



**DEFERIPRONE**  
**EVALUATION IN**  
**PAEDIATRICS**

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# Review on Effectiveness and Safety of combination treatment with Deferoxamine (DFO) – Deferiprone(DFP) treatment

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# MAIN AIMS

- Evaluation of effectiveness and safety on combined chelation treatment with DFO and DFP in patients with Thalassemia Major (TM) using three published meta-analysis studies;
- Review Italian cohorts studies on this kind of treatment;



# WHY TO USE META-ANALYSIS STUDIES ?

Using the levels of evidence for individual class assignments according to the ACC/AHA (Klocke et al, 2003)

<b>A</b>	Data derived from multiple randomised clinical trials
<b>B</b>	Data derived from a single randomised trial, or from non randomised studies
<b>C</b>	Consensus opinion of expert



# OUTCOMES CONSIDERED IN META-ANALYSIS STUDIES

## EFFECTIVENESS

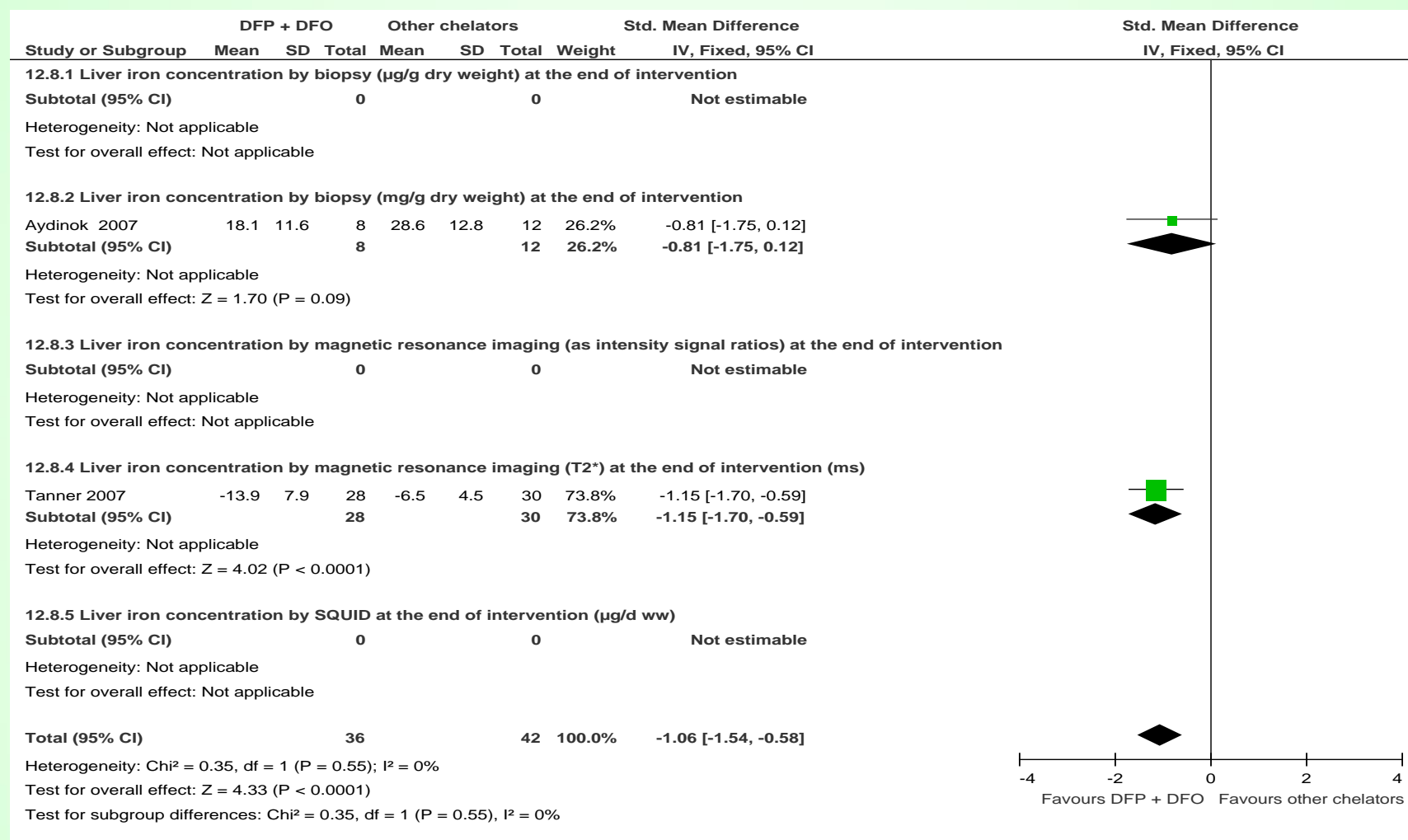
- Liver iron concentration as mean change from baseline
- Serum ferritin at the end of intervention
- Changes in Ejection fraction
- Changes in Urinary Iron Excretion

## SAFETY

- Side Adverse Events (SAEs)



# LIVER IRON CONCENTRATION AT THE END OF INTERVENTION IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS OTHER CHELATORS



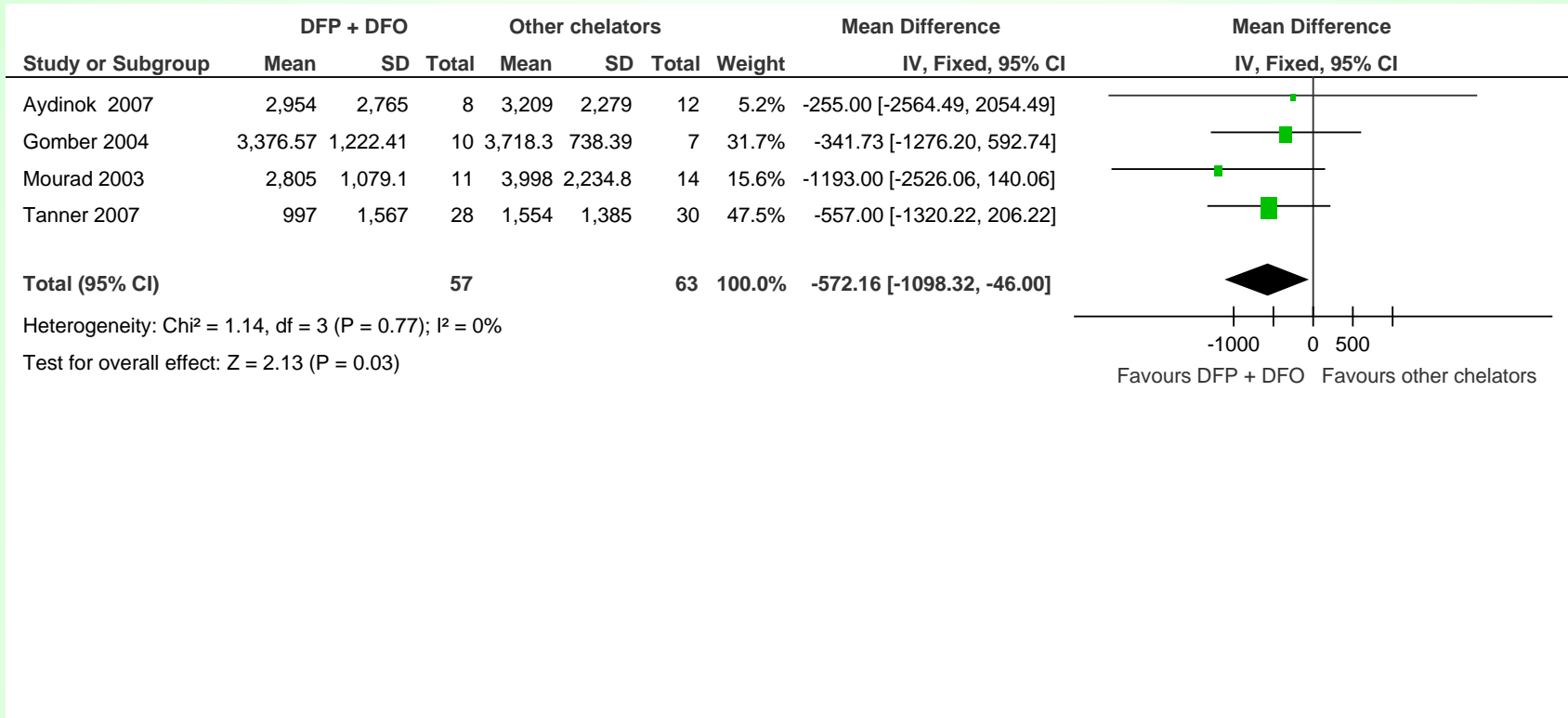
**Maggio A et Al . Iron chelation therapy in thalassemia major: a systematic review with meta-analyses of 1520 patients included on randomized clinical trials. Blood Cells Mol. Dis. 2011 Oct 15;47(3):166-75.**



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# SERUM FERRITIN AT THE END OF INTERVENTION (NG/ML) IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS OTHER CHELATORS



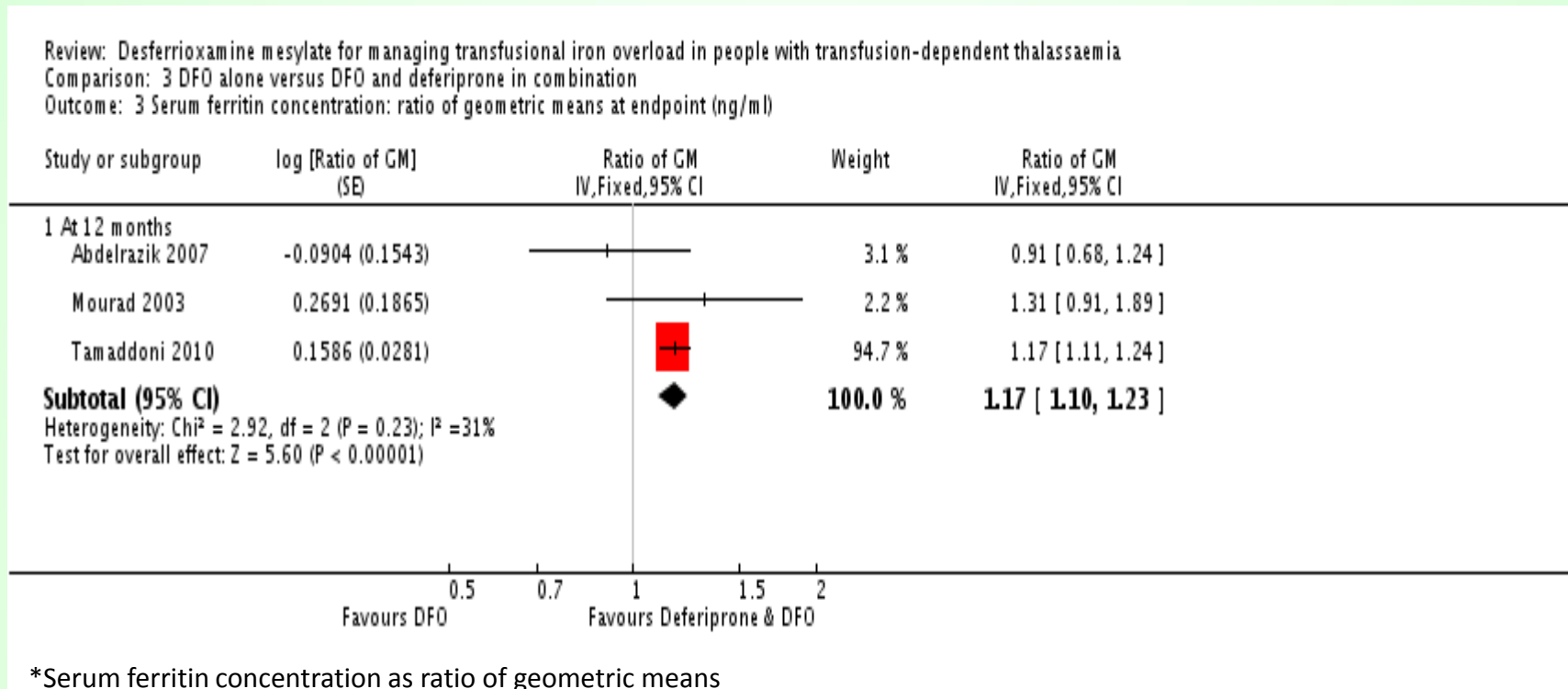
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## \* SERUM FERRITIN AT THE END OF INTERVENTION (NG/ML) IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS DFO



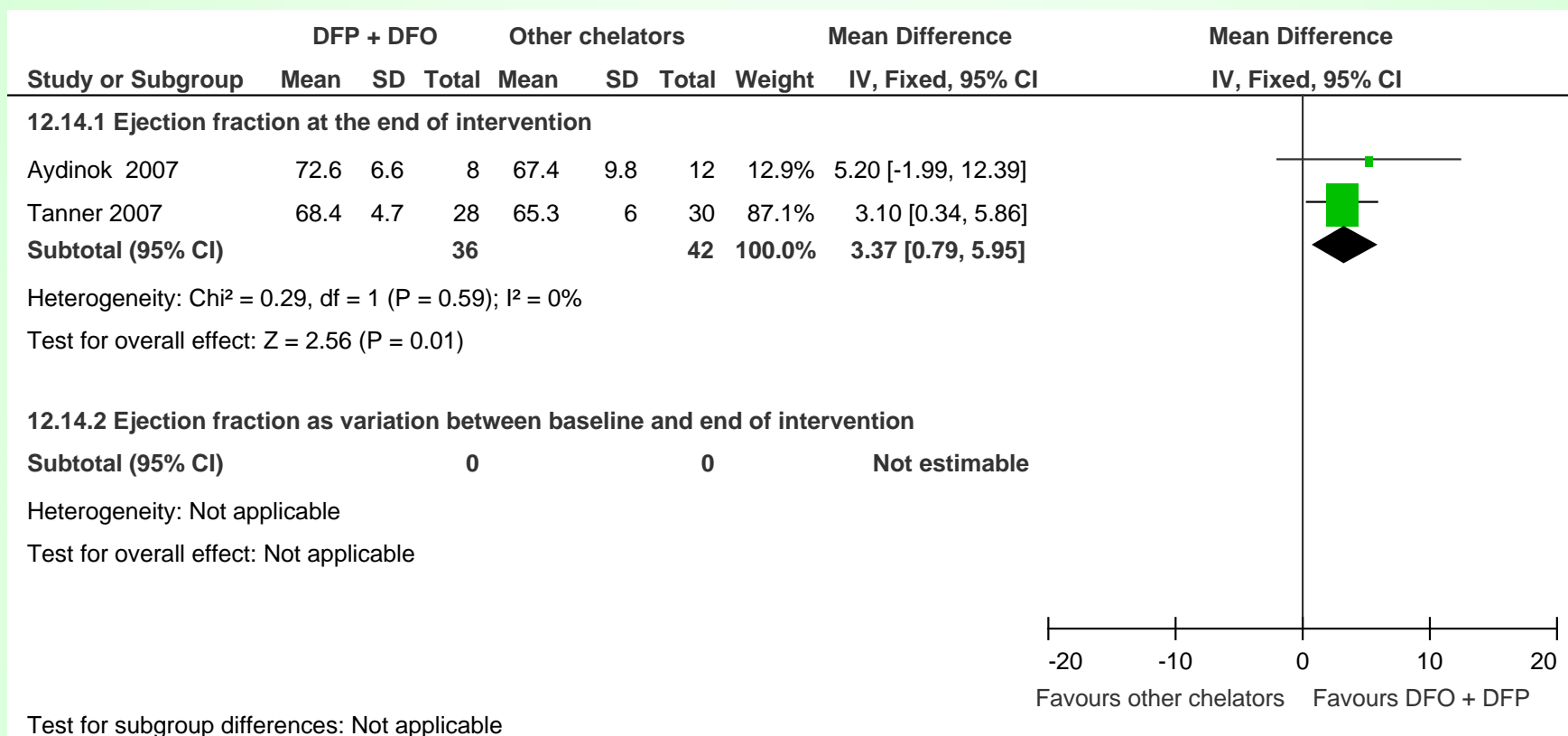
Fisher SA et Al . *Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia*. Cochrane DatabaseSyst. Rev. 2013 Aug 21;8:CD004450.



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# EJECTION FRACTION IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS OTHER CHELATORS



Maggio A et Al . *Iron chelation therapy in thalassemia major: a systematic review with meta-analyses of 1520 patients included on randomized clinical trials. Blood Cells Mol. Dis.* 2011 Oct 15;47(3):166-75.



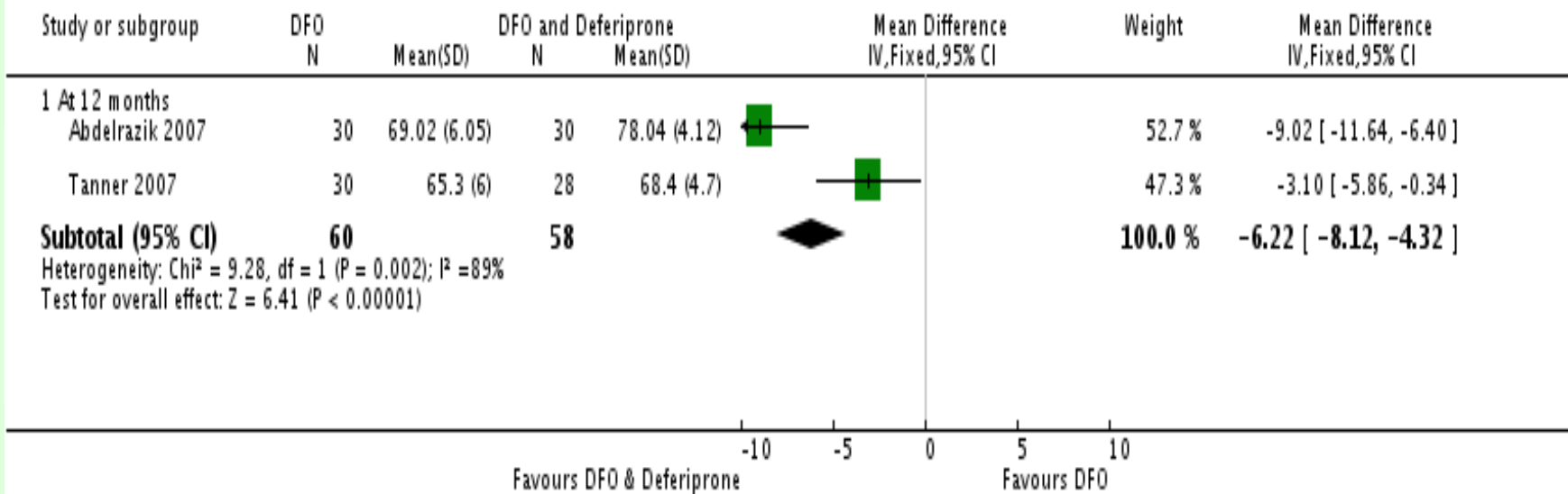
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# EJECTION FRACTION IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS DFO

Review: Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia  
 Comparison: 3 DFO alone versus DFO and deferiprone in combination  
 Outcome: 1 Left ventricular ejection fraction: mean at endpoint (%)



Fisher SA et Al . *Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia*. Cochrane DatabaseSyst. Rev. 2013 Aug 21;8:CD004450.



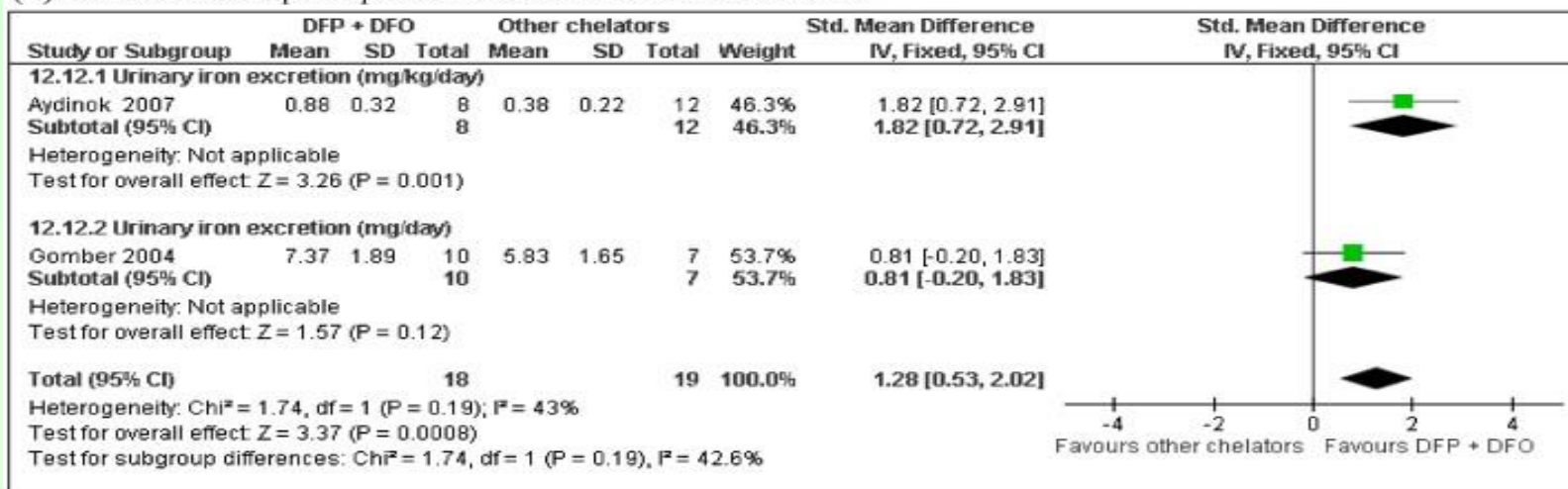
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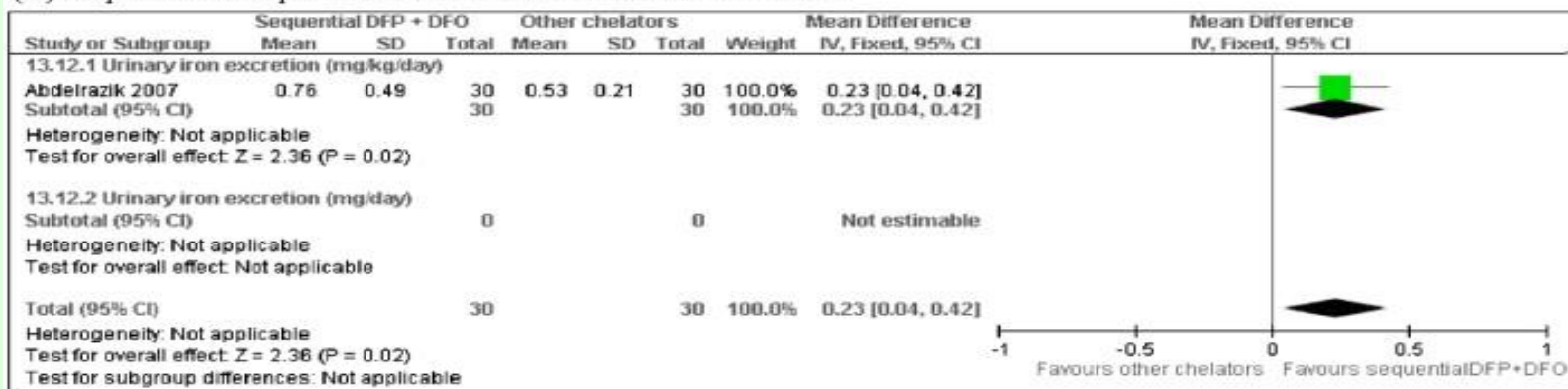
# URINARY IRON EXCRETION IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS OTHER CHELATORS

## Outcome 5 Urinary Iron Excretion

### (a) Associated deferiprone plus deferoxamine versus other chelators



### (b) Sequential deferiprone and deferoxamine versus deferoxamine



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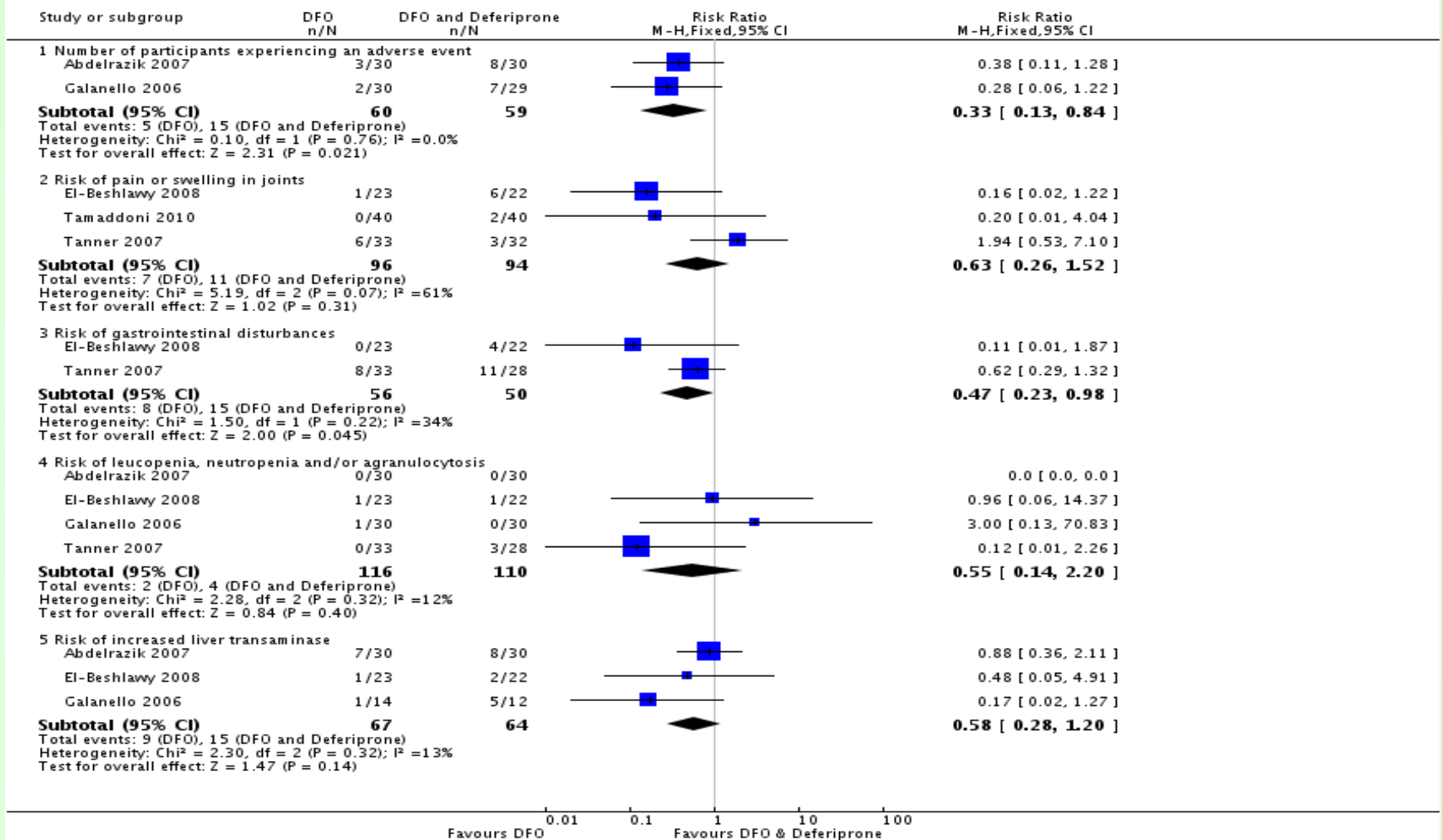


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# ADVERSE EVENTS IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS DFO

Review: Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia  
 Comparison: 3 DFO alone versus DFO and deferiprone in combination  
 Outcome: 11 Adverse events



Fisher SA et Al. *Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia.*  
 Cochrane Database Syst. Rev. 2013 Aug 21;8:CD004450.

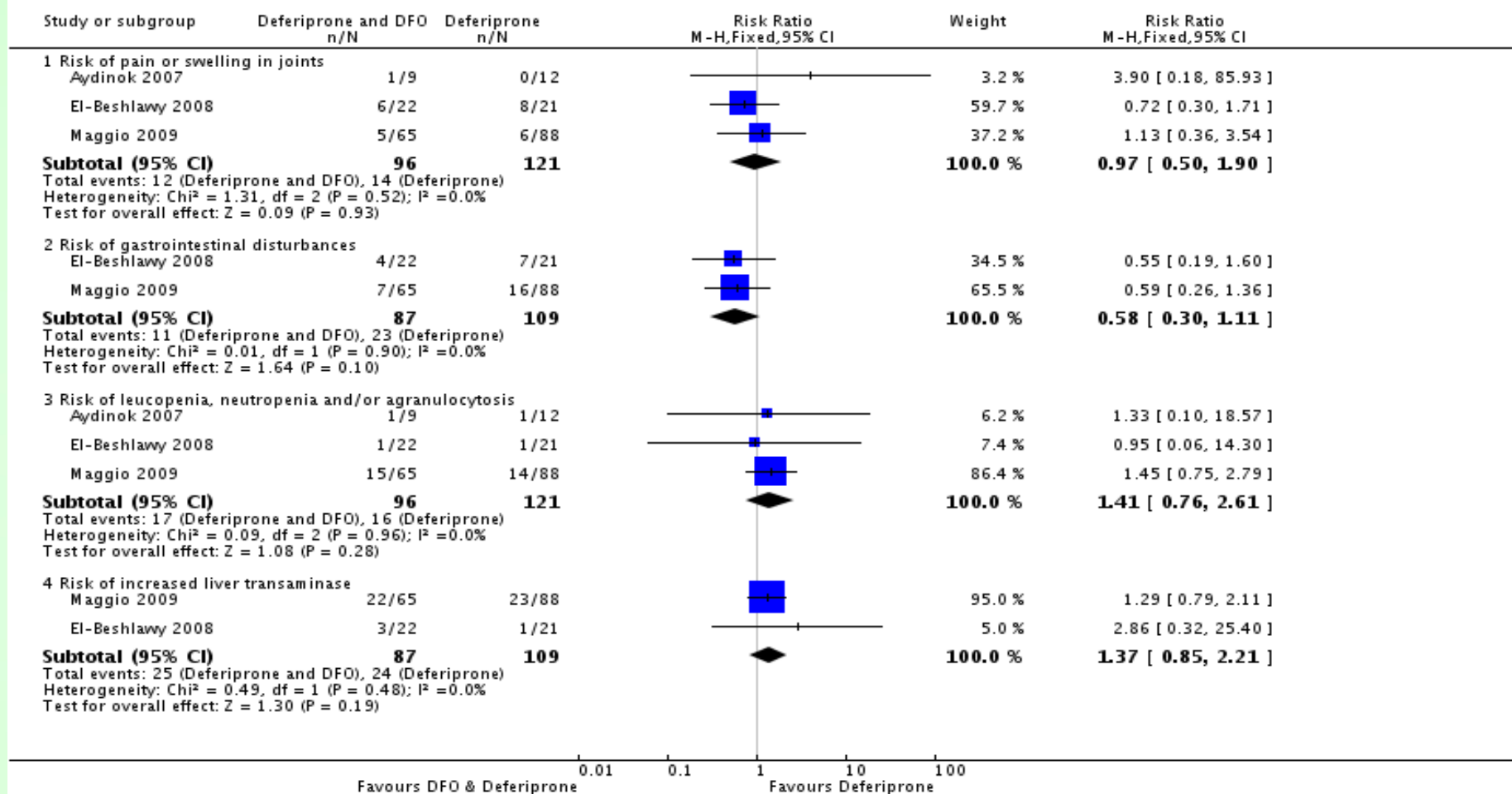


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# ADVERSE EVENTS IN THE COMPARISON OF DEFERIPRONE PLUS DEFEROXAMINE VERSUS DFP

Review: Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia  
Comparison: 2 DFO and deferiprone in combination compared with deferiprone alone  
Outcome: 10 Adverse Events



Fisher SA et Al . *Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia*.  
Cochrane DatabaseSyst. Rev. 2013 Aug 21;8:CD004450.



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# DEFERIPRONE AND DEFEROXAMINE COMBINED CHELATION TREATMENT: PUBLISHED SCHEDULES OF ADMINISTRATION

Study	Interventions	
	Dosage of DFP (mg/kg/day)	Dosage of DFO (mg/kg)
Aydinok, 2005	75 for 7 days/week	40-50 for 2 days/week
Abdelrazik, 2007	75 for 4 days/week	40 for 2 days/week
Gomber, 2004	75 in 2-3 divided doses	40 for 2 days/week
Tanner, 2007	75 in 2-3 divided doses	40-50 for 5 days/week
El-Beshlawy, 2008	60-83 for 7 days/week	23-50 for 2 days/week
Ha, 2006	75 in 3 divided doses for 7 days/week	30-60 for 2 days/week
Mourad, 2003	75 in 3 divided doses for 7 days/week	Total of 2 gr for 2 days/week
Tamaddoni, 2010	75 for 7 days/week	40-50 for 2 days/week
Galanello, 2006	25 weight 3xdaily for 5 days/week	20-60 for 2 days/week



# SUMMARY STATISTICS OF B-THALASSEMIA MAJOR PATIENTS FROM MIOT

Overall TM patients scanned/evaluated	1658/1548
Mean follow-up (months)	42,91 ± 20,36
Dead	23
Causes of death	
Heart failure	11
Cardiac arrest	3
Liver cirrhosis	1
TMO complication	1
Pulmonary embolism	1
Hepatocellular carcinoma	1
HCC	1
Lymphoma	1
Liver failure	1
NND septic shock	1
Car accident	1





# VALIDATION OF MAGNETIC RESONANCE T2\* TECNIQUE BASED ON ITALIAN POPULATION

	Global heart T2* (CoV %)	Mid-ventricular septum T2* (CoV %)	Liver T2* (CoV %)
Ancona	9,9	15,2	12,8
Campobasso	11,2	12,7	13,5
Catania	9,8	7,7	9,6
Palermo	7,7	7,1	17,9
Roma	4,2	22,2	10,3
All sites	8,9	14	14
All sites T2* < 20 ms	9,3	10,5	11,7
All sites T2* > 20 ms	7,9	12,8	10,2

Ramazzotti A, Pepe A, Positano V, Rossi G, De Marchi D, Brizi MG, Luciani A, Midiri M, Sallustio G, Valeri G, Caruso V, Centra M, Cianciulli P, De Sanctis V, Maggio A, Lombardi M. *Multicenter validation of the magnetic resonance T2\* technique for segmental and global quantification of myocardial iron*. J Magn Reson Imaging. 2009 Jul;30(1):62-8. doi: 10.1002/jmri.21781.



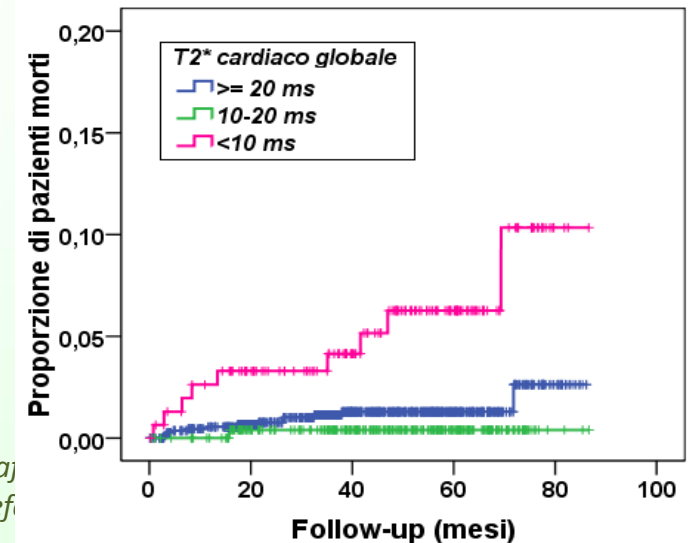
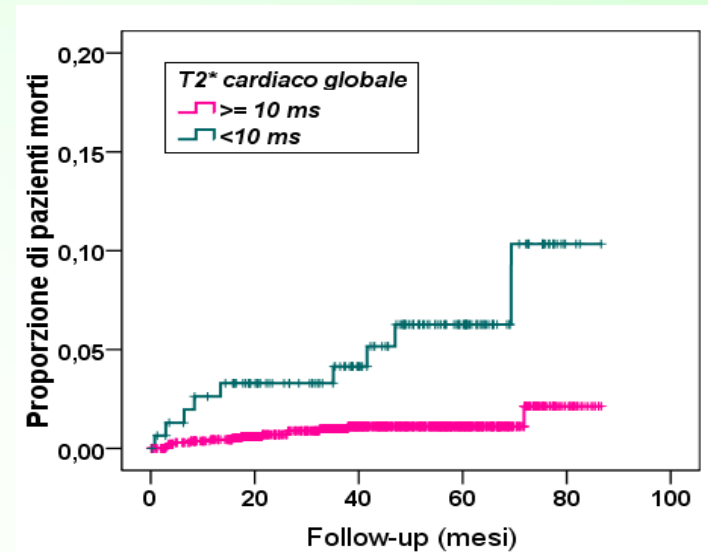
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# UNIVARIATE COX-REGRESSION MODEL FOR ASSESSING RISK OF DEATH IN 1548 TM PATIENTS UNDER MIOT

	n (%)	n° death (%)	HR (95% CI)	p-value
<b>Cardiac T2*, ms</b>				
< 10 ms	156 (10,1)	9 (5,8)	5,24 (2,26-12,15)	<0.0001
≥ 10	1392 (89,9)	14 (1,0)	Reference	
< 20 ms	421 (27,2)	10 (2,4)	1,85 (0,81-4,24)	0,143
≥ 20 ms			Reference	
< 10 ms	156 (10,1)	9 (5,8)	4,48 (1,91-10,52)	0,001
10 -20 ms	265 (17,1)	1 (0,4)	0,29 (0,04-2,27)	0,242
≥ 20 ms	1127 (72,8)	13 (1,2)	Reference	

	n (%)	n° death (%)	HR (95% CI)	p-value
<b>Liver T2*, ms</b>				
< 1.8 ms	292 (18,9)	7 (2,4)	1,80 (0,74-4,39)	0,193
≥ 1.8 ms	1253 (81,1)	16 (1,3)	Reference	



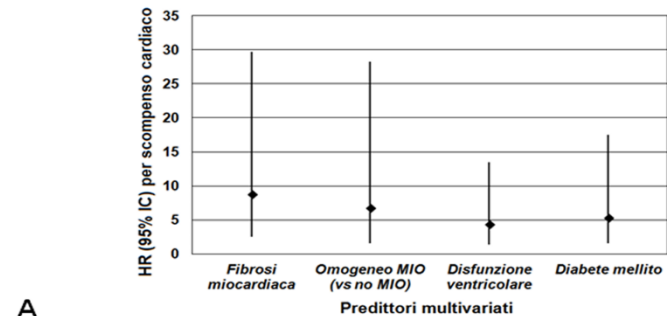
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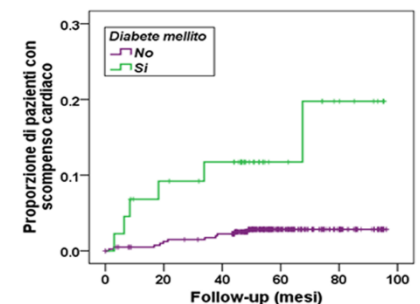
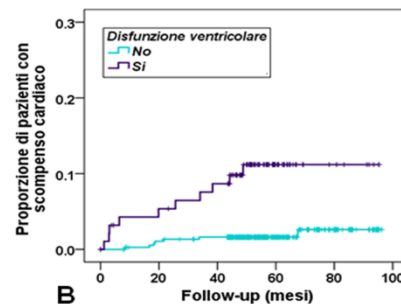
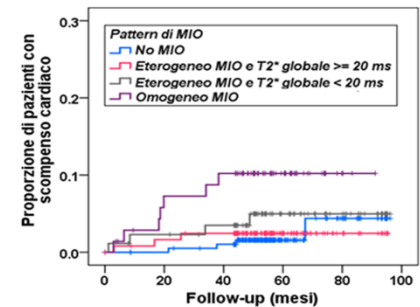
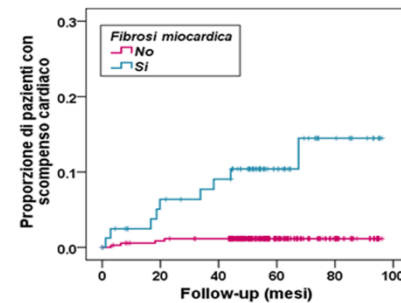


# MULTIVARIATE COX ANALYSIS FOR HEART FAILURE ON INDIPENDENT PROGNOSIS PREDICTORS

Figure A	n (%)	HR (95% CI)	p-value
<b>Myocardial fibrosis</b>			
Yes	82 (19,0)	8,81 (2,62; 29,57)	<0,0001
No	350 (81,0)	reference	
<b>Homogeneous MIO</b>			
Yes	71 (14,8)	6,76 (1,62;28,12)	0,009
No	198 (41,2)	reference	
<b>Mild Left Ventricular dysfunction (&lt;57%)</b>			
Yes	96 (20,3)	4,36 (1,42; 13,35)	0,01
No	377 (79,7)	reference	
<b>Diabetes mellitus</b>			
Yes	44 (9,8)	5,34 (1,64;17,41)	0,006
No	407 (90,2)	reference	



A



B

**Figure B, Log-rank test:**

$p < 0,0001$

$p = 0,016$

$p < 0,0001$

$p < 0,0001$



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# DEMOGRAPHICS SUMMARY STATISTICS OF 652 MR SCANNED B-THALASSEMIA MAJOR PATIENTS FROM UK HEMATOLOGY CENTERS

<b>Demographics</b>	
<b>Total patients, n</b>	<b>652</b>
<b>excluded for heart failure/arrhythmia at first MR scan</b>	<b>17</b>
<b>Age</b>	<b>27,1±9,6</b>
<b>Sex</b>	<b>M: 319, F: 333</b>
<b>Race/ethnicity, n</b>	
<b>White</b>	<b>296</b>
<b>South Asian</b>	<b>283</b>
<b>Chinese</b>	<b>23</b>
<b>Arabic</b>	<b>31</b>
<b>Black</b>	<b>19</b>
<b>Biochemistry</b>	
<b>Transfusional red blood cell input, mL<sup>-1</sup>·kg<sup>-1</sup>·y<sup>-1</sup></b>	<b>113,9±49,7</b>
<b>Serum ferritin, µg/L</b>	<b>2231±1801</b>
<b>Liver T2* geometric mean (95% CI), ms</b>	<b>3,6 (3,5–3,8)</b>
<b>LV ejection fraction, %</b>	<b>66,1±8,5</b>
<b>Therapy</b>	
<b>Combined DFO+DFP (n=105, 16.1%)</b>	
<b>DFO, mg·kg<sup>-1</sup>·wk<sup>-1</sup></b>	<b>160 (111, 235) for 4 (2, 5) d/wk</b>
<b>DFP, mg·kg<sup>-1</sup>·d<sup>-1</sup></b>	<b>20 (12, 43,5)</b>
<b>Combined DFO-DFX</b>	
<b>DFX (n=1, 0,2%)</b>	<b>167 for 5 d/wk</b>
<b>DFO, mg·kg<sup>-1</sup>·d<sup>-1</sup></b>	<b>20</b>
<b>DFO alone (n=433, 66.4%) mg·kg<sup>-1</sup>·wk<sup>-1</sup></b>	<b>202 (164, 270) for 5 (5, 5) d/wk</b>
<b>DFP alone (n=72, 11,0%) mg·kg<sup>-1</sup>·d<sup>-1</sup></b>	<b>70 (57, 82)</b>
<b>DFX alone (n=19, 2,9%) mg·kg<sup>-1</sup>·d<sup>-1</sup></b>	<b>10 (7,5, 15)</b>
<b>No chelation, n (%)</b>	<b>22 (3,4)</b>

Kirk, P et Al. Cardiac T2\* Magnetic Resonance for Prediction of Cardiac Complications in Thalassemia Major. Circulation 2009. 120: 1961-1968.



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# RELATIVE RISK OF HEART FAILURE FOR CARDIAC AND LIVER T2\* AND FOR SERUM FERRITIN LEVELS INCLUDING MULTIPLE SCANS OF THE 652 PATIENTS INCLUDED IN THE STUDY

	n	n° heart failure	RR	p-value
<b>Cardiac T2*, ms</b>				
<6	72	34	270	< 0,001
6 to <8	98	29	171	< 0,001
8 to <10	108	15	81	< 0,001
≥ 10	1164	2	Reference	
<b>Liver T2*, ms</b>				
< 0,96	63	3	1,25	0,74
0,96 to < 1,4	136	14	2,59	0,021
1,4 to < 2,7	382	26	1,68	0,13
2,7 to < 6,3	484	22	1,22	0,57
≥ 6,3	377	15	Reference	
<b>Ferritin, µg/L</b>				
≥ 2500	450	35	0,56	0,02
< 2500	992	45	Reference	

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# MAIN RESULTS OF THE REVIEW USING META-ANALYSIS STUDIES

## Effectiveness

- Combination treatment is able to have advantage versus Deferoxamine alone in term of :
  - - Decreasing of Liver Iron Concentration
  - Serum Ferritin Levels
  - - Increasing of Left Ventricular Ejection Fraction
  - Urinary Iron Excretion

## Safety

- Combination treatment does not have more SAEs in comparison with Deferiprone alone at dosage used in randomized clinical trials



# SUGGESTIONS DERIVED FROM THESE FINDINGS (A)

- A) Effectiveness and Safety of Combined Chelation Treatment is well shown using Level A of Evidence (*Klocke et al, 2003*)
- B) Effectiveness of Combined treatment was shown both in decreasing Liver Iron Concentration and increasing Left Ventricular Ejection Fraction
- C) No data on literature have been reported using Deferiprone and Deferoxamine treatment for 7 days/week in combination. No data on literature have been reported using Deferiprone at 100mg/Kg per os for 7 days during combined chelation treatment.



## SUGGESTIONS DERIVED FROM THESE FINDINGS (B)

- A) MIOT studies suggested as not all patients today have access to heart MRI (1658/7000 (23.6%) Italian patients had scanner for one Heart MRI)
- B) MIOT Multivariate Cox Analysis suggested as Myocardial Fibrosis is the most powerful predictor factor. Moreover, even mild Left Ejection Fraction (<57%) dysfunction and diabetes are independent predictor factors.
- C) Effectiveness of combination treatment in decreasing Liver Iron Concentration suggested to spread its use in patients with Liver Iron Overloading independently of Heart T2\* signal.



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