

Iron chelation:treatment with Desferrioxamine and Deferiprone

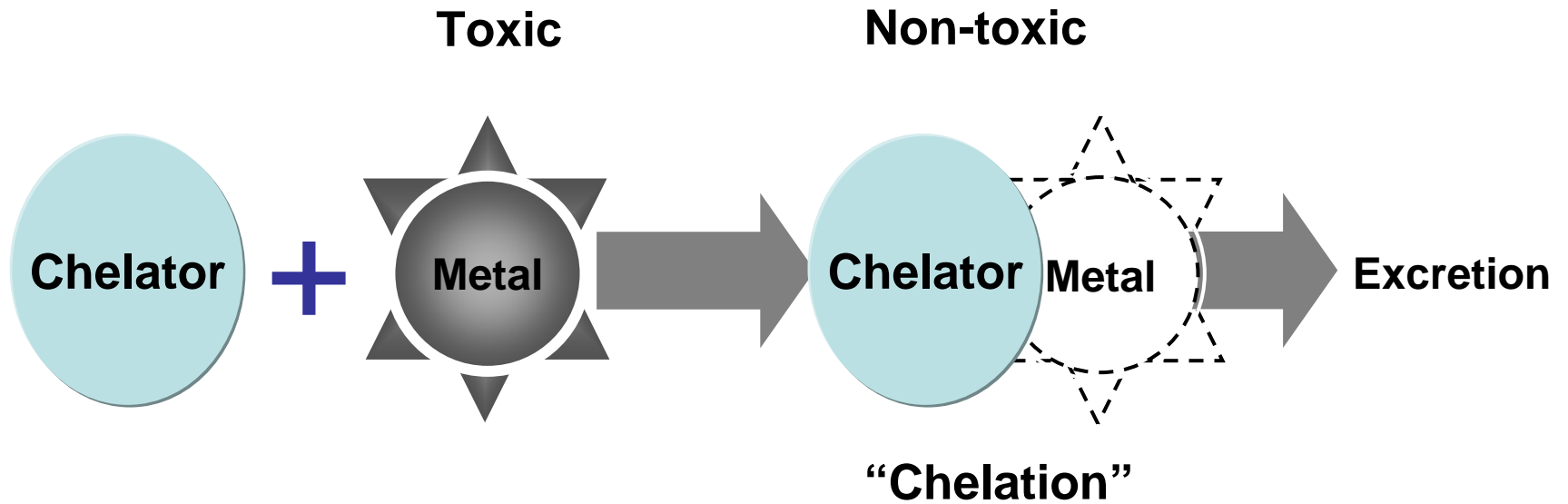
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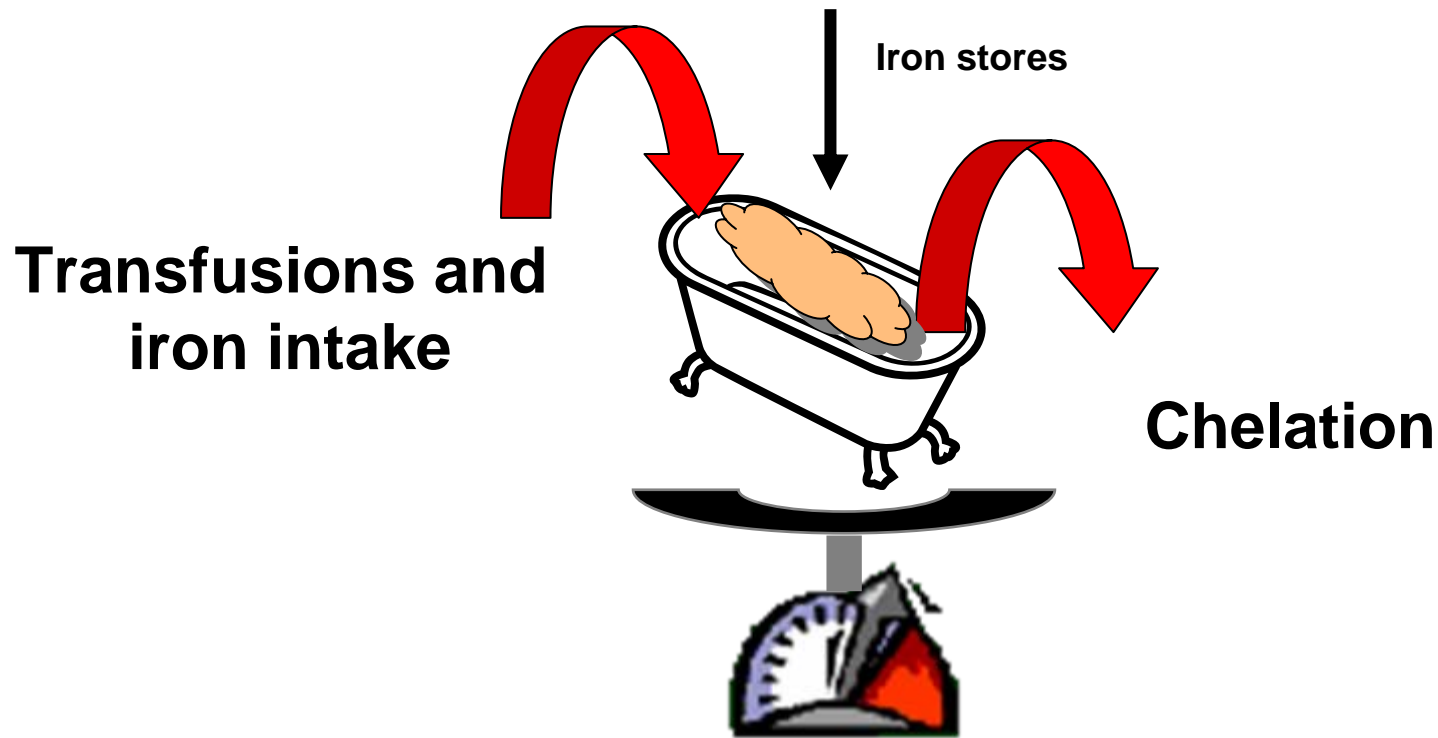


What is chelation therapy?

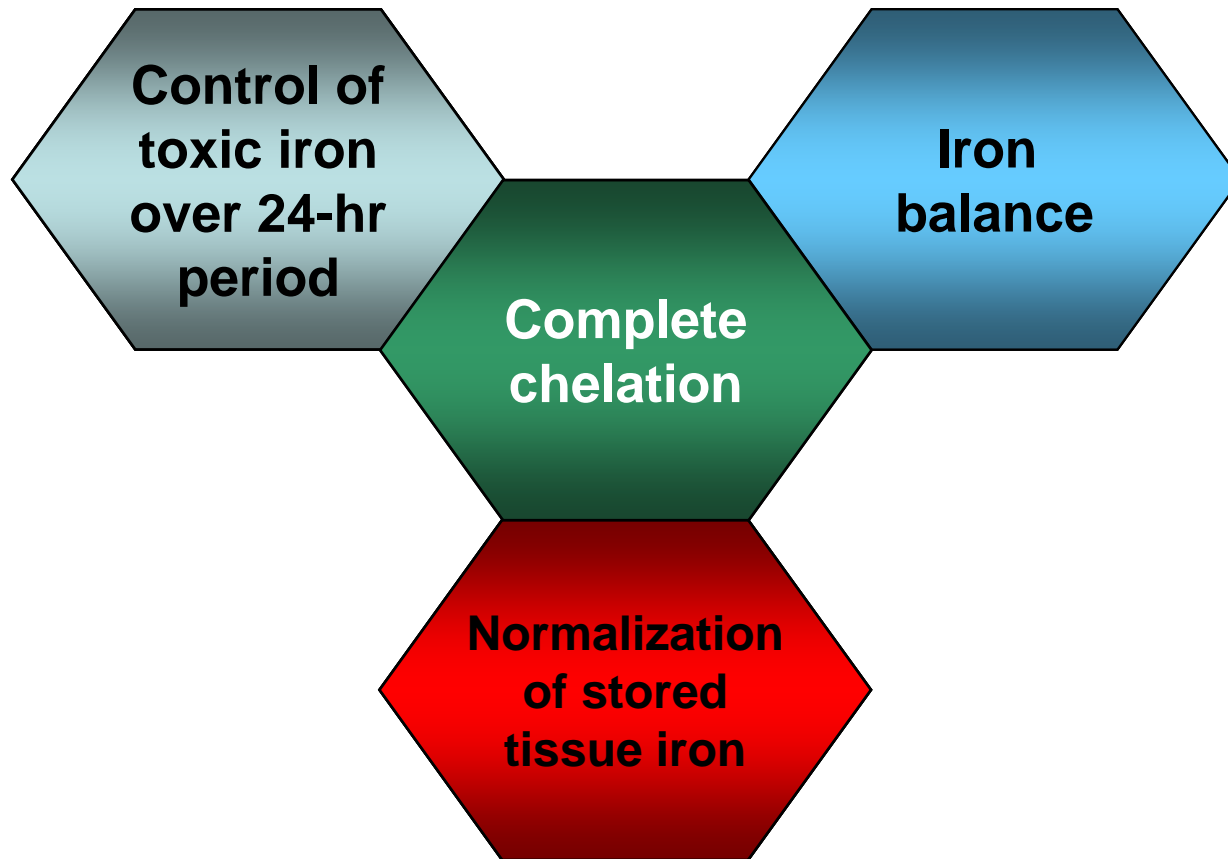


Goals of chelation treatment

The primary goals of iron chelation therapy are to remove excess iron and provide protection from the effects of toxic iron



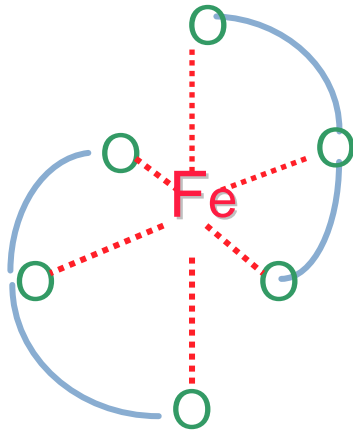
Primary goals of chelation therapy



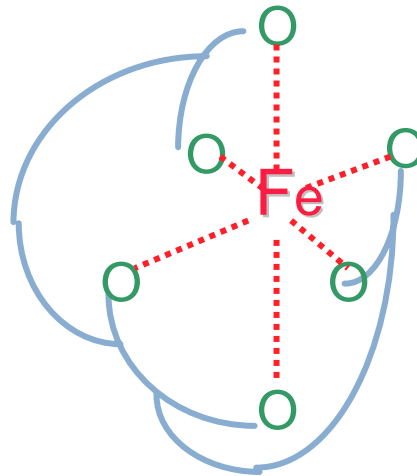
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Iron chelators

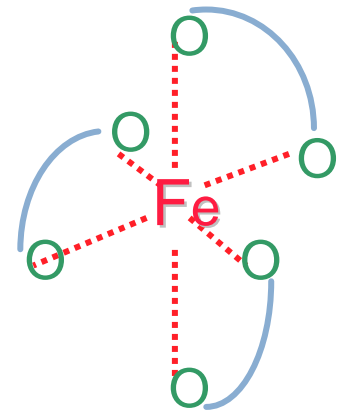
Tridentate
Deferasirox



Hexadentate
DFO



Bidentate
L1

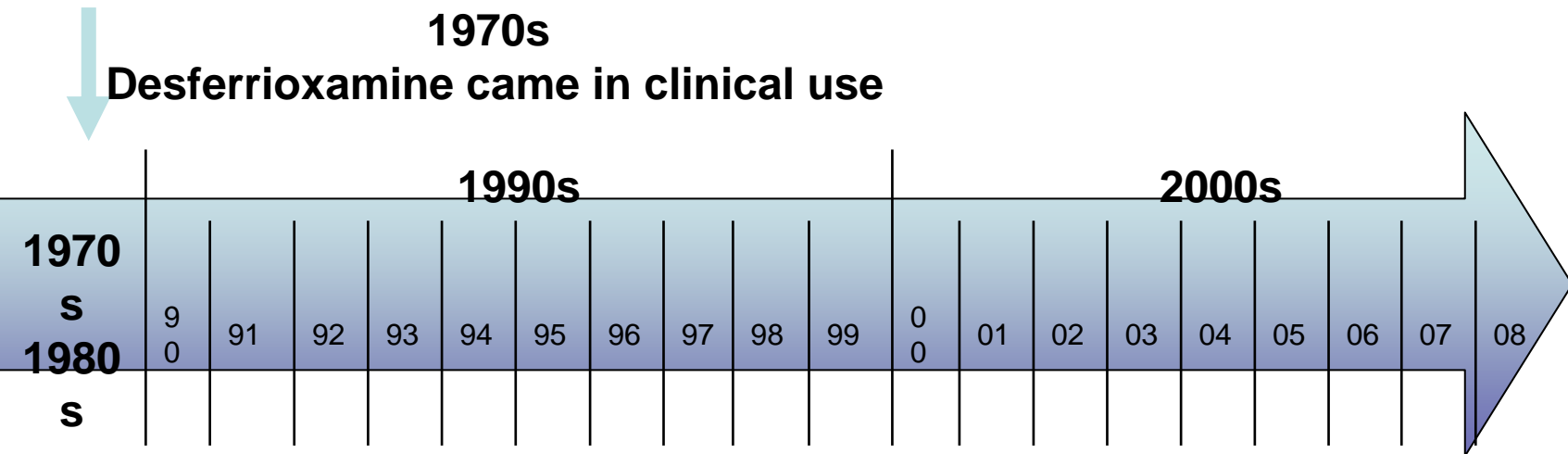


Overview of iron chelators

Property	Desferrioxamine	Deferiprone
Usual dose	20–60 mg/kg/day	75–100 mg/kg/day
Route	s.c., i.v. 8–12 h, 5 days/week	Oral 3 times daily
Half-life	20–30 min	2–3 h
Excretion	Urinary, faecal	Urinary

Deferiprone Summary of Product Characteristics.
Desferrioxamine Summary of Product Characteristics.

Evolution of iron chelation therapy



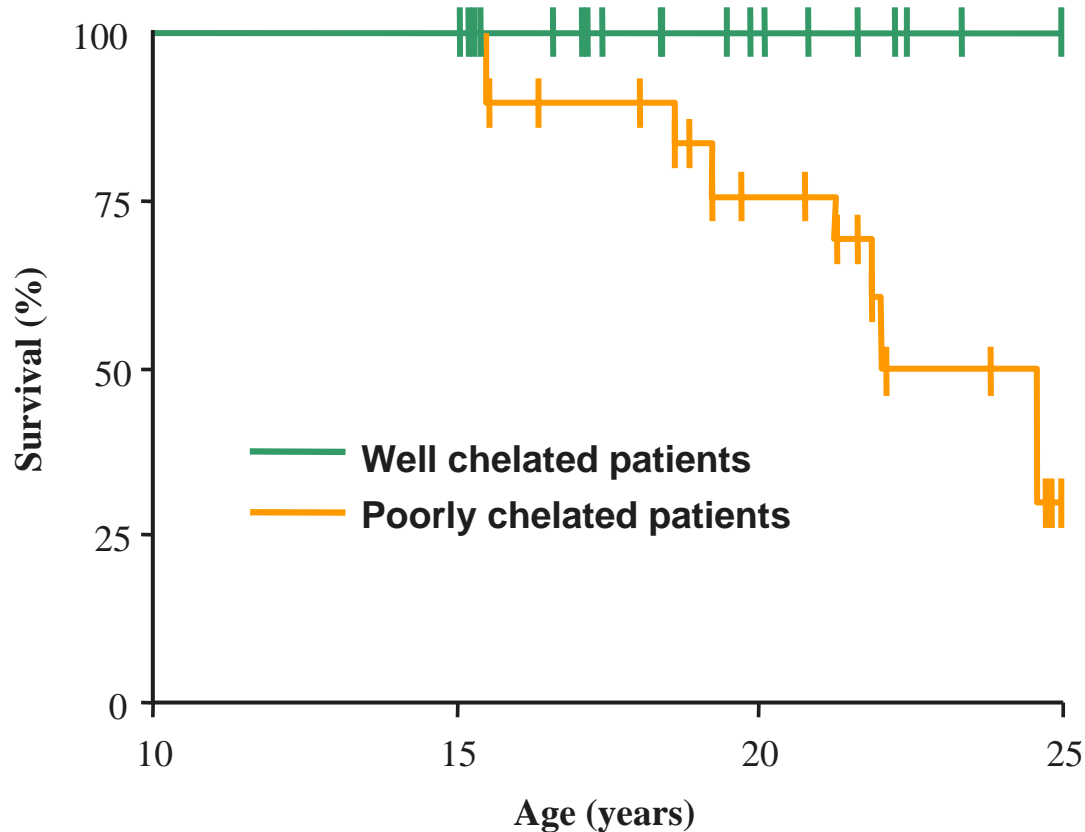
Indication: treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anaemias¹

Chelation therapy with DFO

- In clinical use since the 1970s, DFO has demonstrated impact on survival and iron overload-related complications if:
 - Initiated within 2–3 years of start of transfusions
 - Administered regularly and in adequate doses
 - 30-50 mg/kg \geq 5 times/week to achieve significant decrease in LIC
- Intensive chelation with DFO (continuous 24-hr sc or iv infusions) are indicated for:
 - Persistently high serum ferritin
 - LIC >15 mg/g dw
 - Significant heart disease (cardiac dysrhythmias, \downarrow LVEF)
 - Prior to pregnancy or bone marrow transplantation

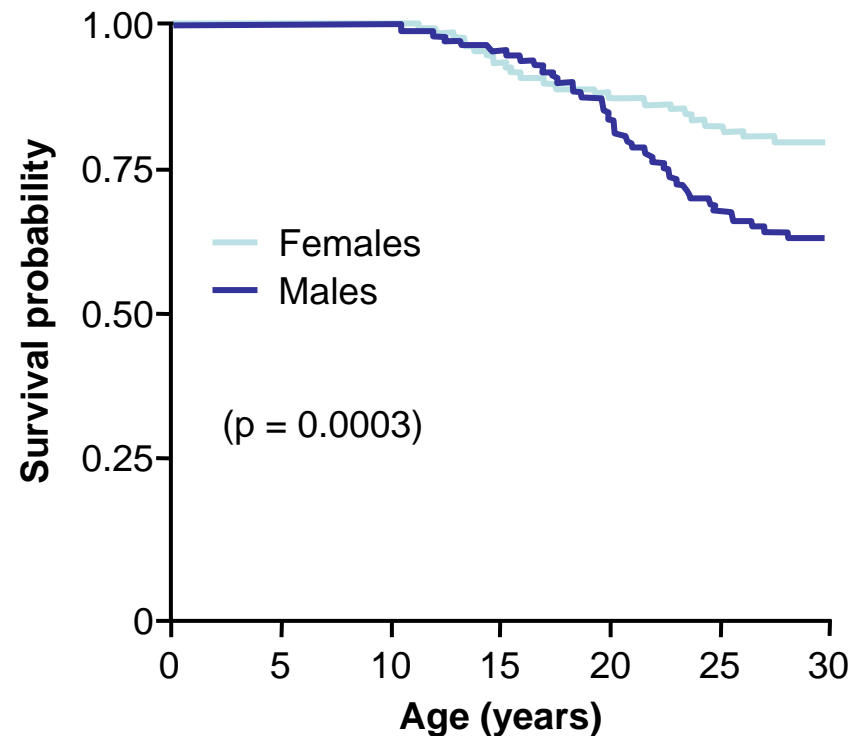
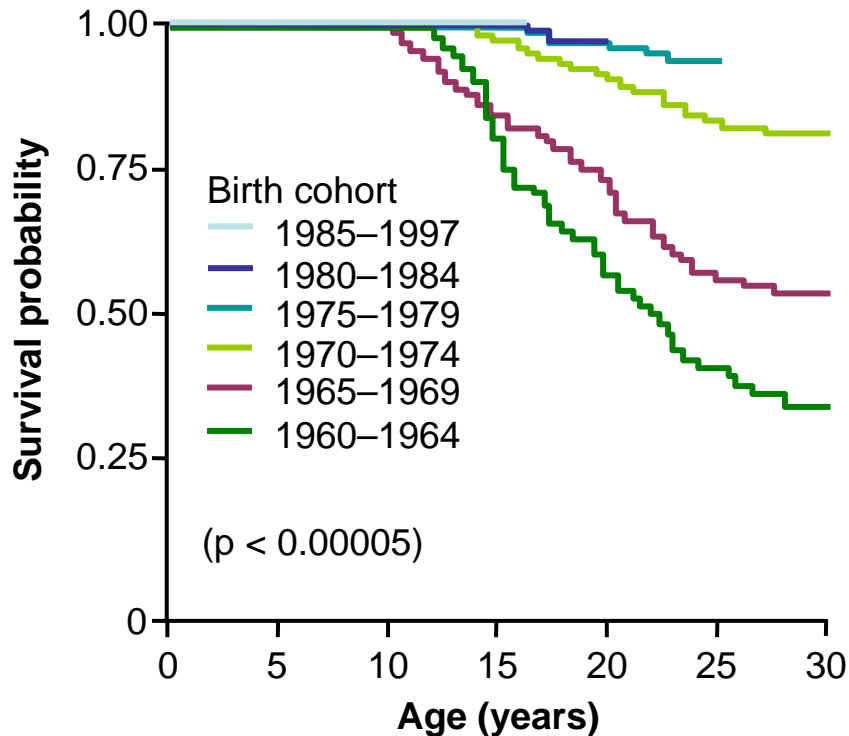
May be used in second and third trimesters of pregnancy

Chelation therapy and survival



The probability of survival to at least 25 years of age in poorly chelated patients was just one-third that of patients whose iron levels were well managed

Survival in β -thalassaemia major



- Risk factors for mortality in β -thalassaemia major include: serum ferritin levels $> 2,500 \mu\text{g/L}$ (HR: 3.7); arrhythmia (HR: 2.4); male sex (HR: 1.9); heart failure (HR: 11.3)

Safety profile of desferrioxamine

- **Adverse events associated with deferoxamine¹**
 - local reactions
 - high-frequency hearing loss
 - retinopathy
 - allergy
 - poor growth
 - gastrointestinal symptoms
 - *Yersinia* infections
- **Risk of over-chelation^{2,3}**
 - there is a link between risk of deferoxamine toxicity and low iron stores
 - the aim is to keep the therapeutic index < 0.025 at all times.² This seems to be especially important in patients with serum ferritin levels < 1,000 µg/L or with diabetes
 - the therapeutic index was initially used with regard to audiometric toxicity. It is also used to limit retinal toxicity and recommended for skeletal toxicity³

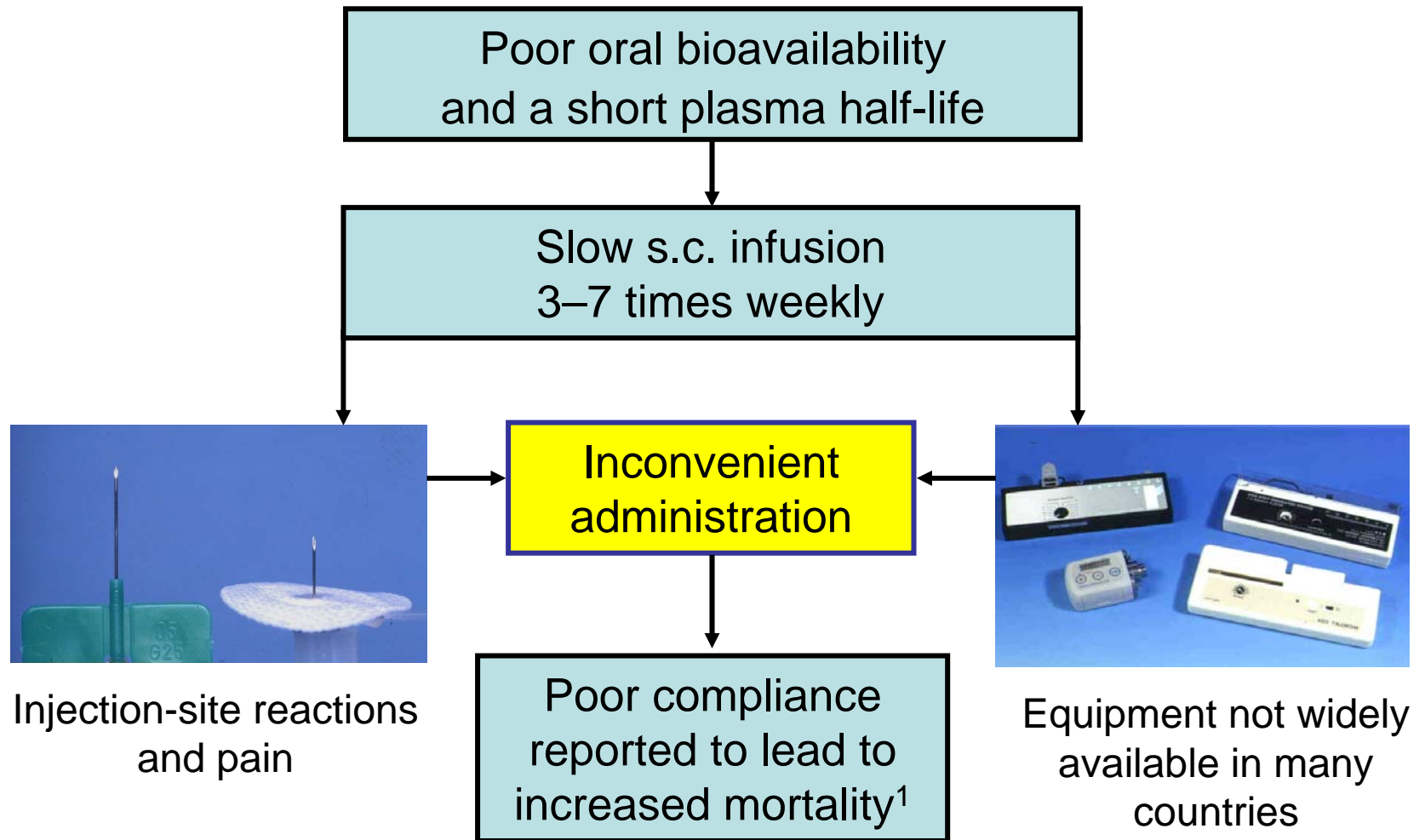
$$\text{Therapeutic index} = \frac{\text{mean daily dose of deferoxamine (mg/kg)}}{\text{serum ferritin (}\mu\text{g/L)}}\text{}$$

1. Cunningham MJ, et al. Blood. 2004;104:34-9.

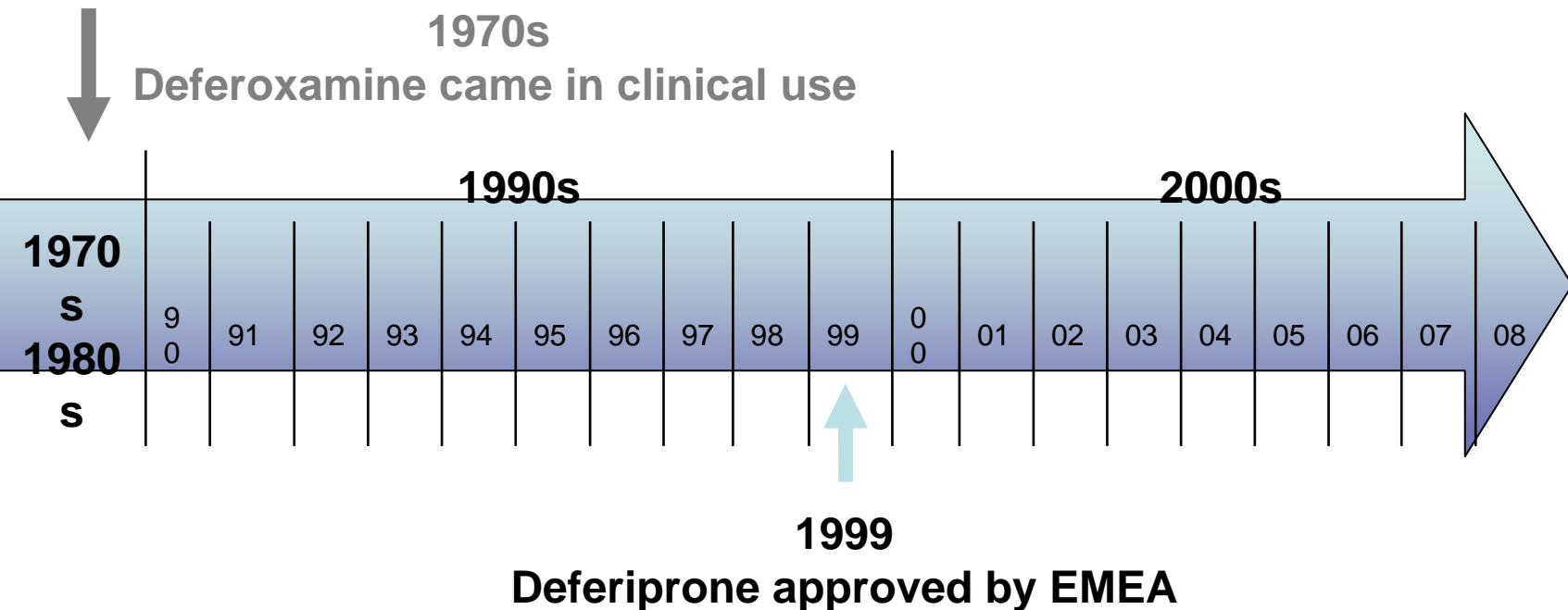
2. Porter JB, et al. Br J Haematol. 1989;73:403-9.

3. Davis BA, Porter JB. Adv Exp Med Biol. 2002;509:91-125.

Limitations of deferoxamine therapy



Evolution of iron chelation therapy



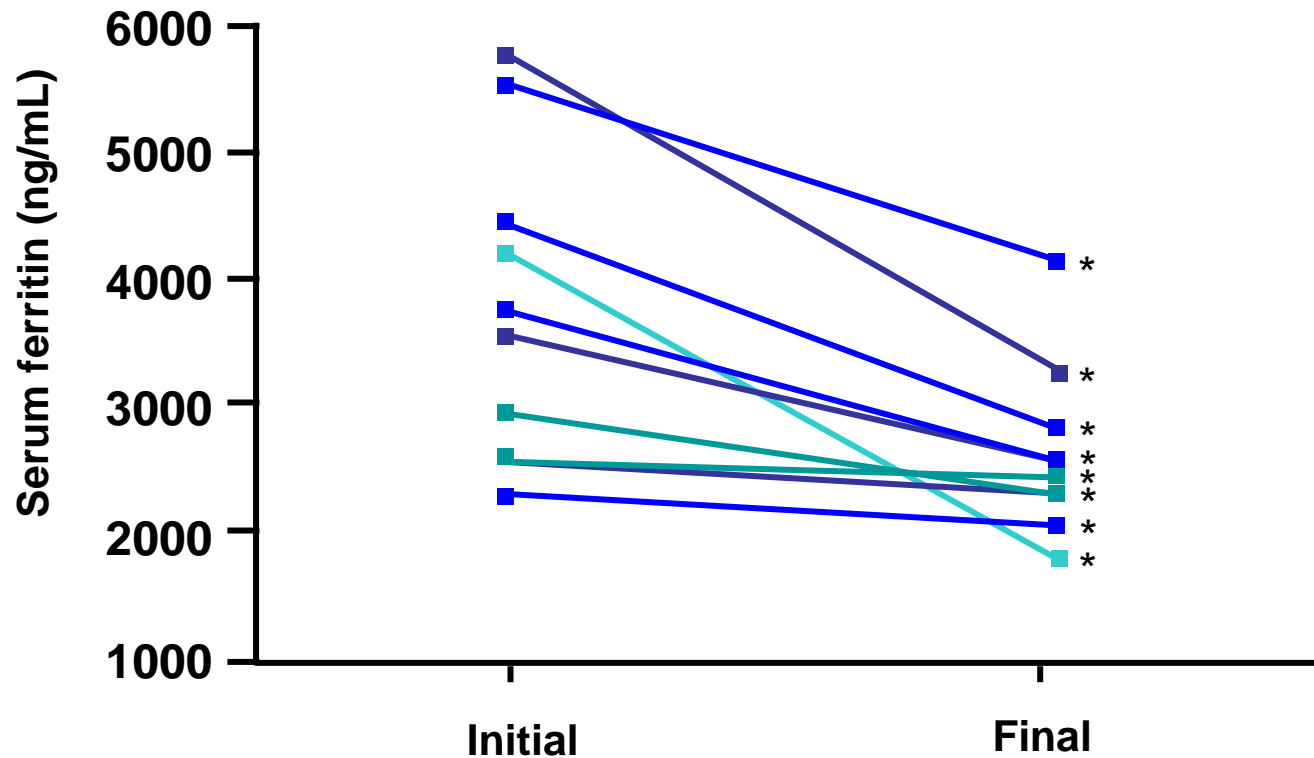
Indication: treatment of iron overload in patients with thalassaemia major for whom desferrioxamine therapy is inadequate, intolerable

Chelation therapy with deferiprone

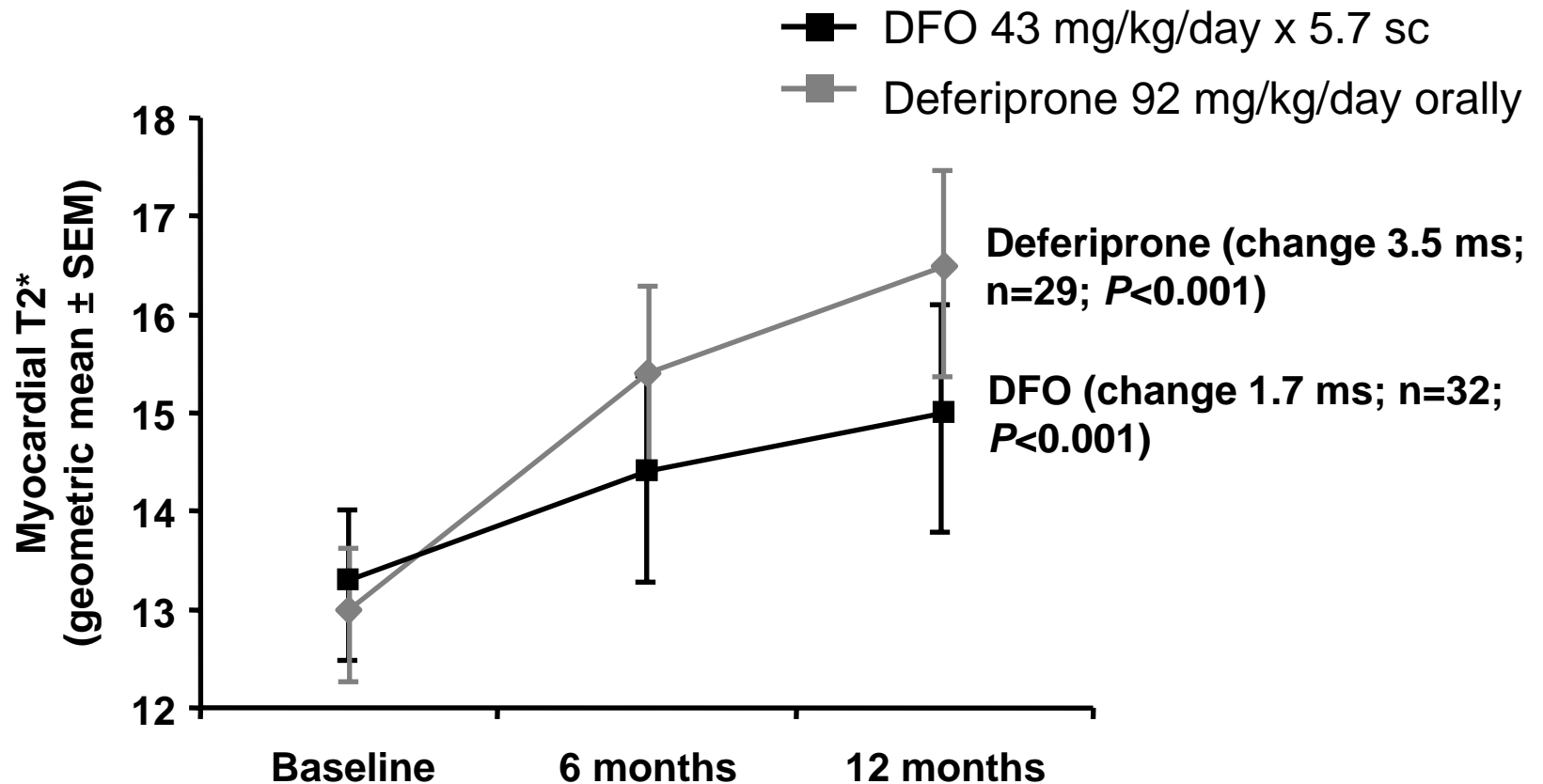
- Deferiprone has been available in various countries outside the US and Canada since the late 1990s
- The European Union granted marketing approval for deferiprone in 1999 under the “exceptional circumstances” policy that requires further studies. Deferiprone achieved full-marketing authorization in Europe in April 2002
- There are a large numbers of publications on effects of deferiprone but mostly not RCT studies
 - 10 small RCTs in 400 patients currently underway
- In Europe, deferiprone is licensed for second-line treatment in patients unable to use DFO or when DFO has been ineffective
 - Children above 10 years
- Standard dose is 75 mg/kg/day in three divided doses
 - Limited data for dosing up to 100 mg/kg/day
- Weekly blood counts are required throughout treatment
- Treatment should be stopped during pregnancy

Effect of deferiprone therapy on serum ferritin levels

10 studies (11–162 patients); duration 6–>56 months



Prospective improvement in myocardial T2* with DFO and deferiprone monotherapy

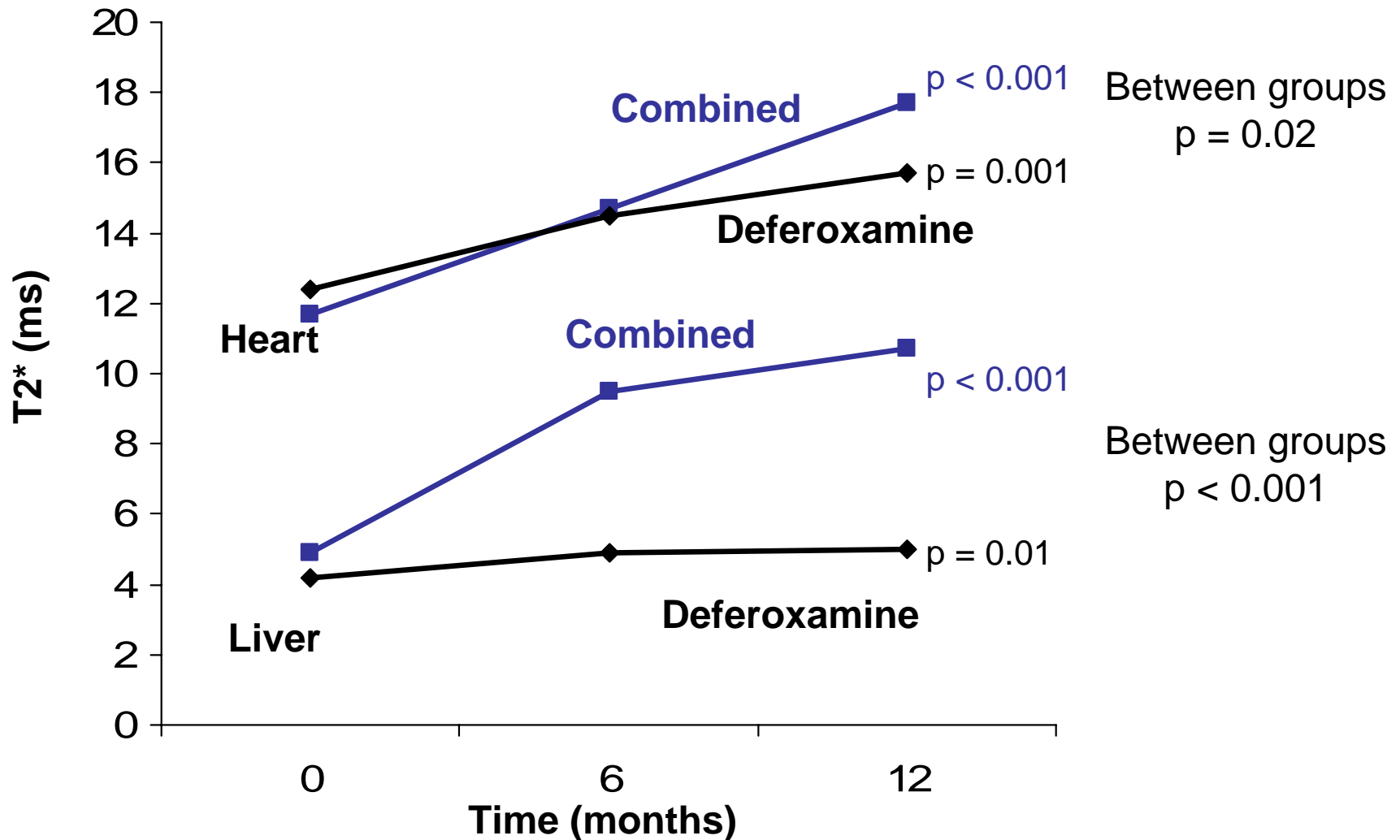


Combination therapy: DFO and deferiprone

- A variety of regimens combining DFO and deferiprone have been used by clinicians
 - usually when monotherapy with either chelator has failed to control the iron burden or its effects
- Most regimens comprised deferiprone daily plus DFO with varying frequency and dosing
 - most used relatively low and intermittent DFO doses and daily deferiprone

The simultaneous use of these drugs has not been tested formally in sufficiently large patient groups to allow firm, evidence-based recommendations about efficacy and safety

Desferrioxamine alone vs combination Regimen



Long-term sequential DFP–DFO versus DFP alone

Year	Sequential DFP–DFO group			DFP group		
	N	Mean ± SD	Difference ± SD	N	Mean ± SD	Difference ± SD
0	105	1,787 ± 735	–	108	1,890 ± 816	–
1	78	1,400 ± 770	-417 ± 589	74	1,633 ± 841	-132 ± 724
2	65	1,480 ± 867	-362 ± 803	53	1,742 ± 923	-126 ± 732
3	55	1,351 ± 754	-403 ± 697	44	1,734 ± 1,037	5.4 ± 870
4	38	1,408 ± 869	-395 ± 940	33	1,856 ± 1,315	184 ± 1,036
5	32	1,369 ± 816	-396 ± 894	26	1,588 ± 1,217	-115 ± 1,009

- Randomized open label trial with 213 patients with β -thalassaemia major
- DFP: 75 mg/kg/day, 4 days a week + DFO s.c. 50 mg/kg/day (8 h), 3 days a week (105 patients)
- DFP: 75 mg/kg/day, 7 days a week (108 patients)
- Decrease of serum ferritin levels was statistically significantly higher in sequential DFP–DFO patients compared with patients on DFP alone
- Kaplan-Meier survival analysis for the 2 chelation treatments did not show any statistically significant differences

Adverse event	Sequential DFP–DFO group		DFP group	
	N	%	N	%
Agranulocytosis	–	–	3	3.4
Neutropenia	15	23.1	11	12.5
Arthralgia	5	7.7	6	6.8
Gastrointestinal problems	7	10.8	16	18.2
↑ALT	22	33.8	23	26.1
Total	49	–	59	–

Survival follow-up of patients initially randomized to monotherapy or combined therapy

- Design
 - survival in 265 Italian patients initially considered for randomization
 - monotherapy DFO or DFP, or sequential or combined DFP–DFO
 - no doses specified
- Analysis
 - analysed as 2 treatment groups
 - 124 patients who received DFO
 - 141 patients who received DFP alone (n = 55), sequential DFP–DFO (n = 68), and combined DFP–DFO (n = 18)
 - patients not randomized also included in analysis
 - deaths in patients switched from DFP or combination with DFO analysed as “death on DFO”
- Results
 - 12 deaths, 7 of which were related to cardiac disease
 - 6/7 had received DFO prior to death
 - none of these had been initially randomized to DFO (4 were not randomized and 2 were initially randomized to DFP)

Survival follow-up of patients initially randomized to monotherapy or combined therapy (cont.)

Age at start trial	Chelation treatment during trial	Cause of trial withdrawal	Months between withdrawal and death	Treatment before death	Cause of death
35	Not in study	–	–	DFO	Heart failure
23	Not in study	–	–	DFO	Heart failure
29	DFP	Failure of treatment	18	DFO	Heart failure
10	Not in study	–	–	DFO	BMT
18	DFP	Gastrointestinal problems	60	DFO	Myocarditis
41	DFP	Pancreas cancer	12	DFO	Pancreas cancer
53	Not in study	–	–	DFO	Liver failure
41	DFP–DFO	Liver cancer	11	DFO	Liver cancer
46	DFP	Gastrointestinal problems	34	DFO	Stroke
26	DFP–DFO	Arrhythmia	5	DFP–DFO	Arrhythmia
15	Not in study	–	–	DFO	Heart failure
40	Not in study	–	–	DFO	Heart failure

Combination therapy: DFO and deferiprone (cont.)

- Combination therapy can control iron overload and improve cardiac iron levels
- No recommendations can currently be made regarding the optimal combination
- Agranulocytosis may be more frequent with combination therapy (particularly simultaneous regimens)
- For patients with very high levels of cardiac iron or cardiac dysfunction, 24-hour treatment with DFO and daily therapy with deferiprone should be strongly considered

The simultaneous use of these drugs has not been tested formally in large enough patient groups to allow firm, evidence-based recommendations about efficacy and safety

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**Improved survival of thalassaemia major in the UK and relation to T2*
cardiovascular magnetic resonance**

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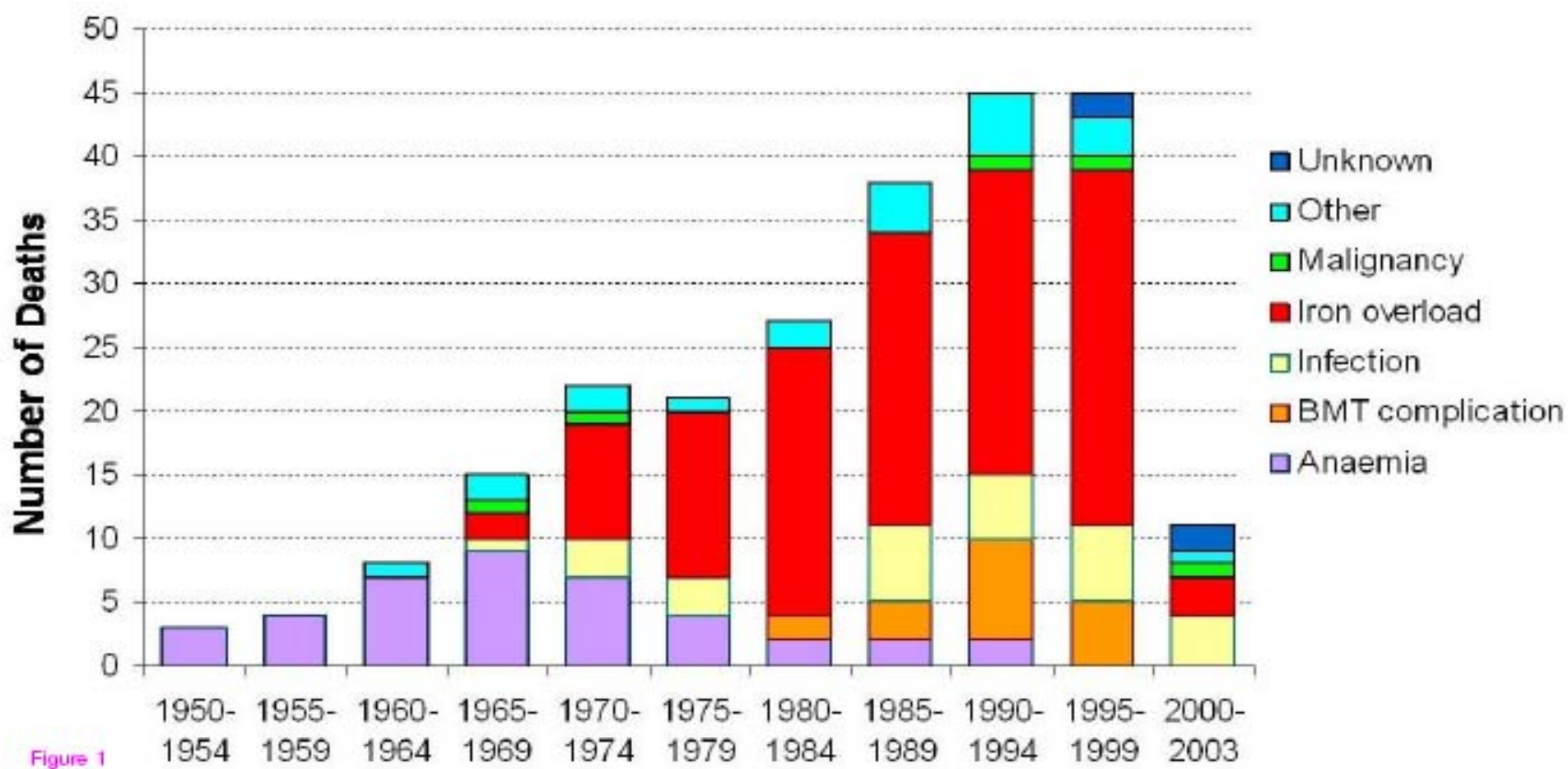
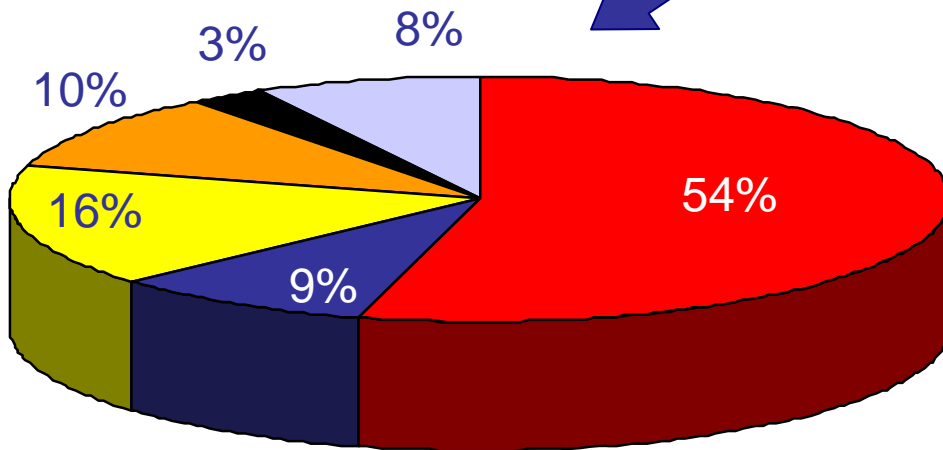
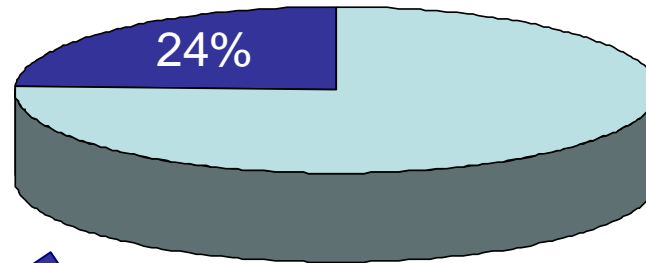


Figure 1

CAUSES OF DEATH

ALIVE
DEAD



CARDIAC
INFECTION
ANEMIA
BMT
NEOPLASM
OTHER

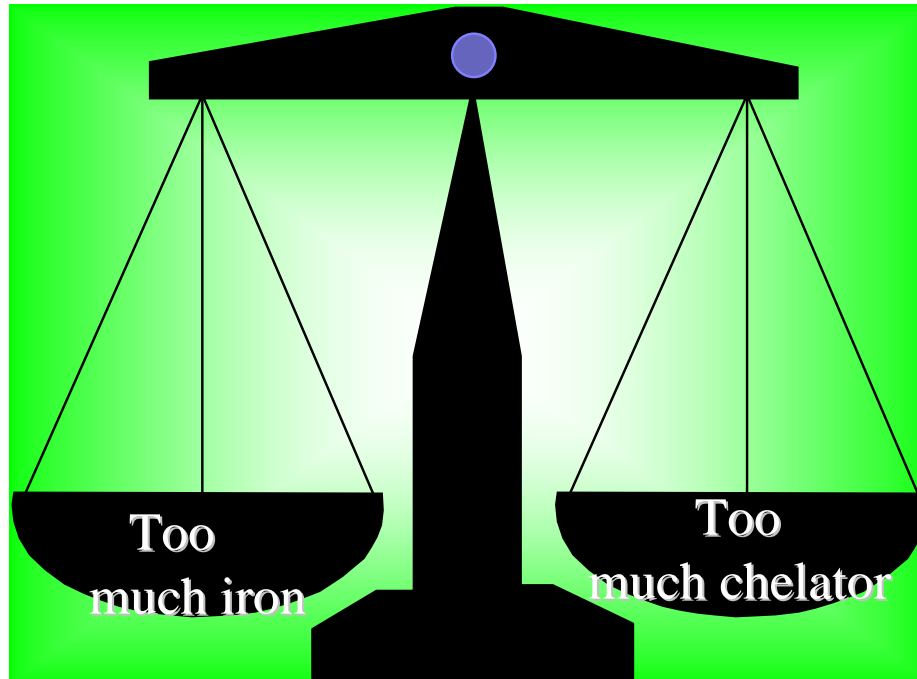
Yersinia	2
Pneumococcus	1
Klebsiella	4

United Kingdom

- ✓ Disposable DFO infusors
- ✓ Deferiprone alone and in combination with DFO
- ✓ T2* Cardiac MRI
- ✓ National register
- ✓ Referral to centres of excellence
- ✓ Activities of UKTS

Chelation treatment of iron overload a question of balance

Uncoordinated
iron
Free radical
generation
Organ damage
Growth failure
Organ failure
Cardiac death



Uncoordinated
chelator
Inhibition of
metalloenzymes
Neurotoxicity
Growth failure
Bone Marrow
toxicity

Chelation treatment algorithm

