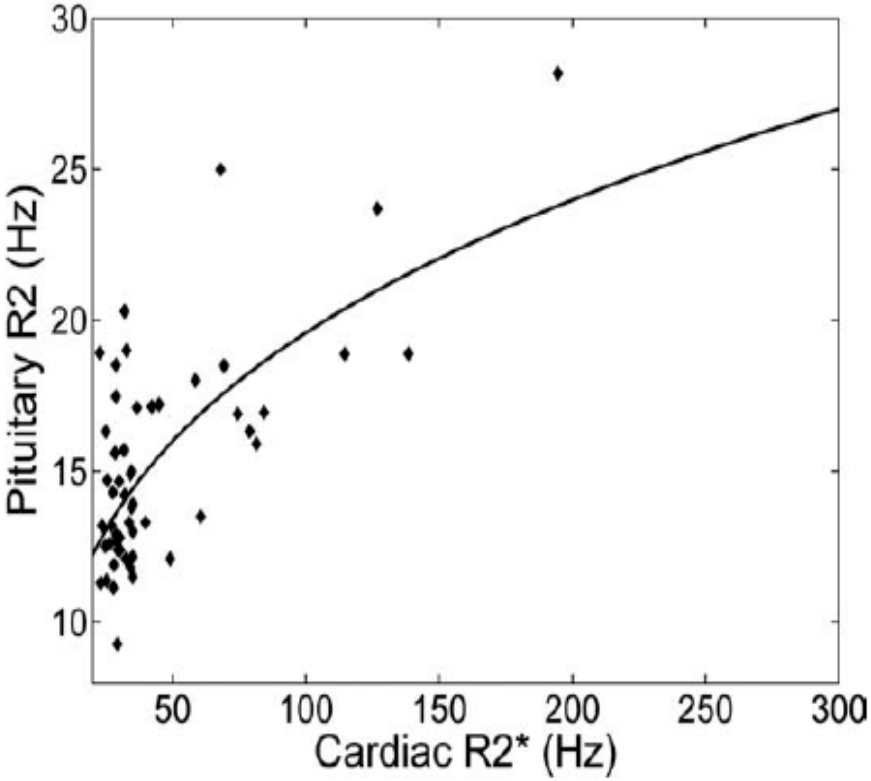
Berdoukas V et al, Amer J Hematol; in press 2013

Iron Loading Parallels in between Endocrine Glands and Heart

r^2= 0.49, p<0.0005

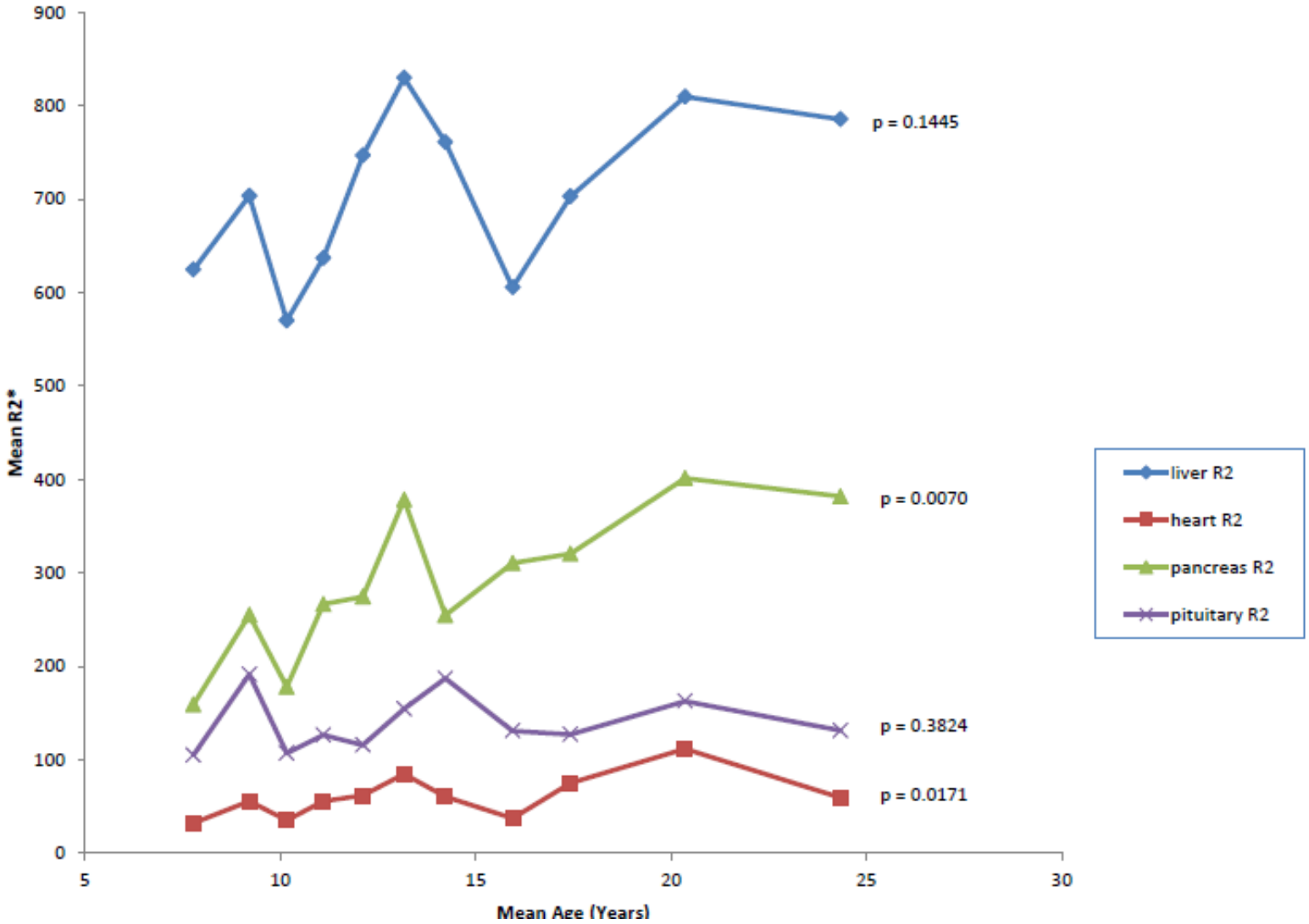


r^2= 0.52, p<0.0005



Noetzli LJ *et al. Am J Hematol* 2012;87:167–171;

Iron Loading Parallels in Different Organs



Au W et al; Hemoglobin 2013 in press

Goals in Chelation Therapy

Prevent Iron Overload

- Iron accumulates very rapidly

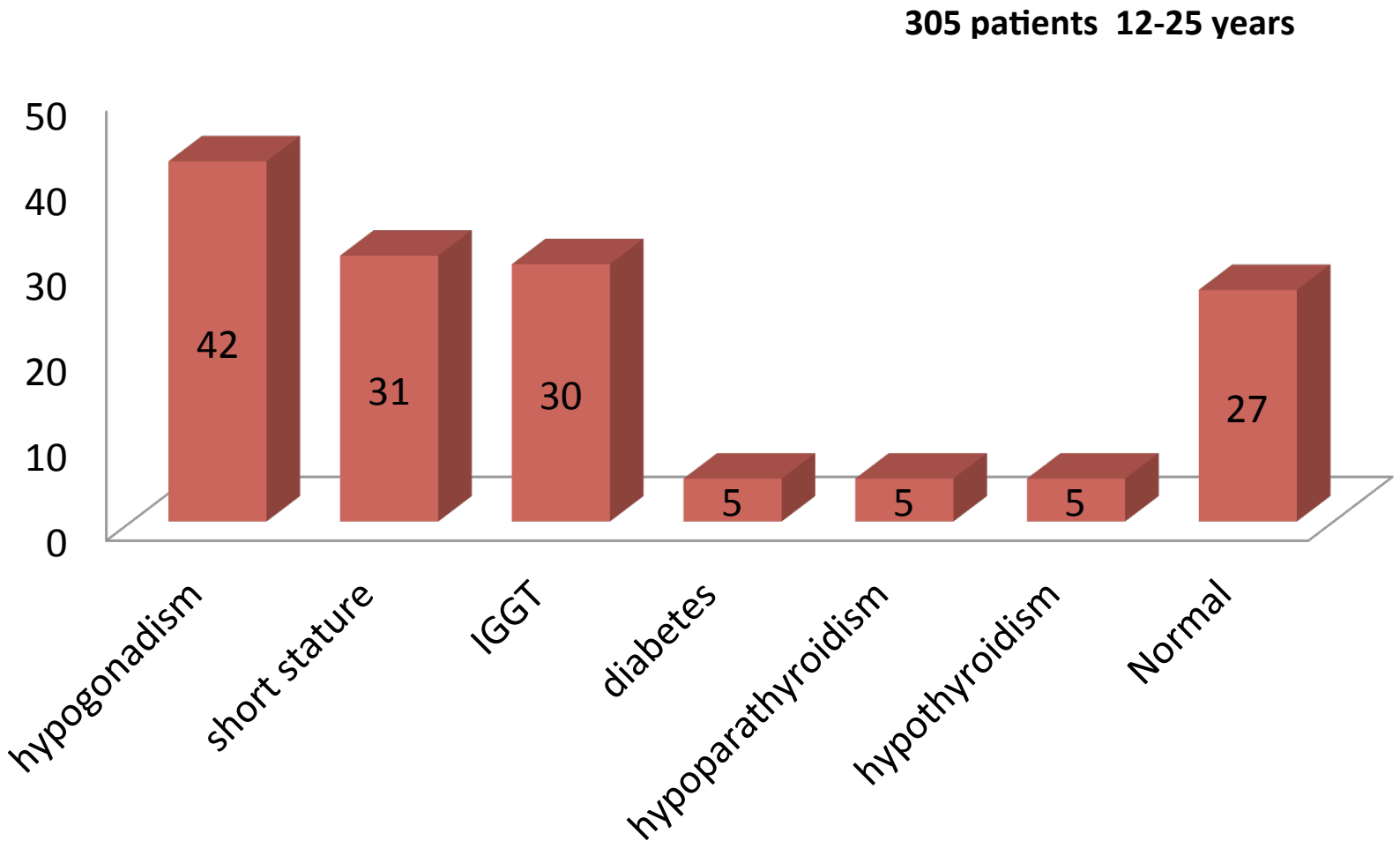
Prevent Iron Toxicity

- When does it start?

Efficacy and Long-term Safety

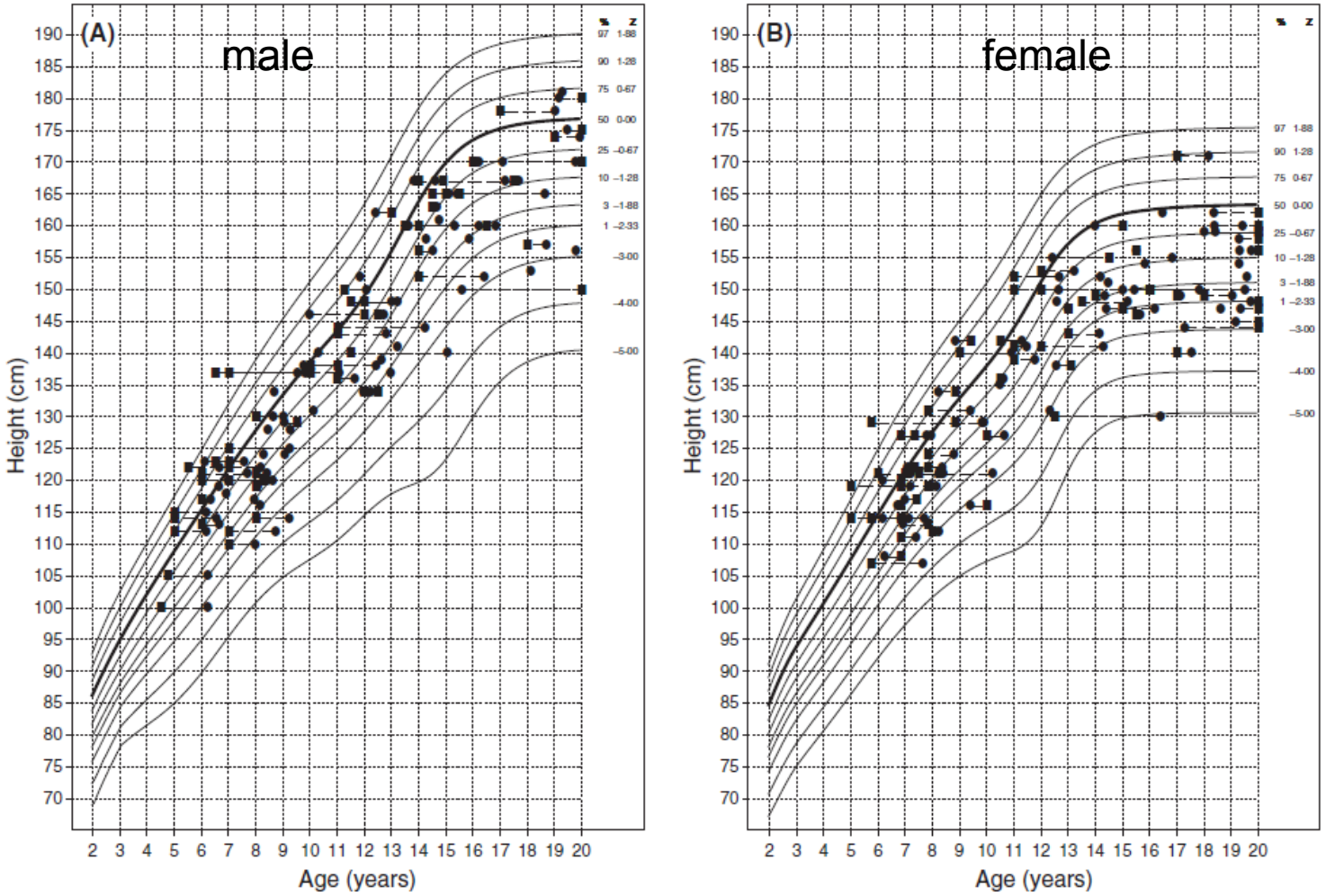
- Differences between chelators

Sequelae of Iron Overload: Prevalence of Endocrinopathies



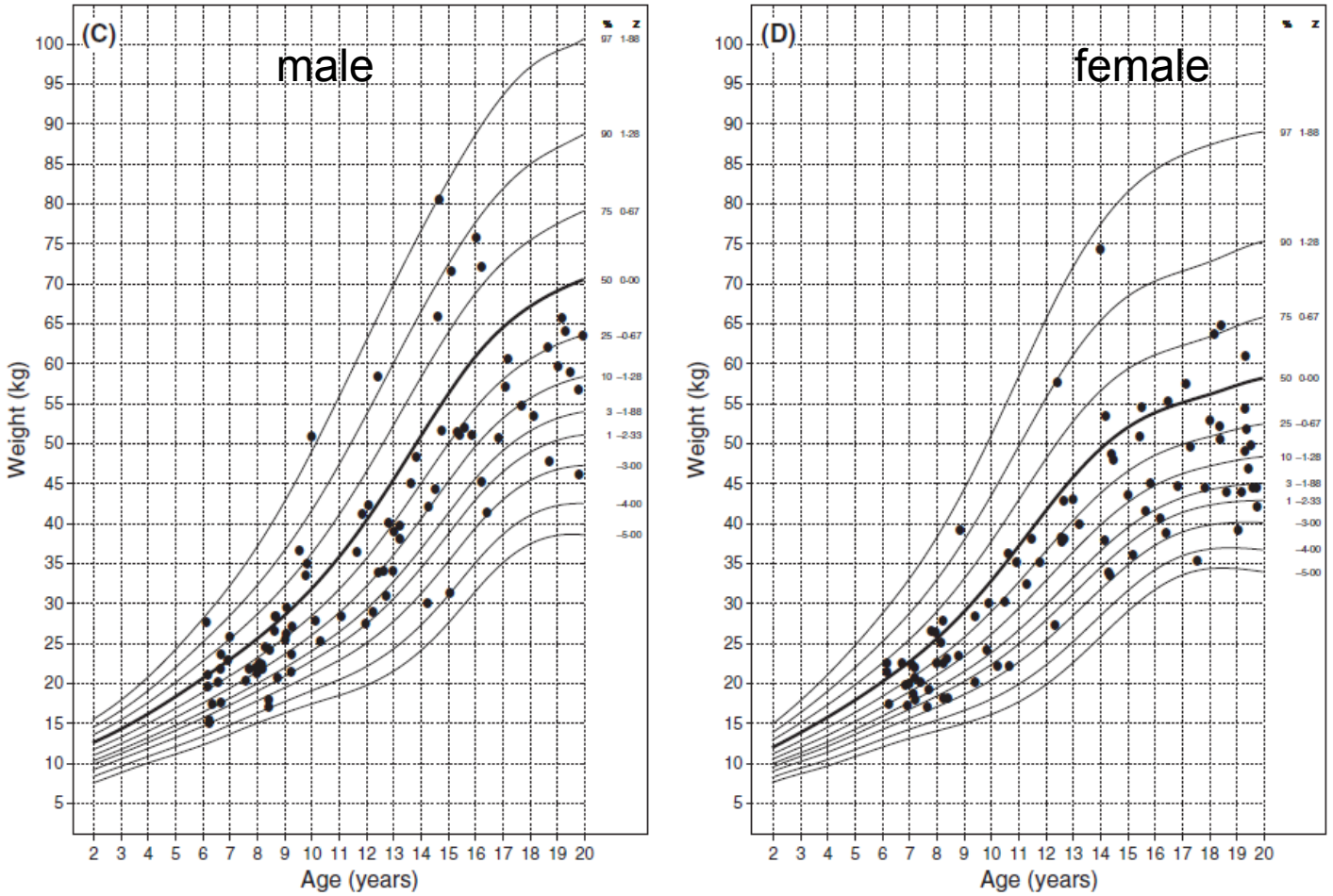
Kattamis C, 2004 unpublished data

Height versus calendar age (●) and bone age (■)



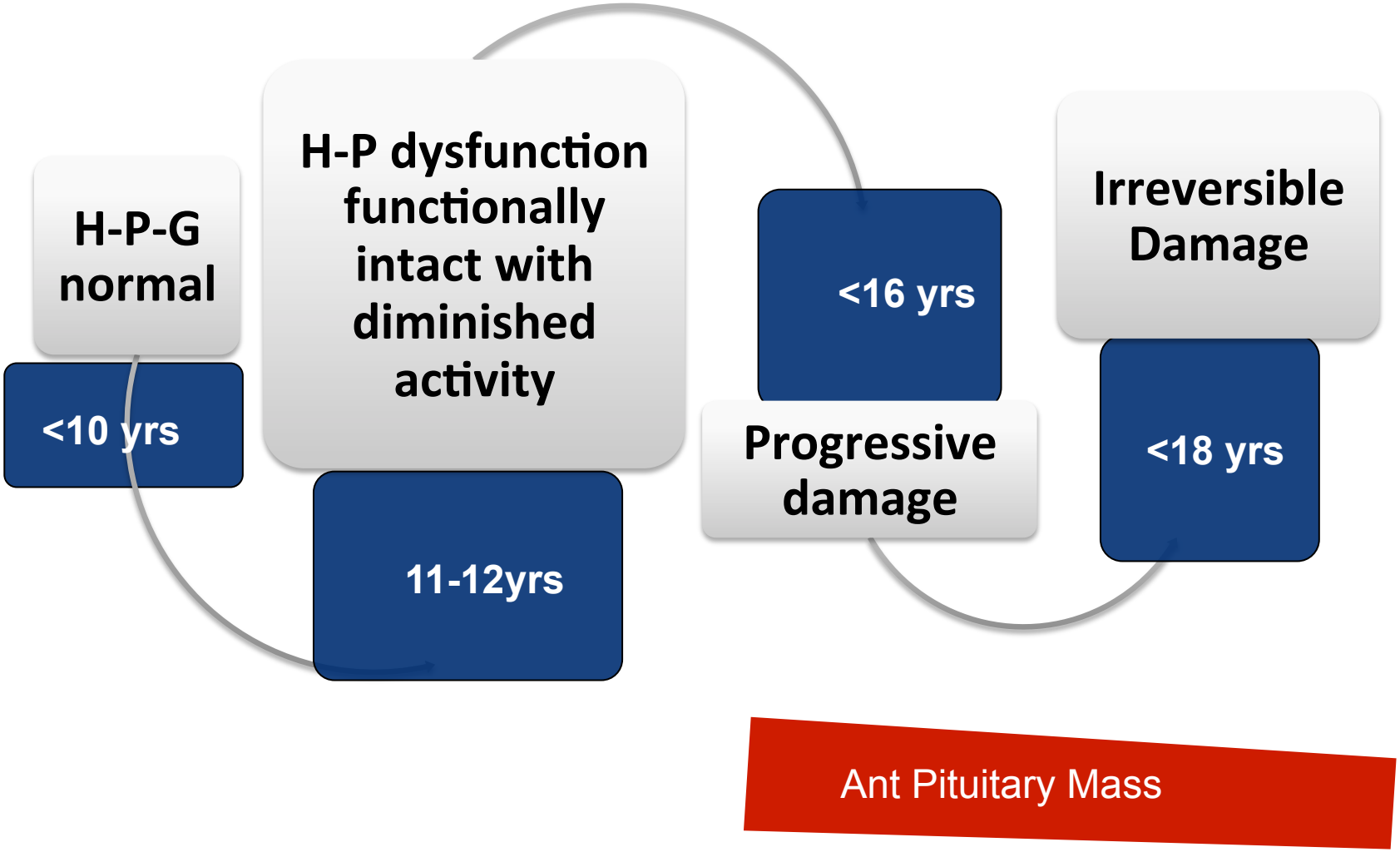
Vogiatzi MG, et al; British Journal of Haematology, 146, 546–556,2009

Weight versus calendar age (●) and bone age (■)



Vogiatzi MG, et al; British Journal of Haematology, 146, 546–556,2009

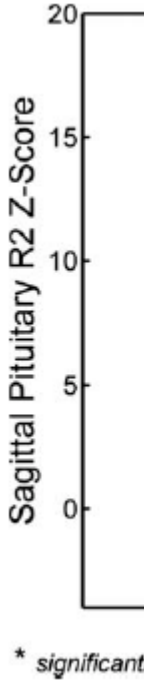
Sequelae of Iron Overload: H-P-G dysfunction



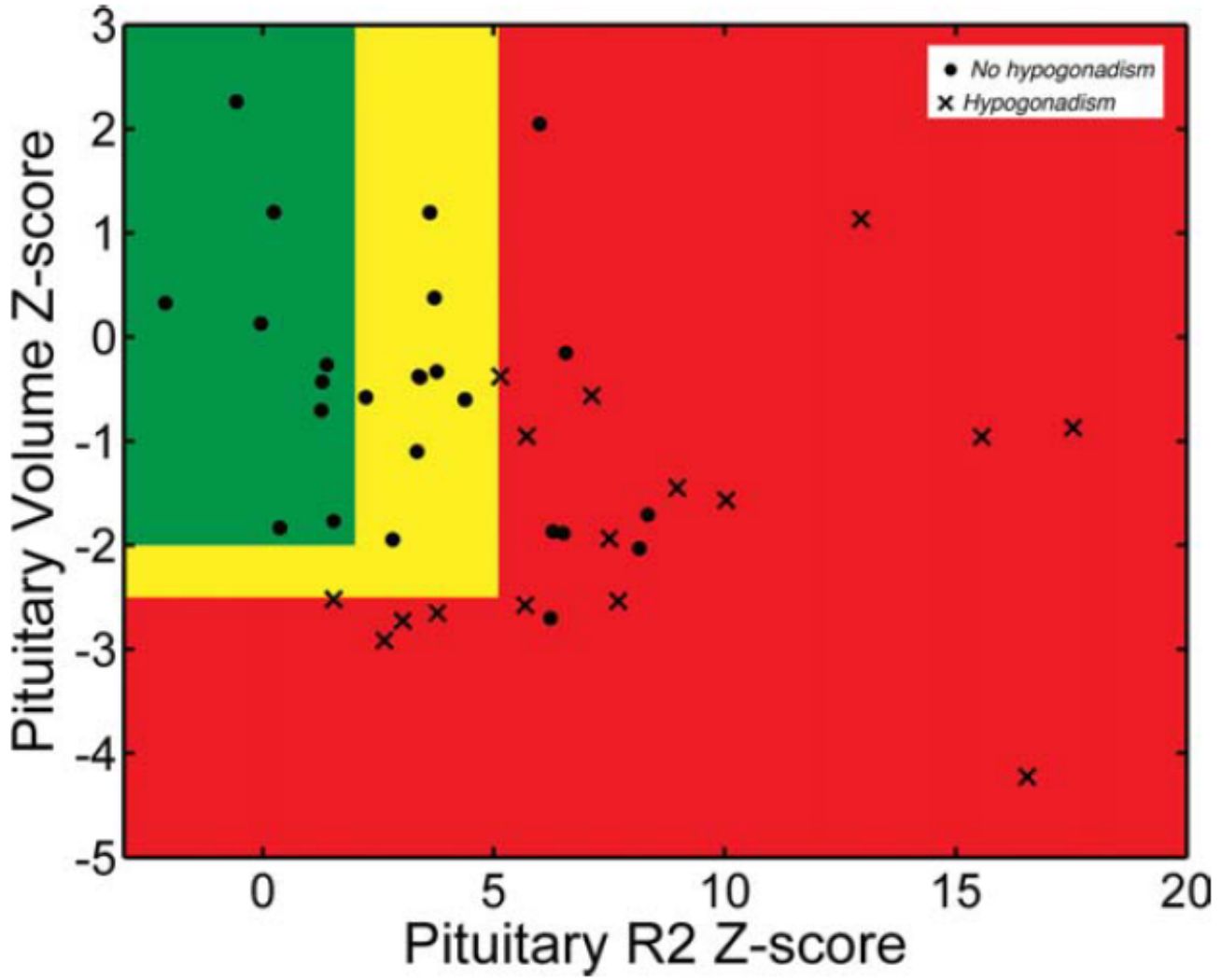
Chatterjee R et al: Ann. N.Y. Acad. Sci. 1202 (2010) 100–114

Iron load and Volume of Anterior Pituitary

Pituitary iror
develops as



* *significant*



onadism

Noetzli LJ *et al. Am J Hematol* 2012;87:155–160;

Goals in Chelation Therapy

Prevent Iron Overload

- Iron accumulates very rapidly

Prevent Iron Toxicity

- When does it start?

Efficacy and Long-term Safety

- Differences between chelators

Desferrioxamine (DFO) – Good Old Friend

- **Established long-term efficacy**
- **Prevention of endocrine/cardiac disturbances is suboptimal**
- **Unpleasant, cumbersome treatment**

  -Needs parental education

  -May be perceived as punishment by the child

- **Introducing a more difficult (parenteral) treatment may later improve adherence with an oral therapy**

Mednick LM et al. Pediatr Blood Cancer 2010;55:603–605

DFO – Good Old Friend

Manageable toxicity

Risks of over-chelation

- Risks of starting too early

  -effects on growth

  -effects on bones, especially < 3 y.o.[1,2]

- Risks at low iron loads

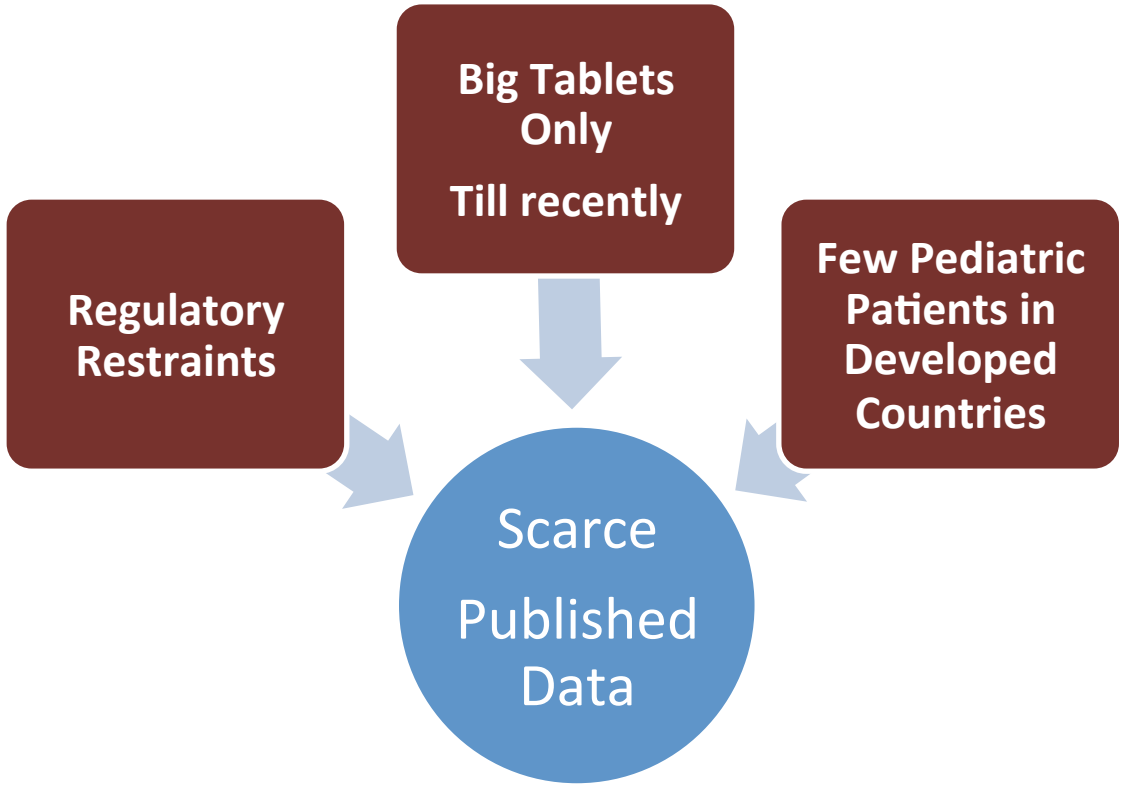
  -effects on growth: patients had mean ferritin of 1,300 µg/L[3]

  -otoxicity: with serum ferritin < 2,000 µg/L or when ratio dose/ferritin too high[5]

1. Olivieri NF, et al. Am J Pediatr Hematol Oncol. 1992;14:48-56.
2. Brill PW, et al. Am.J.Roentgenol. 1991;156:561-5. 3. Piga A, et al. Eur J Haematol. 1998;40:380-1.
4. Olivieri NF, et al. N Engl J Med. 1986;314:869-73. 5. Porter JB, et al. Br J Haematol. 1989;73:403-9.

Deferiprone in pediatric patients

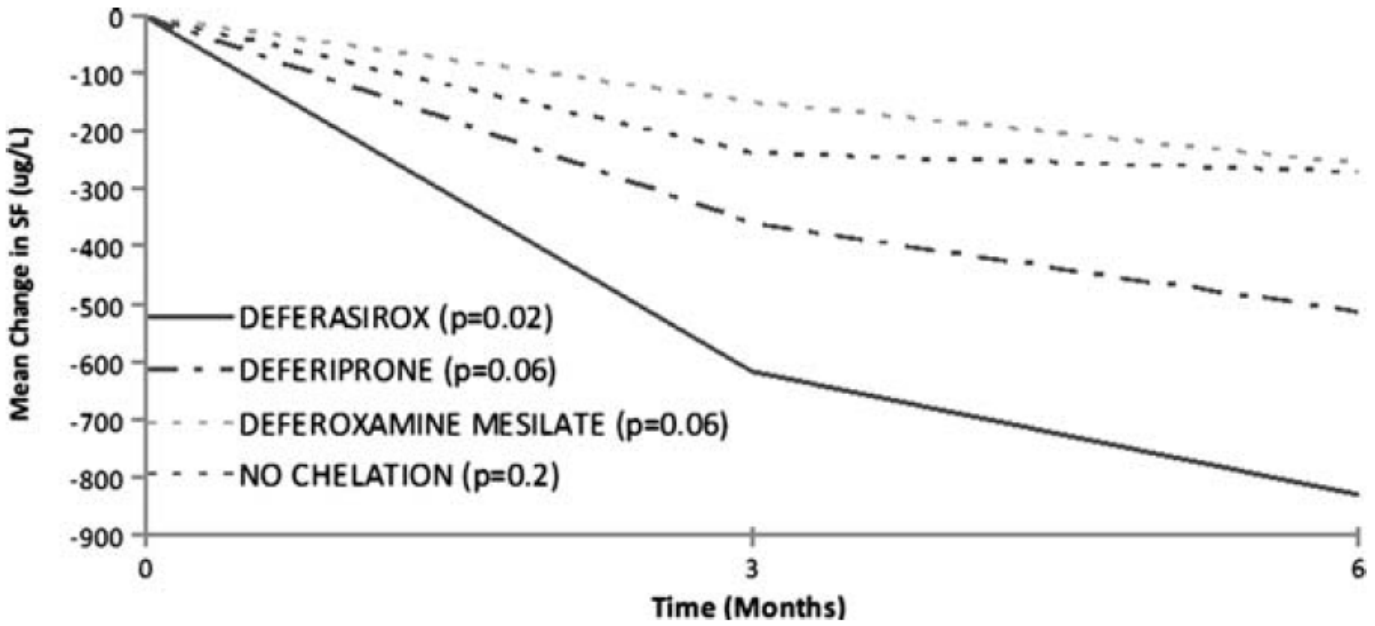
Many young patients have been using deferiprone either as monotherapy or combination therapy with DFO



Aydinok Y et al , 1999; Ha S-Y et al., 2006; Daar S & Pathare AV, 2006; El-Beshlawy A et al, 2008;

Deferiprone in pediatric patients

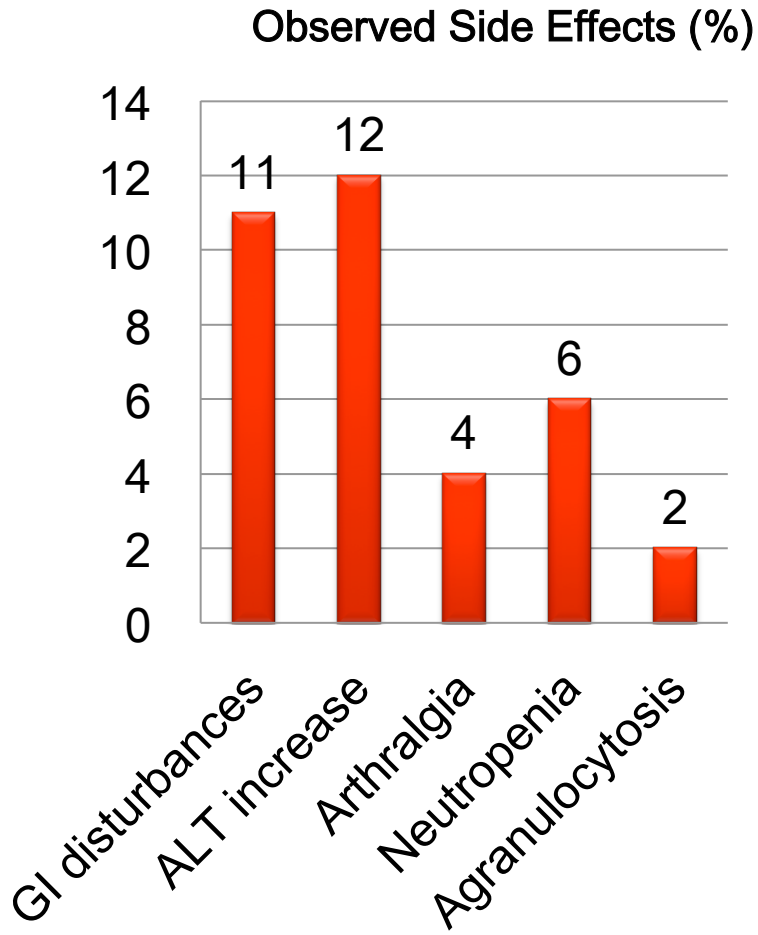
- Ferriprox oral solution
- 6-month prospective study in 100 children, mean age 5.1 years
- Dose 50-100mg/kg/day:3



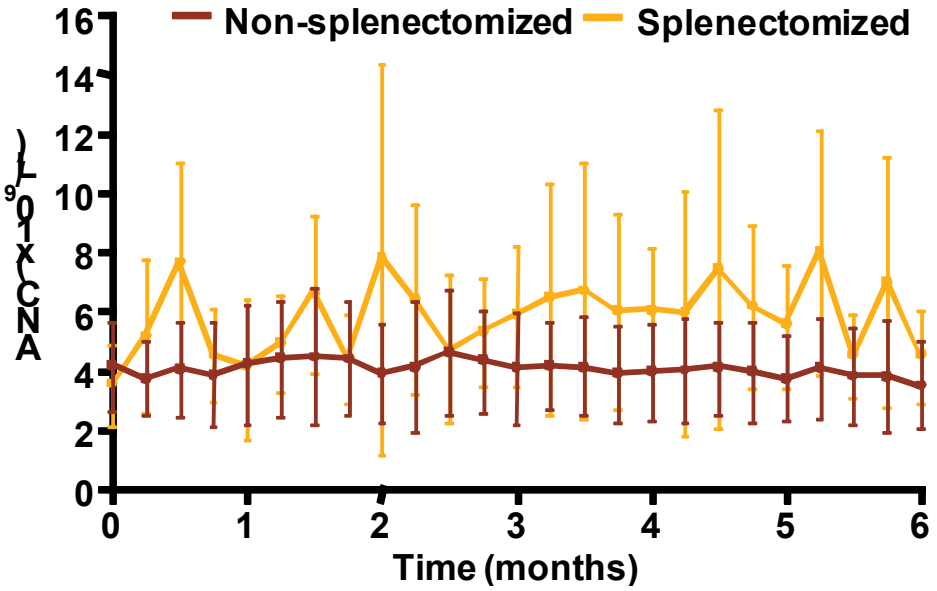
Serum ferritin levels were reduced from 2532 ± 1463 ng/mL at baseline to 2176 ± 1144 ng/mL after treatment (*P*<0.0005). Changes differ according to previous chelation treament

Elalfy M *et al. J Pediatr Hematol Oncol* 2010;32:601–605

Deferiprone oral solution in pediatric patients



Mean absolute neutrophil count over time: Non-splenectomized patients had lowest counts

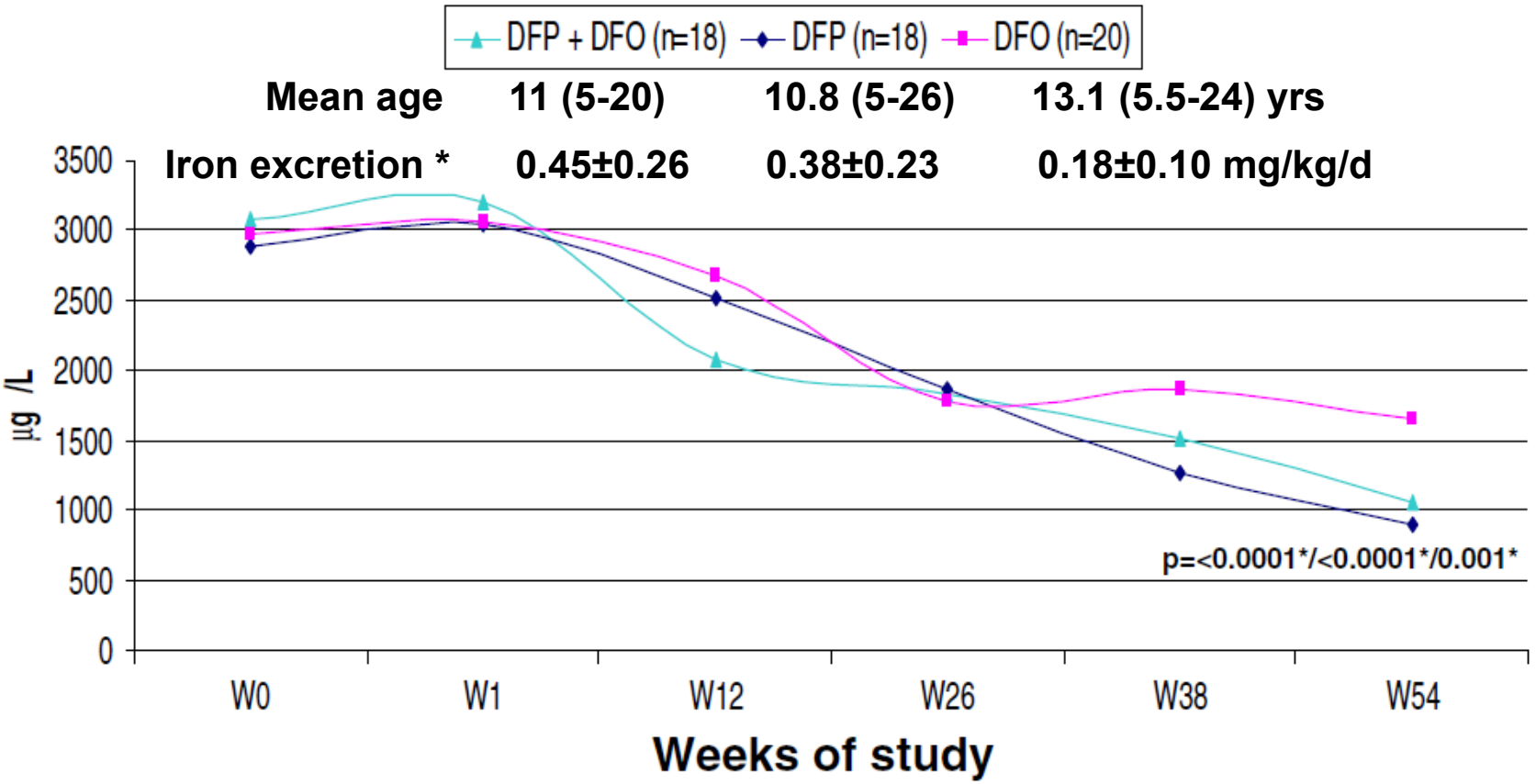


Elalfy M *et al. J Pediatr Hematol Oncol* 2010;32:601–605

Chelation in Pediatric Patients

Combination therapy (DFO+DFP) have been studied in few small series (in some studies mixed adult/pediatric)

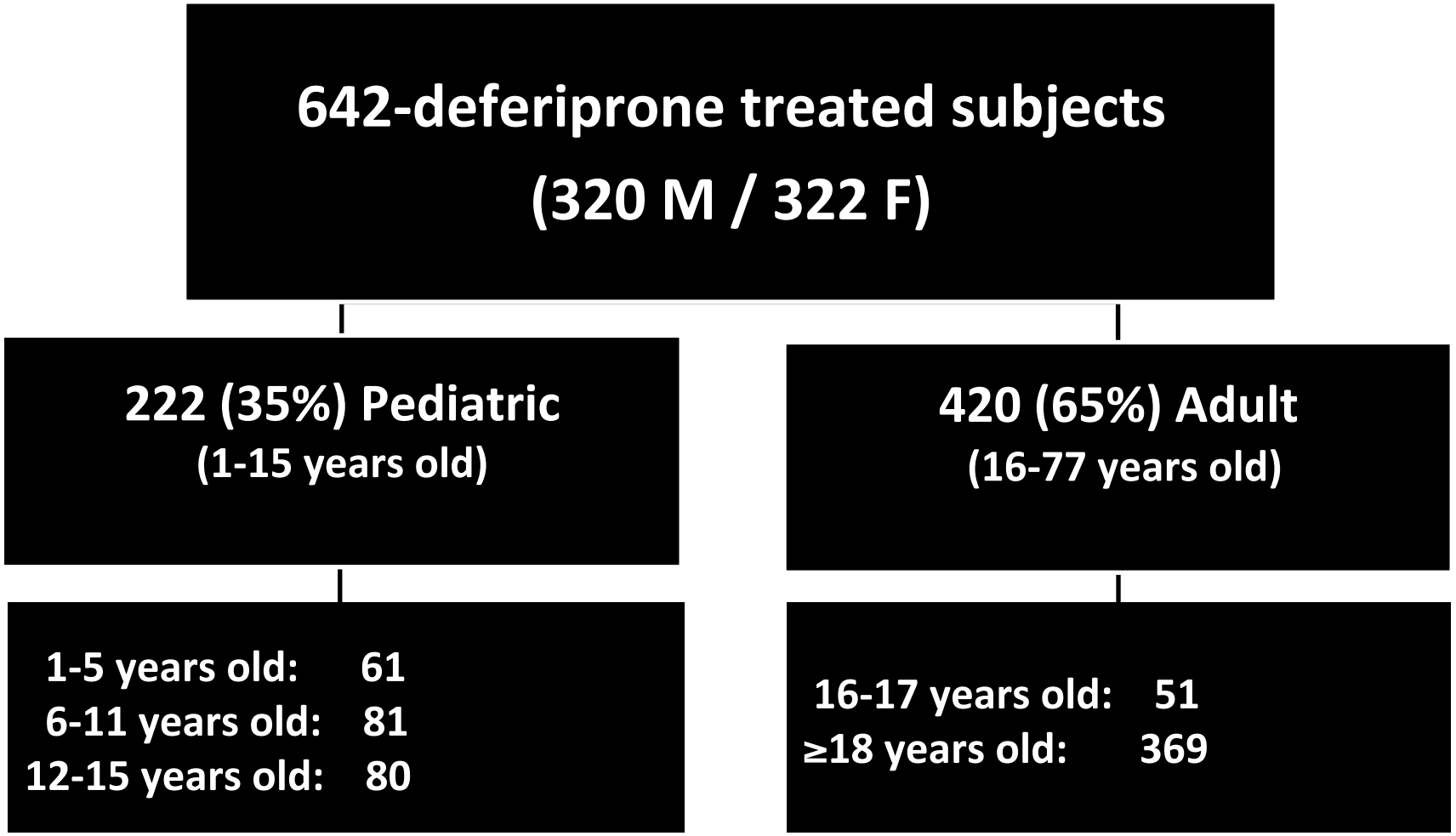
Results showed enhanced efficacy and no additional safety issues



*** calculated based on LIC changes**

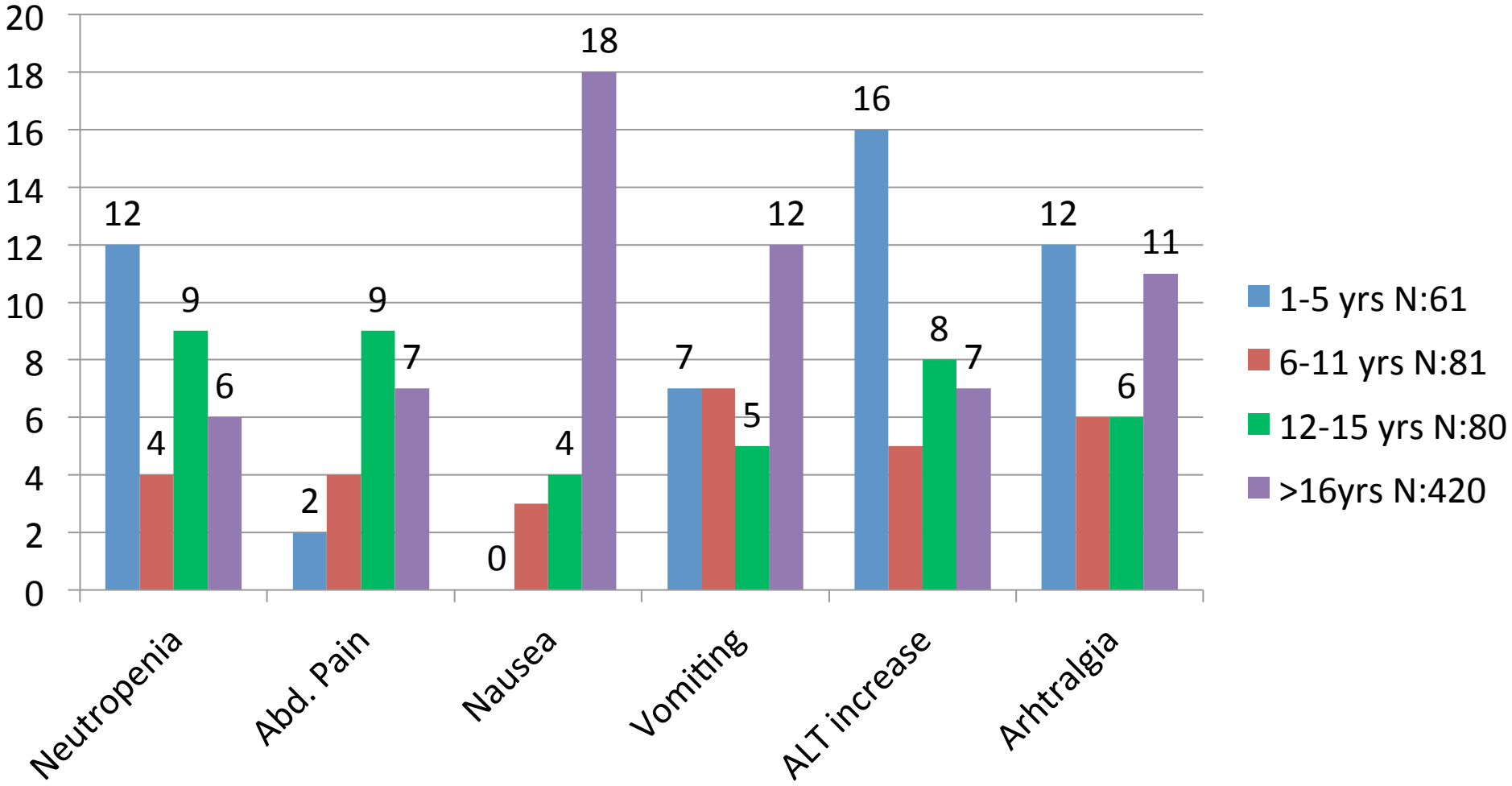
Amal El-Beshlawy et al. Ann Hematol (2008) 87:545–550

ApoPharma Pooled Clinical Studies on Ferriprox



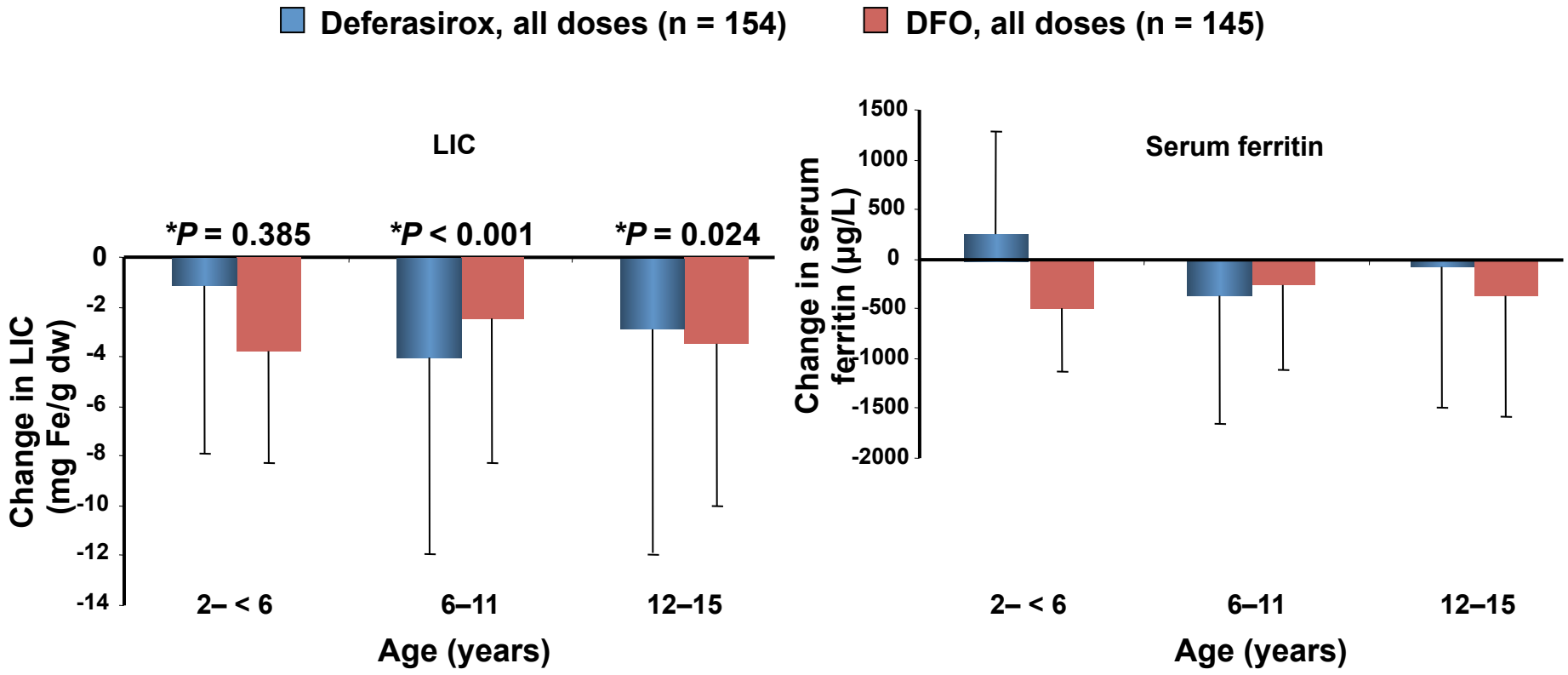
Kindly provided by F. Tricta, 2012

Adverse Drug Reactions during Ferriprox therapy in Pooled Clinical Studies Occurring in >5% of Pts



Kindly provided by F. Tricta, 2012

Deferasirox is effective in children as young as 2 years old

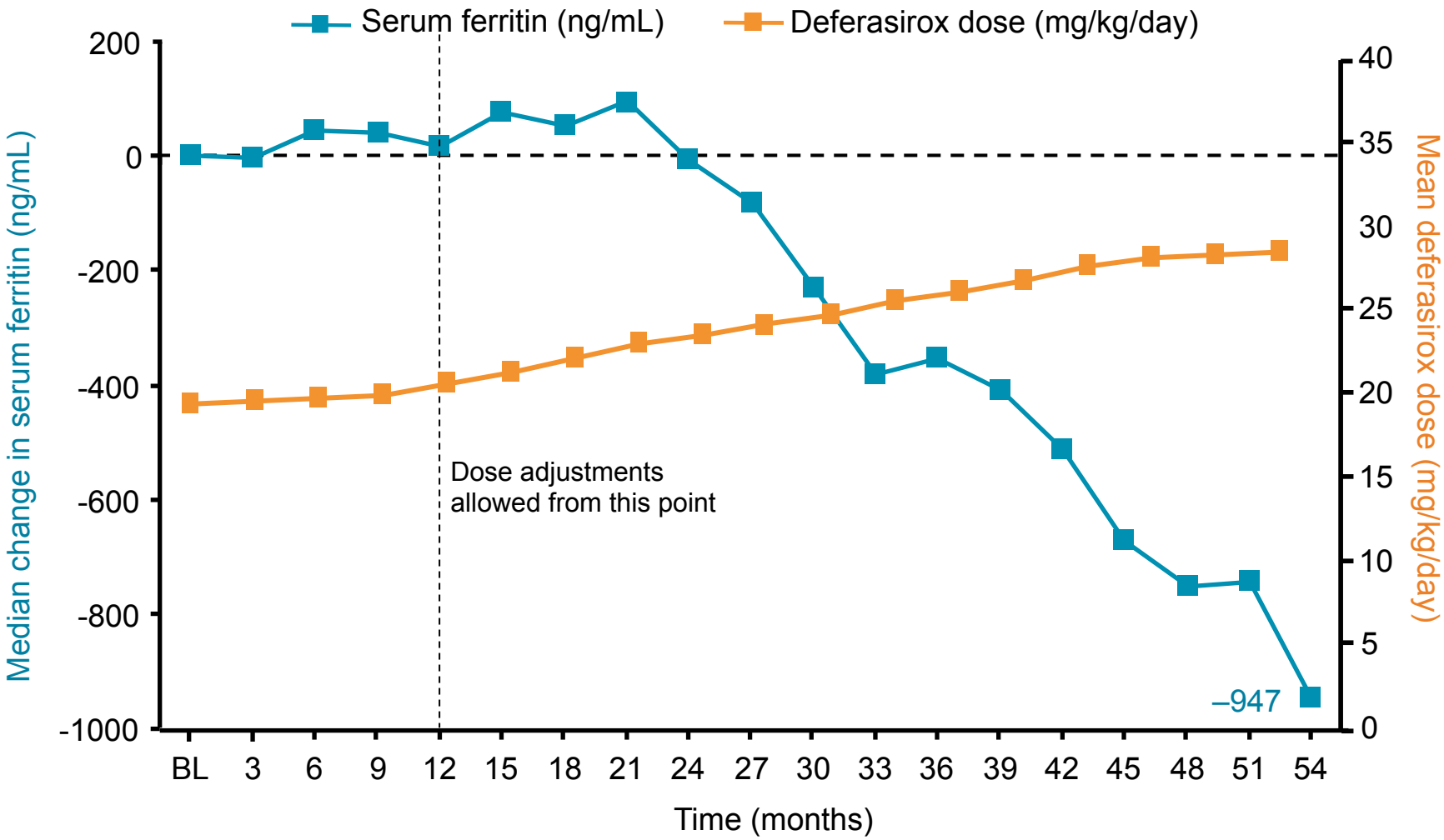


* vs baseline

Kattamis C et al. Presented at ASH 2005 [*Blood* 2005;106(11):abst 2692]

Study 107

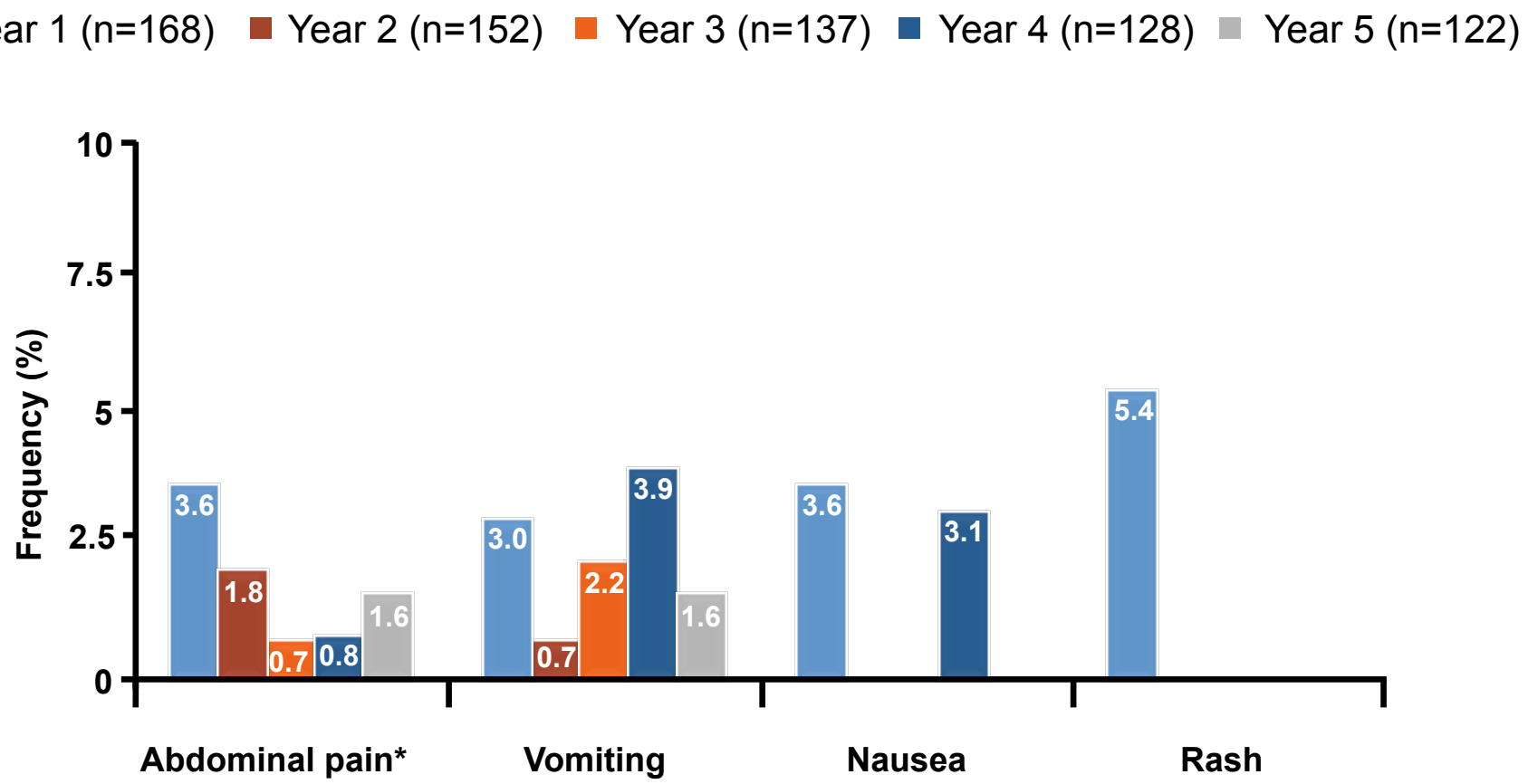
Change in serum ferritin levels in pediatric patients with β-thalassemia on treatment with deferasirox over 4.7 years



Piga A *et al*. Presented at ASH 2008 [*Blood* 2008;112(11):abst 3883]

Studies 107 and 108

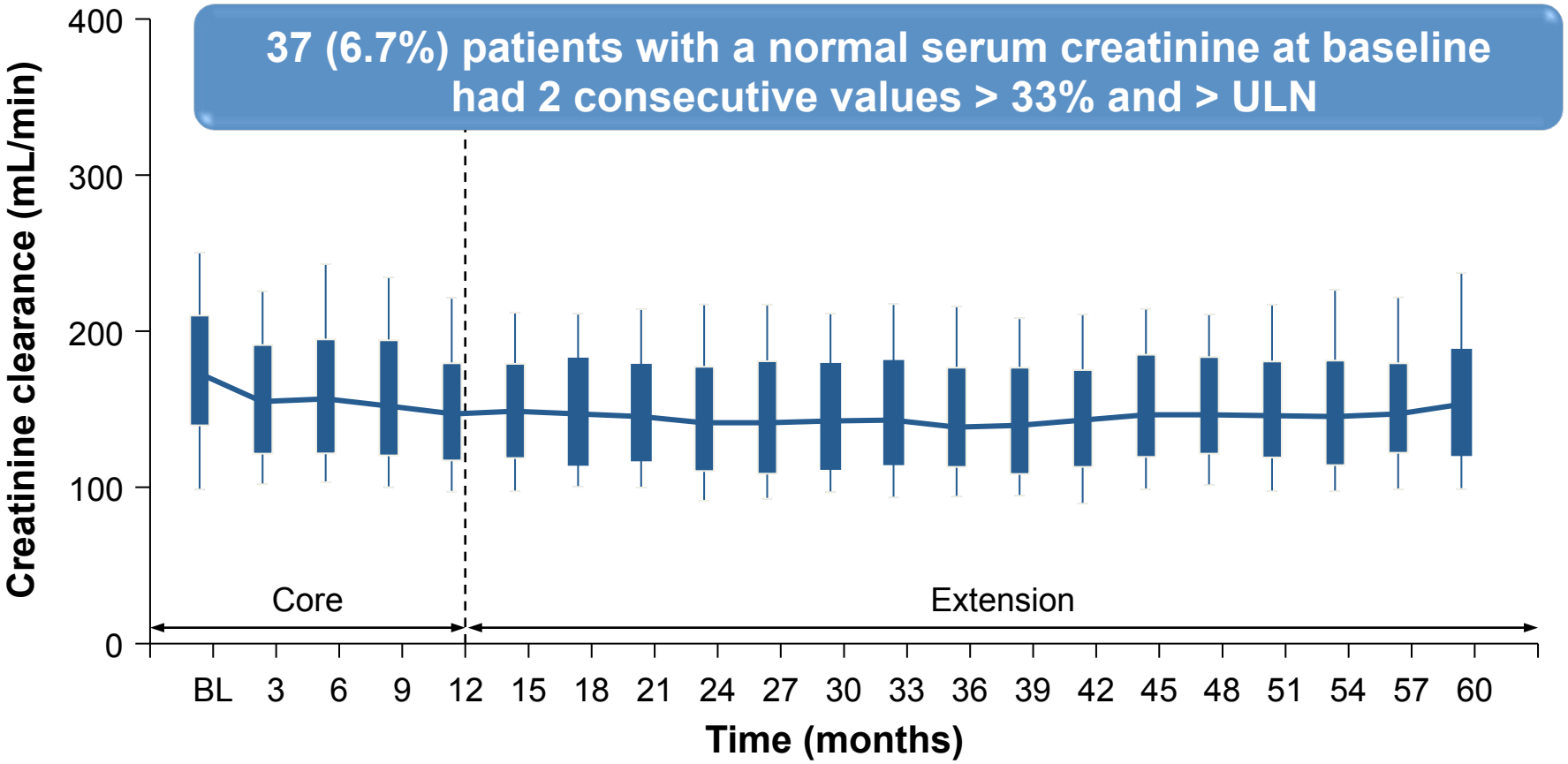
AEs decrease in frequency over long term deferasirox treatment in pediatric patients



*Includes abdominal pain, abdominal pain upper and lower

Piga A *et al*. Presented at ASH 2008 [*Blood* 2008;112(11):abst 3883]

Creatinine clearance remains stable over long term deferasirox treatment in pediatric patients



- Reversible creatinine increase similar to adults
- Renal tubular toxicity (Fanconi syndrome reported)

ULN = upper limit of normal

Cappellini MD *et al. Blood* 2011;118:884–893; Rheault MN *et al. Pediatr Blood Cancer* 2011;56:674–676

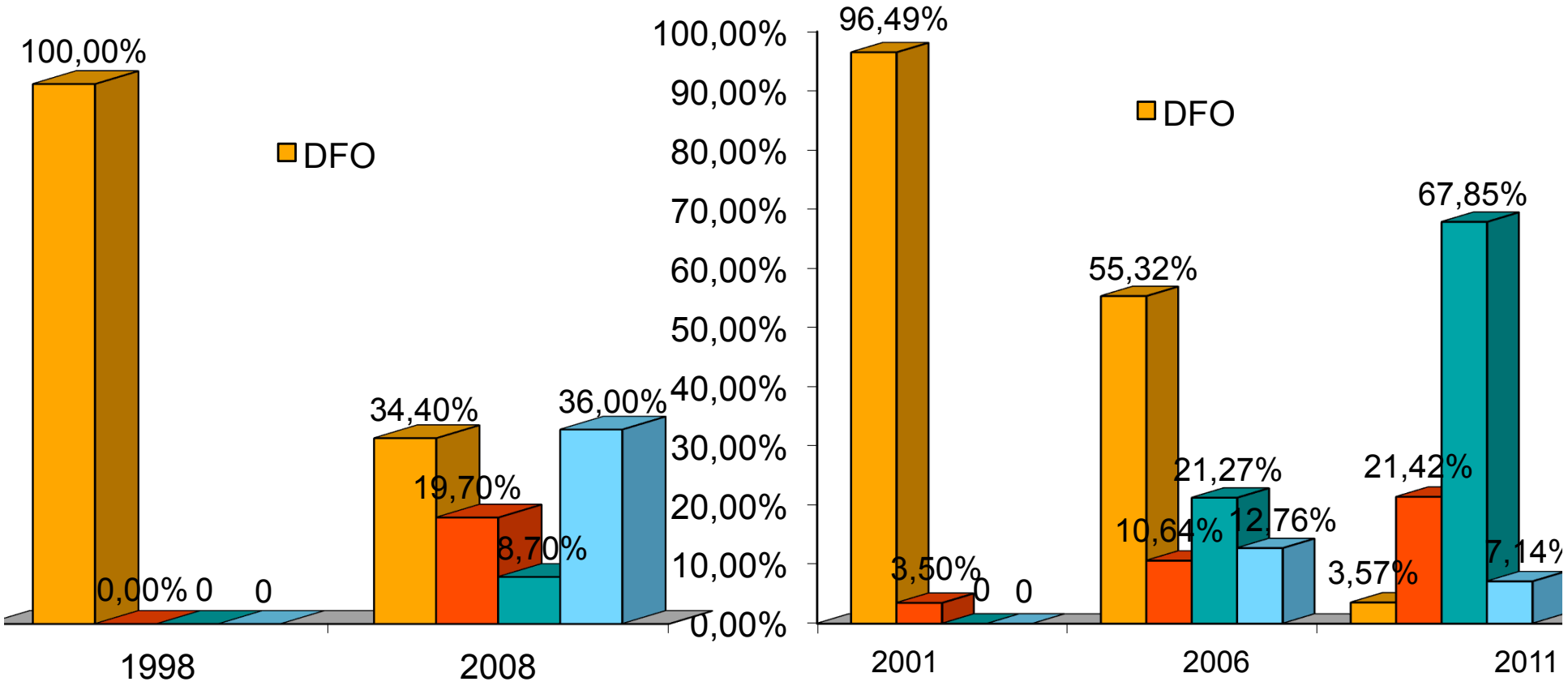
Concerns with Renal Toxicity

Main clinical and biological characteristics[a]	Number of patients	Baseline	Number of patients	After the introduction of deferasirox treatment	*p*
Daily dosage (mg/kg)	10	0	10	24.8±9.6 (10.0–36.0)	
Ferritin (µg/L)	10	1534±804 (300–2,697)	10	1558±923 (476–3,440)	NS
Glycosuria (mmol/L)	4	Normal (<0.5) *n*=4	10	Normal (< 0.5) *n*=7 Pathological n=3; 1.6±1.2 (0.6–2.9)	NS

Parameter	Baseline (N=10)	After DFX (N=10)	P
iGFR (ml/min per 1.73m^2)	125 ± 15 (103-155)	99 ± 13 (6-124)	0.005
eGFR (ml/min per 1.73m^2)	149 ± 33 (95-216)	124 ± 35 (72-180)	0.01
Pcr (µmol/L)	36 ± 9 (25-57)	47 ± 18 (31-85)	0.008
Ca/Ucr (mmol/mmol)	0.4 ± 0.2 (0.1–0.7)	0.8 ± 0.4 (0.3–1.6)	0.03
Magnesemia(mmol/L)	0.83 ± 0.09 (0.67–0.95)	0.94 ± 0.09 (0.83–1.09)	0.005
Plasma uric acid (µmol/L)	251 ± 52 (176-358)	187 ± 73 (96-336)	0.007
Uric acid clearance (ml/min per 1.73m^2)	11.1± 3.8 (8.4-20.2)	20.4 ± 11.6 (10.1-49.4)	0.007
Fractional excretion of uric acid (%)	9.2 ± 3.8 (5.8-18.1)	20.4 ± 10.1 (10.6-44.0)	0.005

Dubourg L, et al; Pediatr Nephrol (2012) 27:2115–2122

Treatment Allocation in Patients <18 years old



Elalfy MS et al;
Hematol Oncol Stem Cell Ther 2010; 3(4)-174-8

Kattamis et al, ESPHI 2011

Summary

- Iron overload and toxicity develop early
- Timely initiation of chelation therapy
- Choose iron chelator judiciously and adjust therapy accordingly
  - Growing / Developing body
  - Events may affect the rest of his/her life
  - Make treatment less painful
- Desferioxamine is effective but cumbersome a low therapeutic index and especially in young patients
- Deferasirox is effective, but close follow up of renal function necessary
- Data on deferiprone in pediatric patients parallel data on adults
- DEEP project underway

DEFERIPRONE EVALUATION IN PAEDIATRICS

شكرا

Ευχαριστώ

Thank you