

INTERESSAMENTO CARDIACO IN CORSO DI EMOCROMATOSI

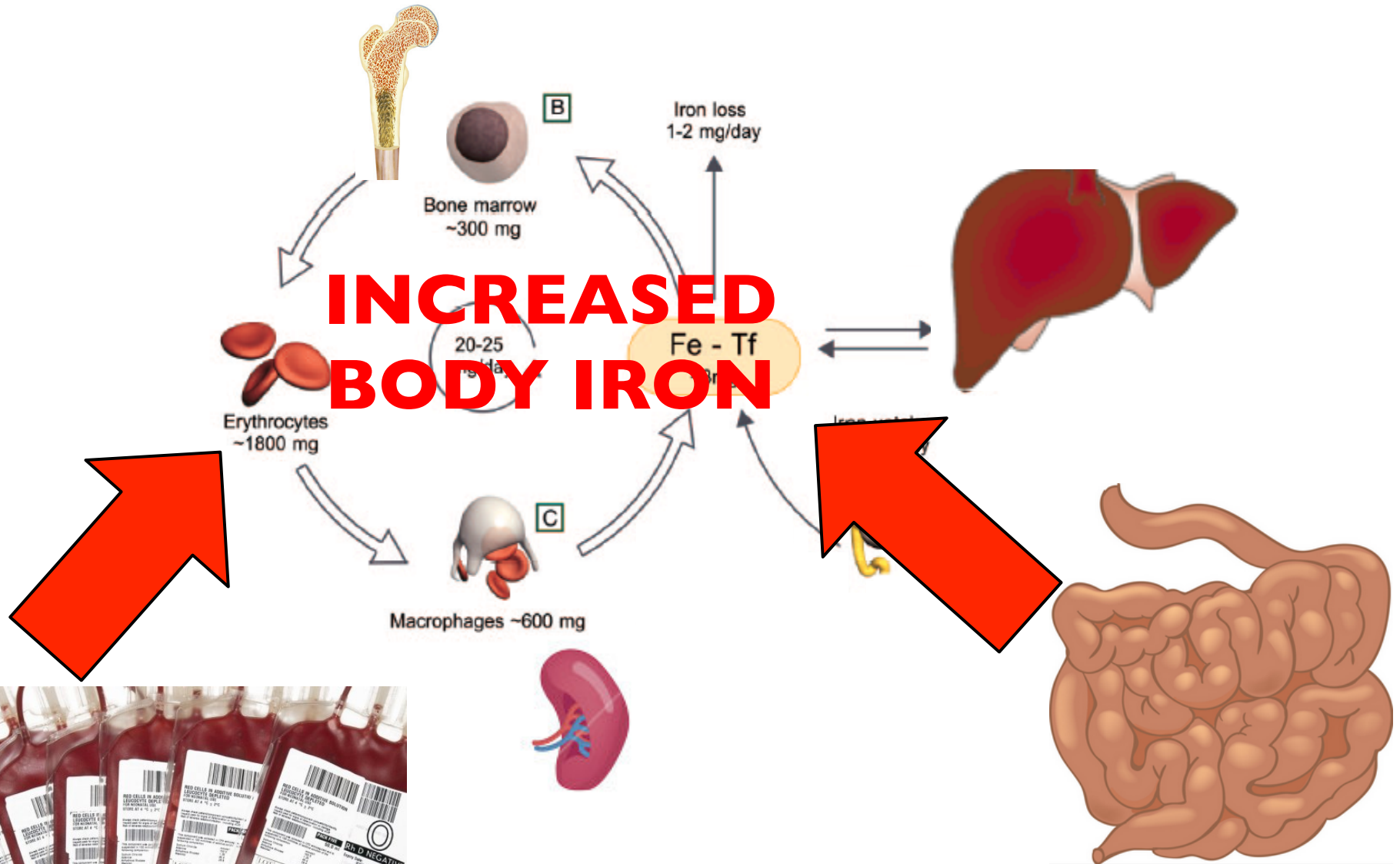


Giacomo Marchi, Medicina Interna AOUI Verona
Highlights in Ematologia, Treviso 23 novembre 2018

HIGHLIGHTS CARDIOPATIE IN EMOCROMATOSI

- Principale causa morbidità/mortalità in pazienti politrasfusi
- Prevalenza è in aumento (> sopravvivenza porta a > complicanze)
- Se diagnosticate in fase tardiva il trattamento è difficile
- Diagnosi precoce è possibile: bisogna pensarci!
- **La terapia precoce può modificare sostanzialmente la prognosi del paziente**
- Cardiologi non conoscono sufficientemente l'argomento: ematologo/internista deve essere protagonista principale!

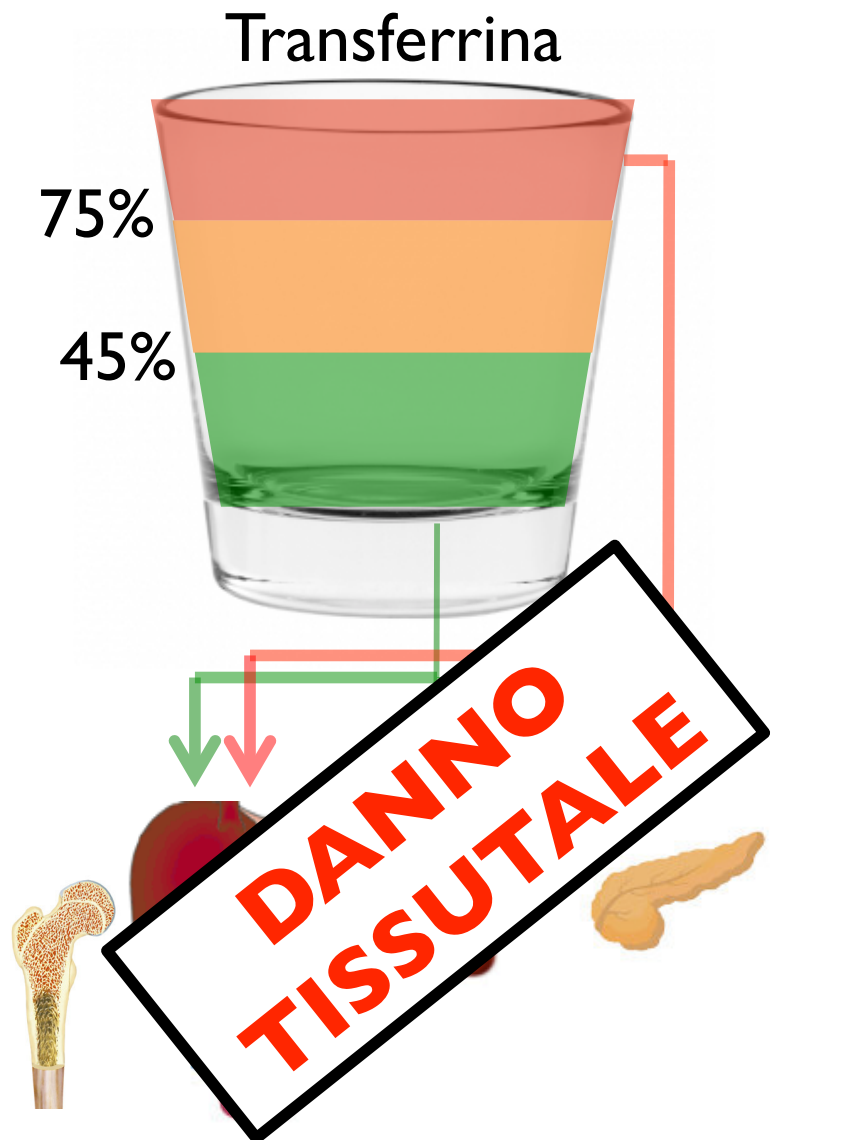
Omeostasi del ferro



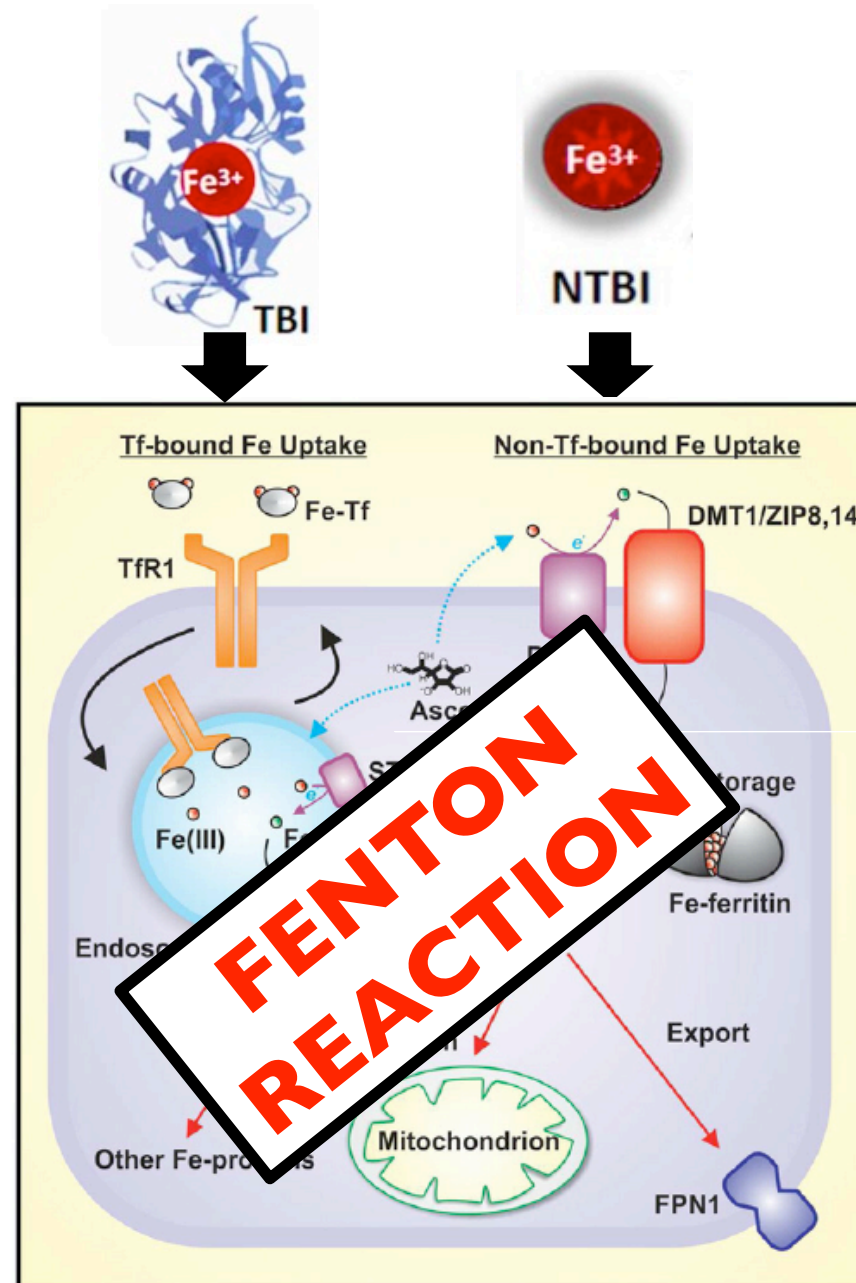
Talassemia major
Sickle cell disease
MDS trasfusione-dipendenti

Emocromatosi genetiche
Talassemia intermedia
MDS trasfusione-indipendenti

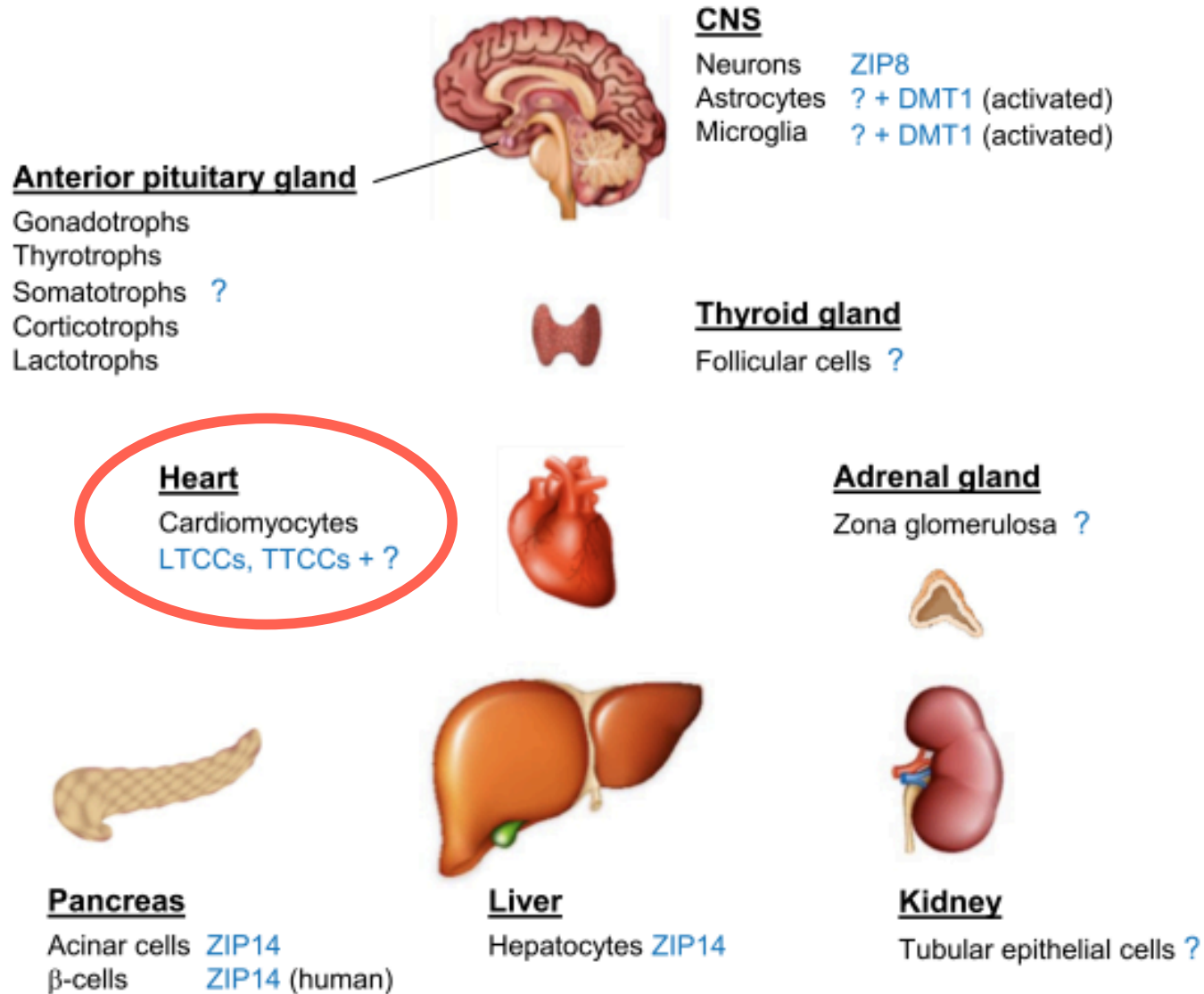
TBI e NTBI



Cellular iron uptake, trafficking and metabolism: Key molecules and mechanisms and their roles in disease.
Lane et al. BBA 2006

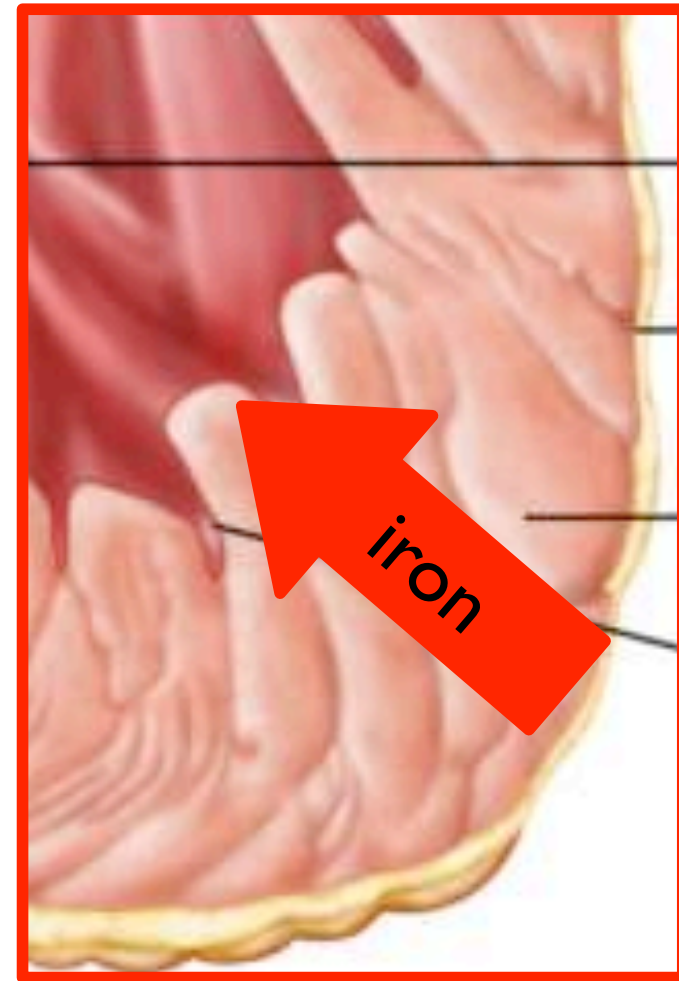
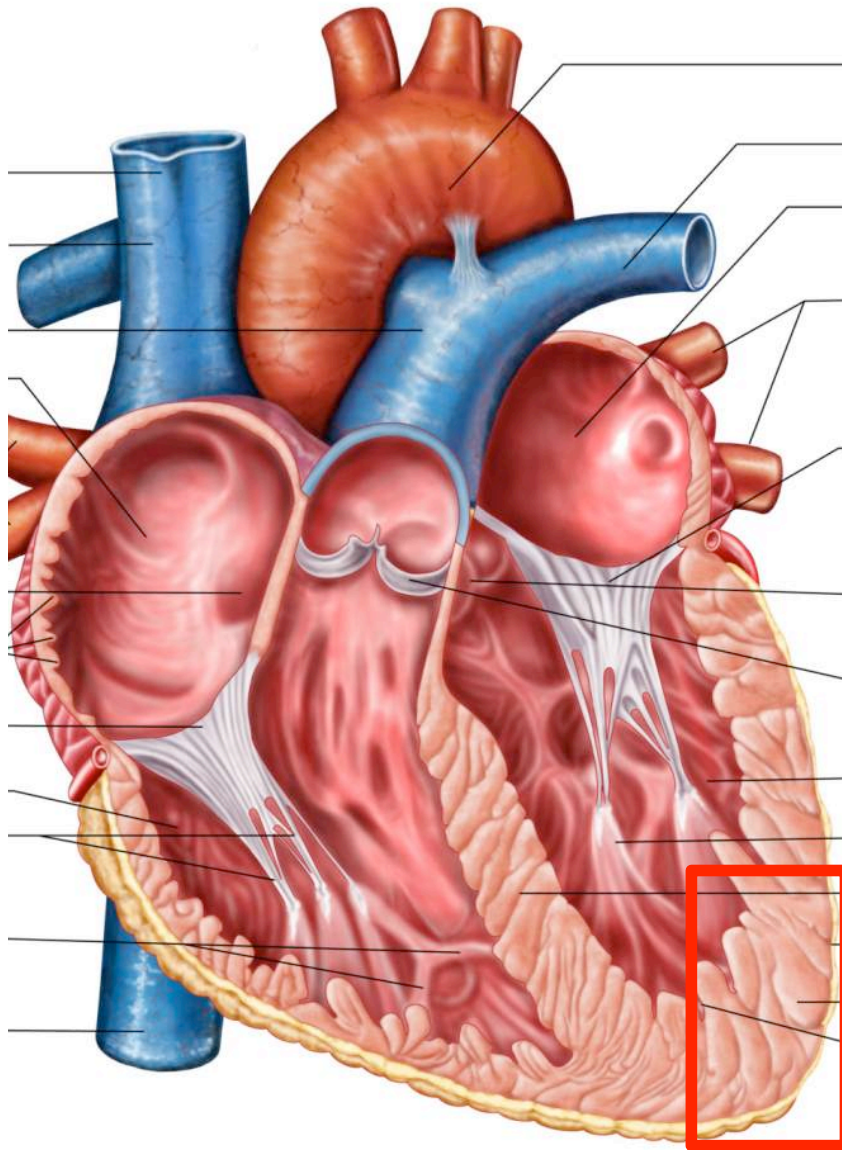


NTBI



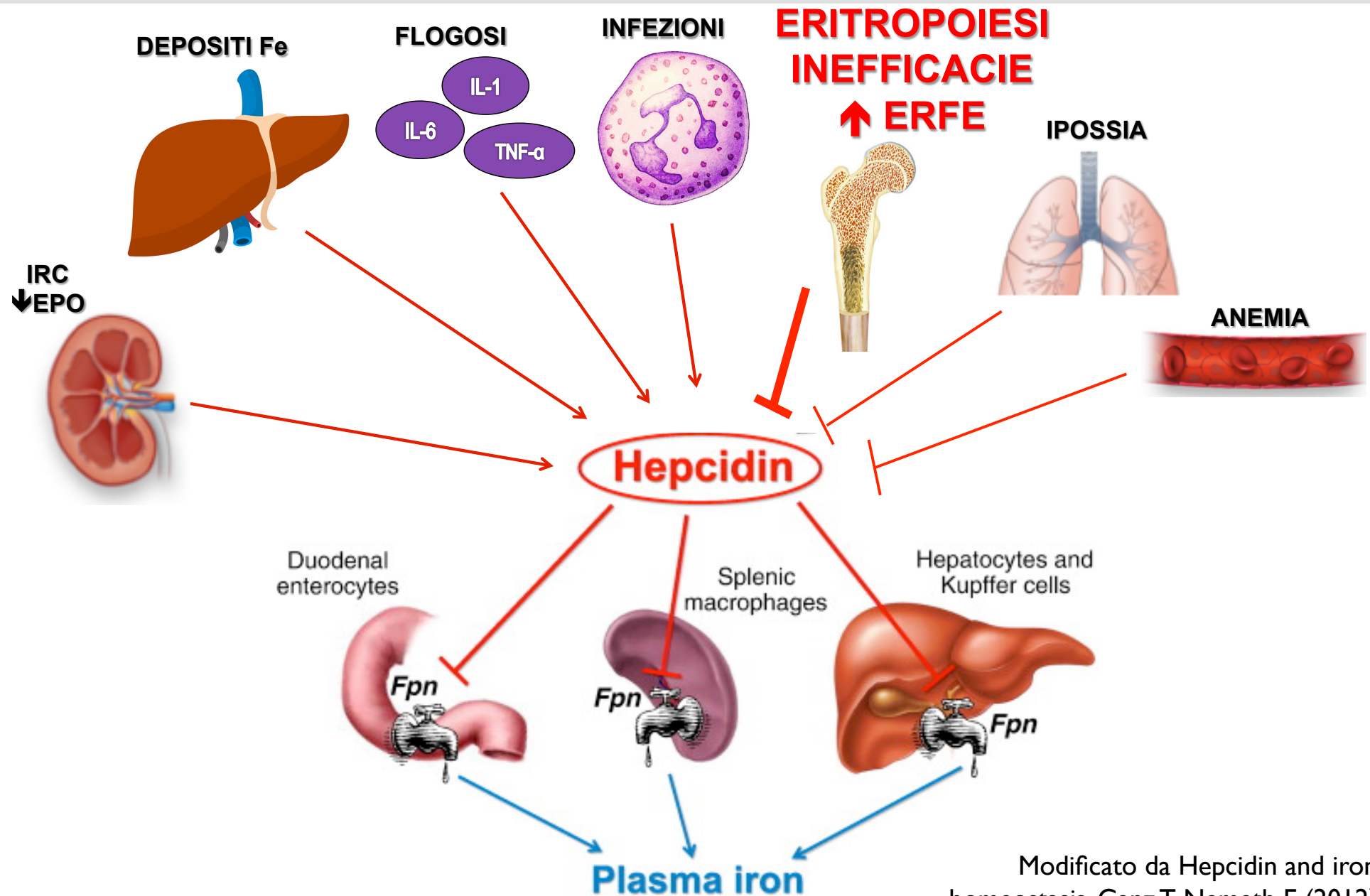
Iron overload cardiomyopathy. Better understanding of an increasing disorder. Gujja et al, JACC 2010
Non transferrin bound iron transporters. Knutson 2018

NTBI



Iron overload cardiomyopathy. Better understanding of an increasing disorder. Gujja et al, JACC 2010
Non transferrin bound iron transporters. Knutson 2018

Epcidina



Modificato da Hepcidin and iron homeostasis. Ganz T, Nemeth E (2012)

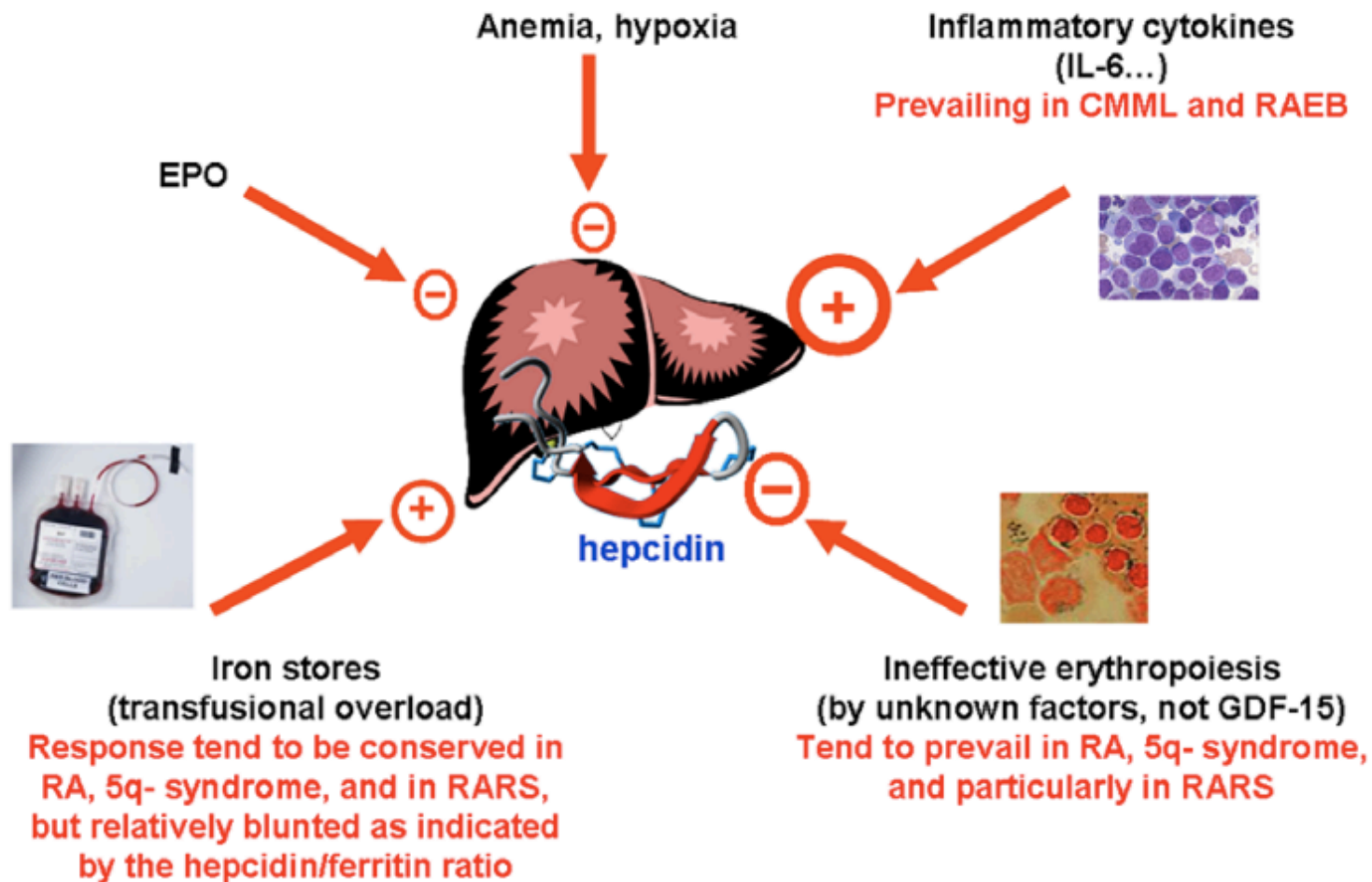
Epcidina nelle MDS

OPEN ACCESS Freely available online

PLOS one

Hepcidin Levels and Their Determinants in Different Types of Myelodysplastic Syndromes

Valeria Santini^{1,5}, Domenico Girelli^{2,5}, Alessandro Sanna¹, Nicola Martinelli², Lorena Duca³, Natascia Campostrini², Agostino Cortelezzi⁴, Michela Corbella², Alberto Bosi¹, Gianluigi Reda⁴, Oliviero Olivieri², Maria Domenica Cappellini³



Come sospettare e diagnosticare una cardiopatia da sovraccarico di ferro?

NO

- Sintomi
- Ferritina da sola
- Ecocardiogramma
- Biopsia epatica (spesso non riflette accumulo extraepatico)
- RM epatica per LIC (non correla con T2* cardiaca in corso di tp chelante)

SI'

- Volume di sangue trasfuso
- TSat
- Patologia di base (apoptosi progenitori eritroidi, eritropoiesi inefficacie)
- RM con valutazione T2* pancreatica (rule out)
- **RM con valutazione T2* cardiaca**

RM cardiaca T2*

| IRON HOMEOSTASIS & CHRONIC DISEASE: DISORDERS OF IRON OVERLOAD |



Guidelines for quantifying iron overload

John C. Wood¹

¹Division of Cardiology, Department of Pediatrics and Radiology, Children's Hospital of Los Angeles, Los Angeles, CA

patients may be divided into cohorts using a “stoplight” scheme: green ($T2^* > 20$ ms), yellow ($10 \text{ ms} < T2^* < 20$ ms) and red ($T2^* < 10$ ms) based upon their risk of arrhythmias and cardiac dysfunction.^{21,31} As a result, a $T2^*$ value < 10 ms is often used as a “trigger” for aggressive escalation of chelator therapy.³² Cardiac $T2^*$ is routinely used to monitor response to iron chelation therapy in high-risk disorders such as beta thalassemia major and Blackfan-Diamond syndrome. Cardiac $T2^*$ also serves as an end point for

45 year old male
with idiopathic CM



Iron
Overload

Heart (-)
Liver (-)

35 year old female
with sickle cell anemia



Heart (+)
Liver (+)

45 year old male
with HH

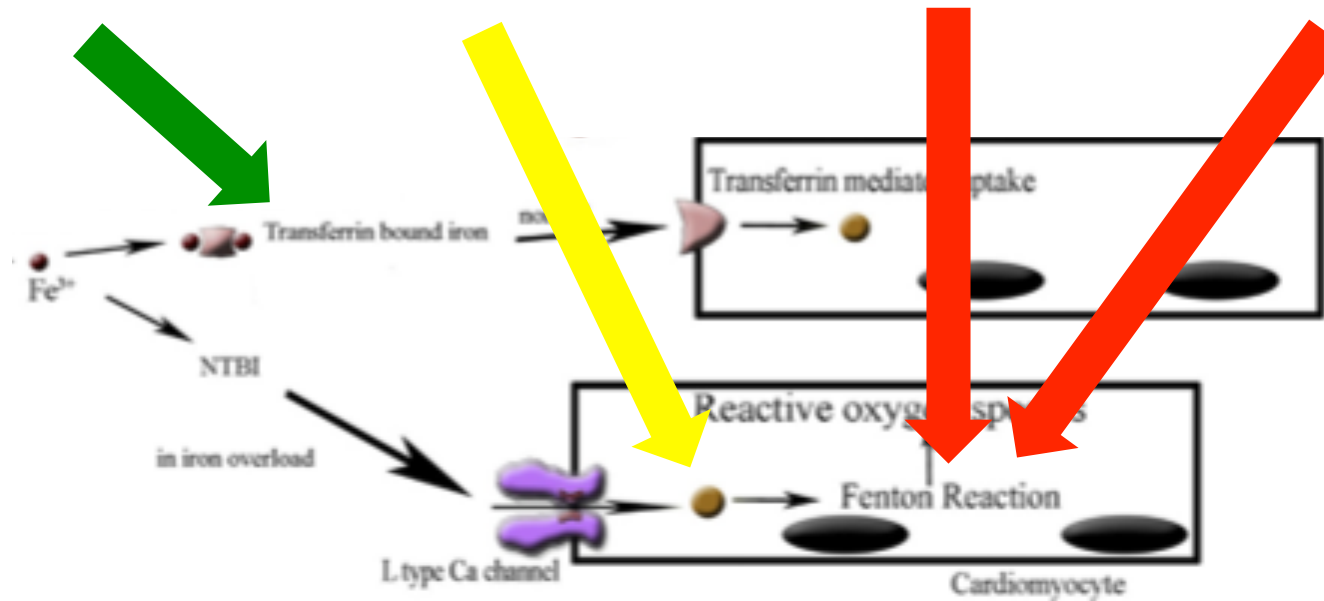
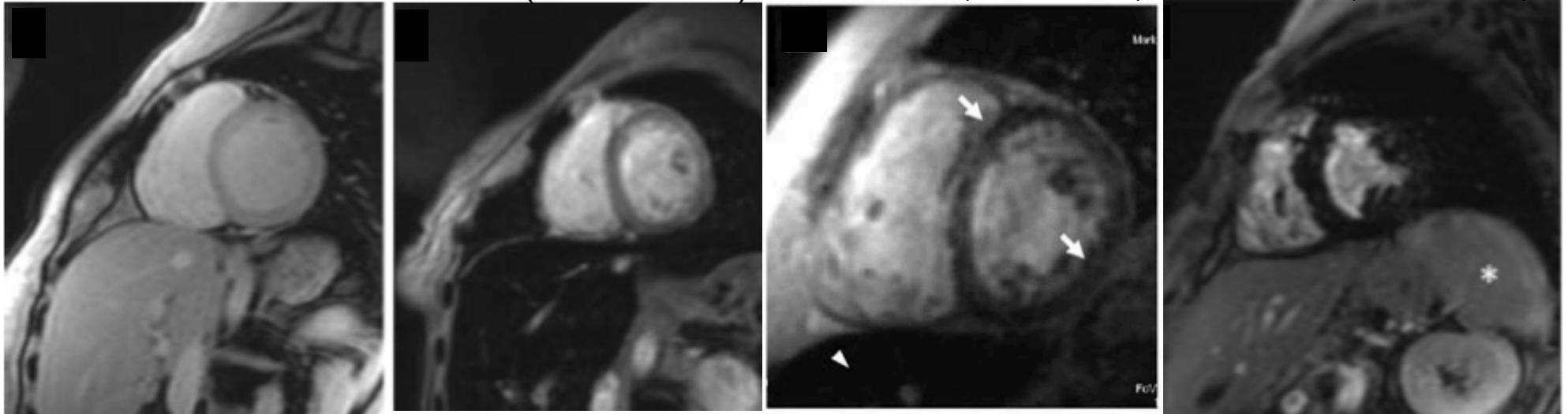


Heart (-)
Liver (+)

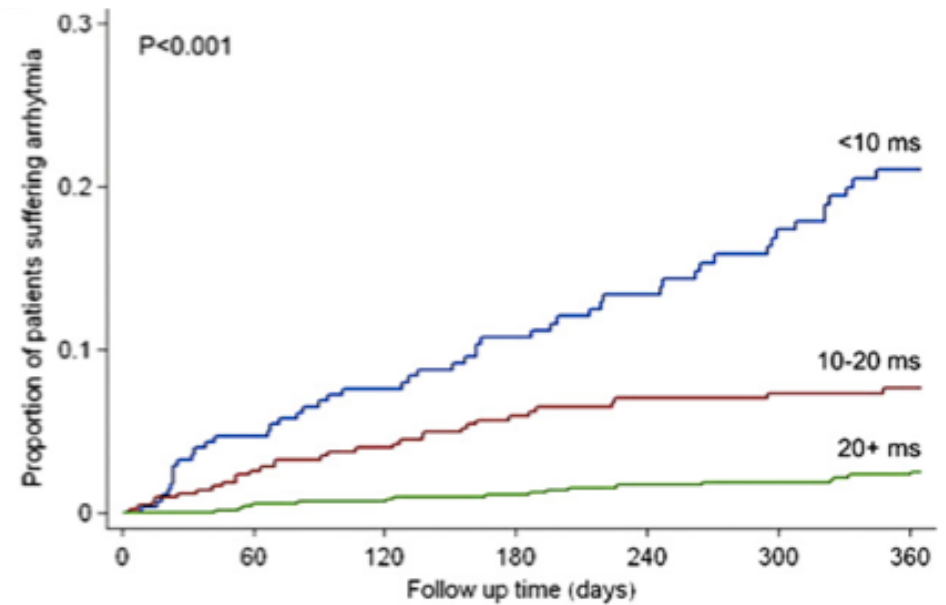
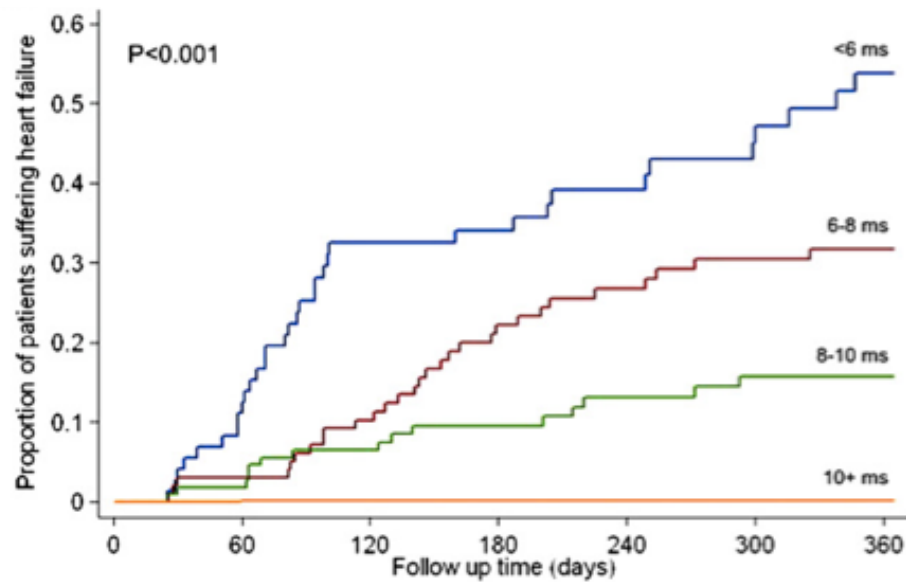
Iron overload cardiomyopathy. Better understanding of an increasing disorder. Gujja et al, JACC 2010

RM cardiaca T2 e prognosi*

fegato norm fegato +++ fegato +++ fegato +
cuore norm ($T2^* > 20$ ms) cuore + ($T2^* 10-20$ ms) cuore +++ ($T2^* < 10$ ms) cuore +++ ($T2^* < 10$ ms)



RM cardiaca T2 e prognosi*



Come trattare una cardiopatia da sovraccarico di ferro?

How I treat

How I treat transfusional iron overload

A. Victor Hoffbrand,¹ Ali Taher,² and Maria Domenica Cappellini³



Dipende da:

- Pz trasfusione-dipendente? E quanto?
- Severità sovraccarico cardiaco
- Controindicazioni a chelanti?

Opzione 1: Salassi



- Non praticabili in pz trasfusione-dipendenti
- Poco praticabili in caso di severo accumulo marziale con disfunzione sistolica per problemi di tolleranza
- Praticabili in pz non-trasfusione dipendenti con sovraccarico marziale cardiaco non severo e normale FE



Opzione 2. Chelanti



Table 4. Chelation strategies in adult patients with β -TM

	DFO*	DFP	DFO + DFP combination	DFX
T2* $\geq$ 20 ms				
Iron intake < 0.3 mg/kg/d				
LIC $\geq$ 15 mg Fe/g dw	40-50 mg/kg per day, 8-10 h/d, 6 or 7 d/wk, SQ	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/2 d + DFP 75 mg/kg/d	30-40 mg/kg/d
LIC 7- < 15 mg Fe/g dw	30-40 mg/kg per day, 8-10 h/d, 5 d/wk, SQ	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/1-2 d + DFP 75 mg/kg/d	20-30 mg/kg/d
LIC 3- < 7 mg Fe/g dw	30-40 mg/kg per day, 8-10 h/d, 5 d/wk, SQ	75 mg/kg/d	Suspend DFO/DFP 75 mg/kg/d	20-30 mg/kg/d
LIC < 3 mg Fe/g dw	Suspend	Suspend	Suspend DFO/Suspend DFP	Suspend
Iron intake 0.3-0.5 mg/kg/d				
LIC $\geq$ 15 mg Fe/g dw	40-50 mg/kg per day, 8-10 h/d, 6 or 7 d/wk, SQ	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/2 d + DFP 75 mg/kg/d	30-40 mg/kg/d
LIC 7- < 15 mg Fe/g dw	40-50 mg/kg per day, 8-10 h/d, 6 or 7 d/wk, SQ	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/1-2 d + DFP 75 mg/kg/d	30-40 mg/kg/d
LIC 3- < 7 mg Fe/g dw	30-40 mg/kg per day, 8-10 h/d, 5 d/wk, SQ	75 mg/kg/d	Suspend DFO/DFP 75 mg/kg/d	20-30 mg/kg/d
LIC < 3 mg Fe/g dw	Suspend	Suspend	Suspend DFO/Suspend DFP	Suspend
Iron intake > 0.5 mg/kg/d				
LIC $\geq$ 15 mg Fe/g dw	40-50 mg/kg per day, 8-10 h/d, 6 or 7 d/wk, SQ	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/2 d + DFP 75 mg/kg/d	30-40 mg/kg/d
LIC 7- < 15 mg Fe/g dw	40-50 mg/kg per day, 8-10 h/d, 6 or 7 d/wk, SQ	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/2 d + DFP 75 mg/kg/d	30-40 mg/kg/d
LIC 3- < 7 mg Fe/g dw	30-40 mg/kg per day, 8-10 h/d, 5 d/wk, SQ	75 mg/kg/d	DFO 40 mg/kg/10-12 h/1 d + DFP 75 mg/kg/d	20-30 mg/kg/d
LIC < 3 mg Fe/g dw	Suspend	Suspend	Suspend DFO/Suspend DFP	Suspend
T2* 10- < 20 ms				
LIC $\geq$ 15 mg Fe/g dw	50-60 mg/kg per day, continuous IV	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/7 d + DFP 75 mg/kg/d	40 mg/kg/d
LIC 7- < 15 mg Fe/g dw	40-50 mg/kg per day, 8-10 h/d, 6 or 7 d/wk, SQ	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/5 d + DFP 75 mg/kg/d	30-40 mg/kg/d
LIC 3- < 7 mg Fe/g dw	40-50 mg/kg per day, 8-10 h/d, 6 or 7 d/wk, SQ	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/2 d + DFP 75-100 mg/kg/d	30-40 mg/kg/d
LIC < 3 mg Fe/g dw	Adjust to therapeutic index,† monitory safety closely	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/1-2 d + DFP 75-100 mg/kg/d/Monitor safety closely	Adjust dose, monitor safety closely
T2* < 10 ms				
LIC $\geq$ 15 mg Fe/g dw	50-60 mg/kg per day, continuous IV	Not recommended	DFO 40 mg/kg/10-12 h/7 d + DFP 75-100 mg/kg/d	Not recommended
LIC 7- < 15 mg Fe/g dw	40-50 mg/kg per day, continuous IV	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/5-7 d + DFP 75-100 mg/kg/d	30-40 mg/kg/d
LIC 3- < 7 mg Fe/g dw	40-50 mg/kg per day, continuous IV	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/3-5 d + DFP 75-100 mg/kg/d	30-40 mg/kg/d
LIC < 3 mg Fe/g dw	Adjust to therapeutic index,† monitory safety closely	75-100 mg/kg/d	DFO 40 mg/kg/10-12 h/1-2 d + DFP 75-100 mg/kg/d	Adjust dose, monitor safety closely

Opzione 3. Calcio-antagonisti???

Cochrane Database of Systematic Reviews

Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia

Cochrane Systematic Review - Intervention | Version published: 12 July 2018

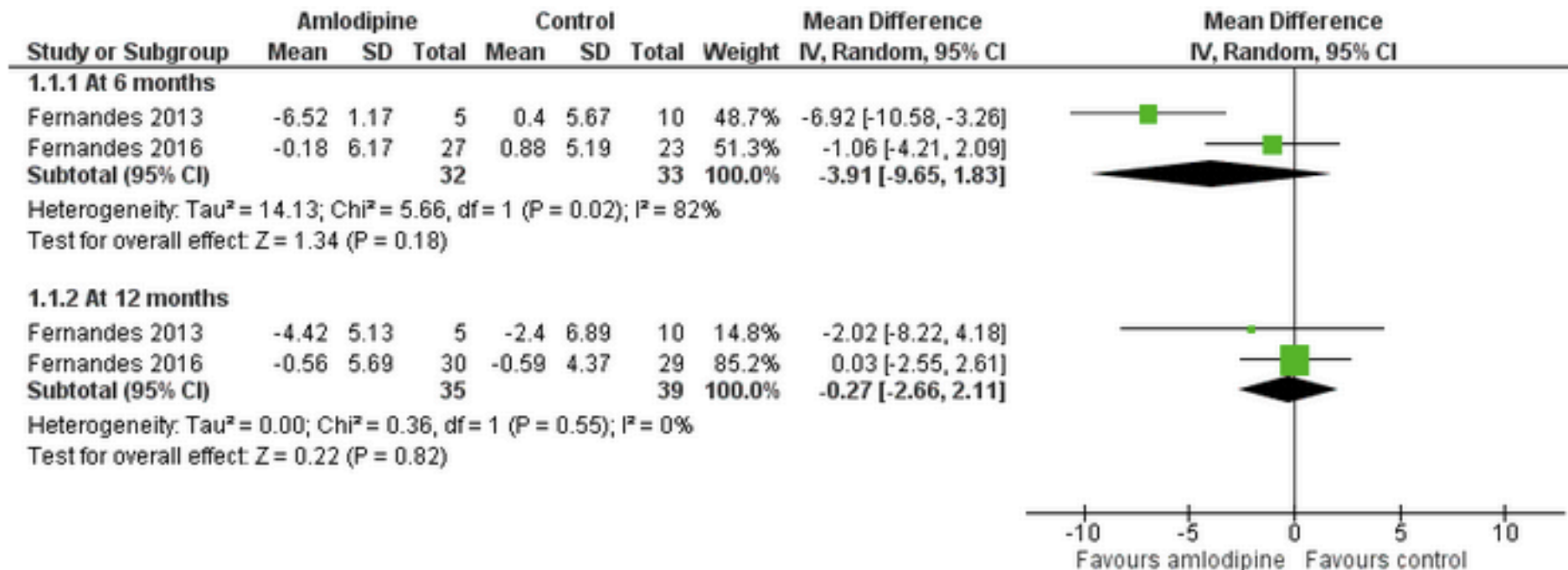


Figure 2 Forest plot of comparison: 1 Amlodipine versus control, outcome: 1.1 Heart T2* (m/s) (change from baseline).

Opzione 3. Calcio-antagonisti???

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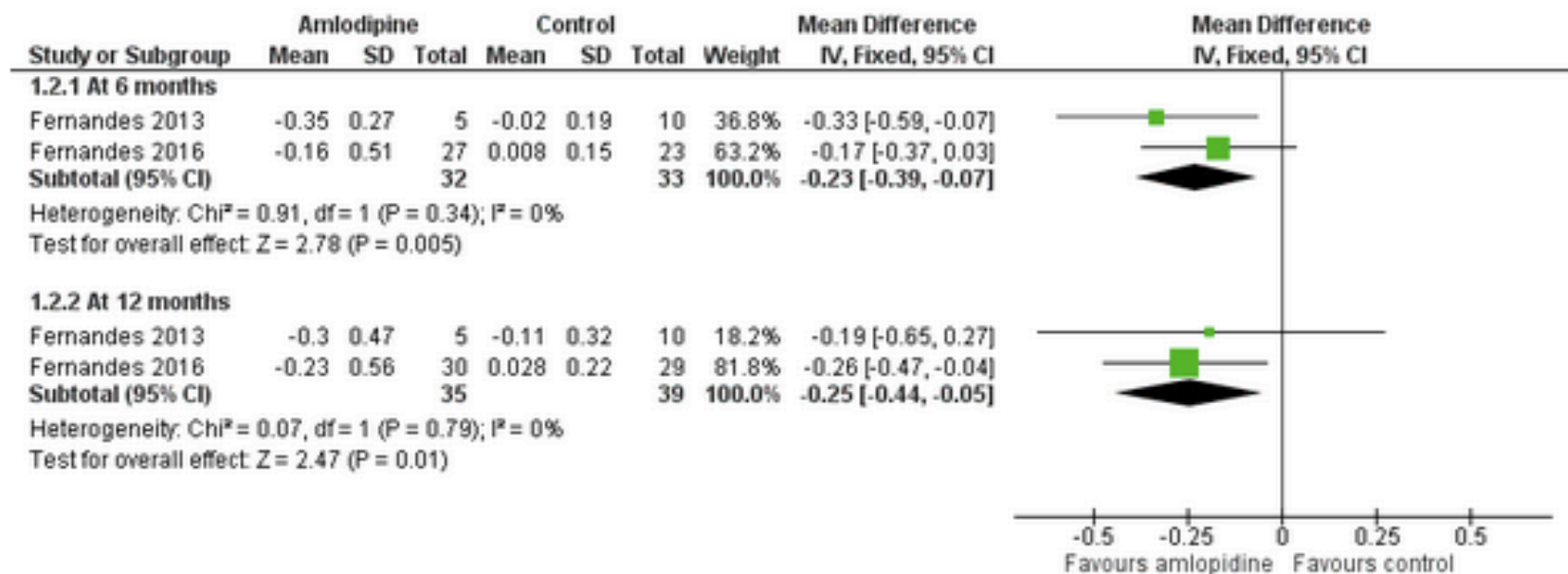


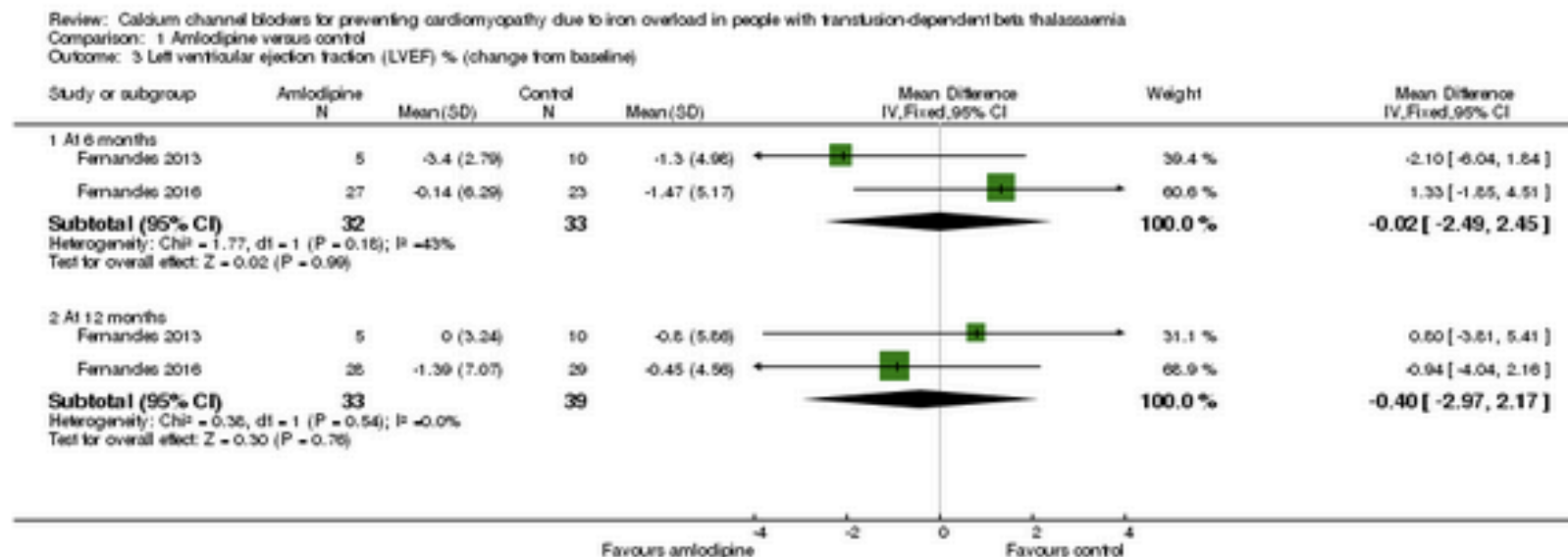
Figure 3 Forest plot of comparison: 1 Amlodipine versus control, outcome: 1.2 Myocardial iron concentration (MIC) (mg/g) (change from baseline).

Opzione 3. Calcio-antagonisti???

Cochrane Database of Systematic Reviews

Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia

Cochrane Systematic Review - Intervention | Version published: 12 July 2018



Analysis 1.3 Comparison 1 Amlodipine versus control, Outcome 3 Left ventricular ejection fraction (LVEF) % (change from baseline).

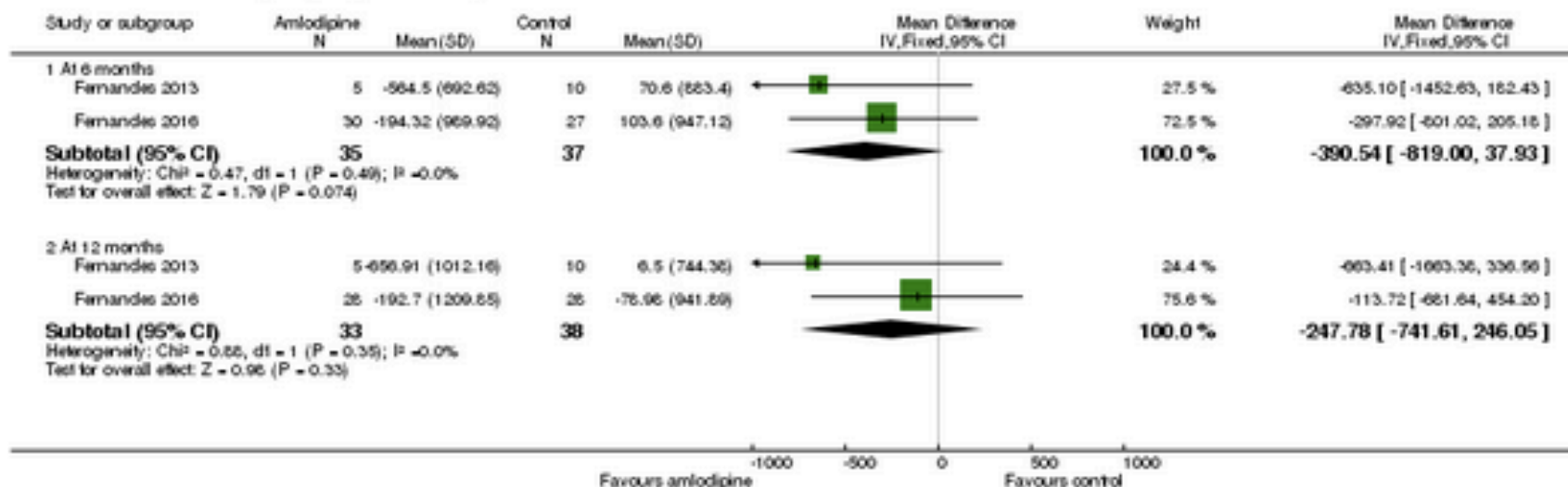
Opzione 3. Calcio-antagonisti???

Cochrane Database of Systematic Reviews

Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia

Cochrane Systematic Review - Intervention | Version published: 12 July 2018

Review: Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia
Comparison: 1 Amlodipine versus control
Outcome: 4 Serum ferritin ng/mL (change from baseline)



Analysis 1.4 Comparison 1 Amlodipine versus control, Outcome 4 Serum ferritin ng/mL (change from baseline).

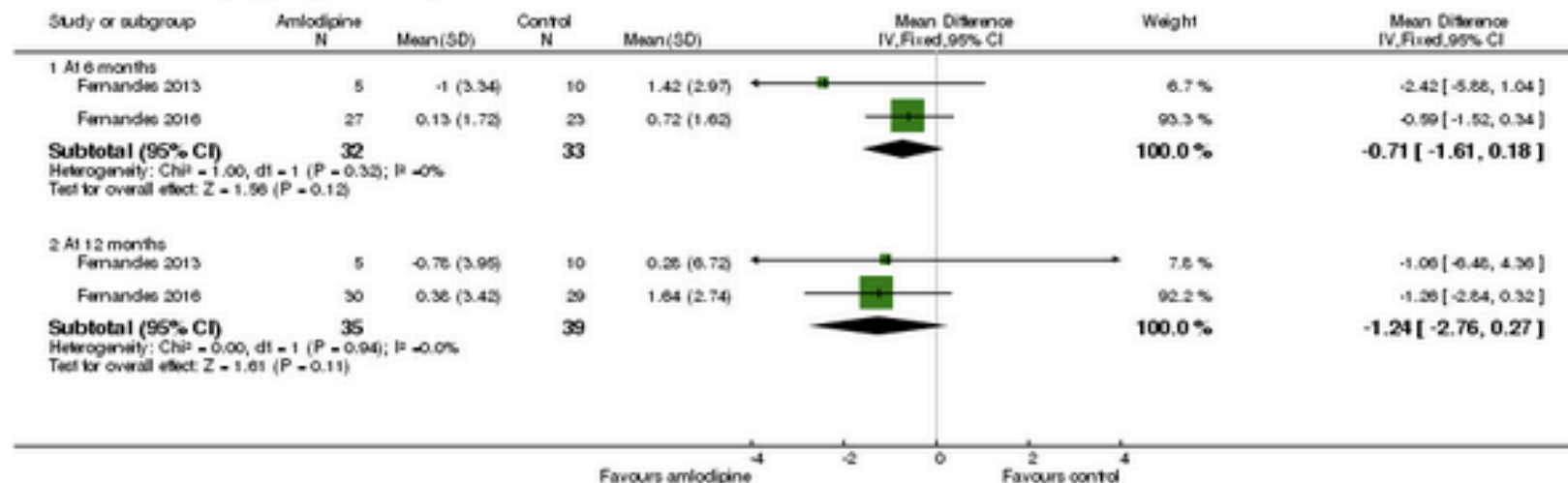
Opzione 3. Calcio-antagonisti???

Cochrane Database of Systematic Reviews

Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia

Cochrane Systematic Review - Intervention | Version published: 12 July 2018

Review: Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia
Comparison: 1 Amlodipine versus control
Outcome: 5 Liver T2* (m/s) (change from baseline)



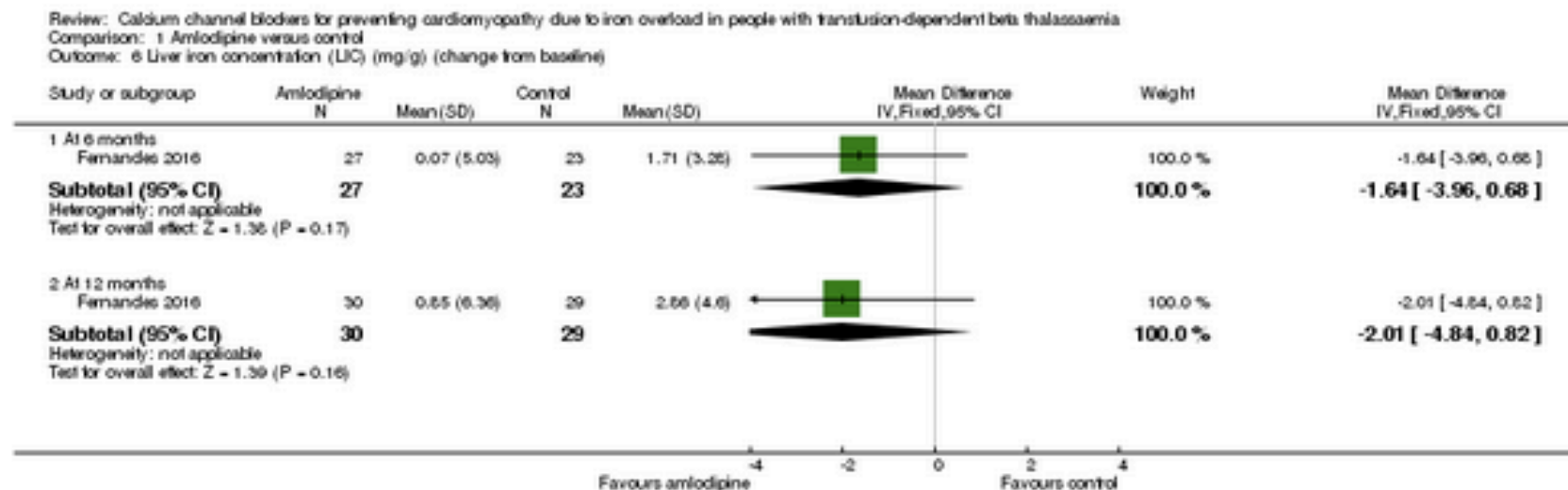
Analysis 1.5 Comparison 1 Amlodipine versus control, Outcome 5 Liver T2* (m/s) (change from baseline)

Opzione 3. Calcio-antagonisti???

Cochrane Database of Systematic Reviews

Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia

Cochrane Systematic Review - Intervention | Version published: 12 July 2018



Analysis 1.6 Comparison 1 Amlodipine versus control, Outcome 6 Liver iron concentration (LIC) (mg/g) (change from baseline).

CONCLUSIONI: 1. Ricercare cardiopatia da accumulo di ferro in situazioni ad alto rischio

- Blackfan-Diamond anemia
- Aplasia midollare
- Talassemia major
- MDS trasfusione-dipendenti/RARS
- Anemie sideroblastiche congenite
- Anemie diseritropoietiche congenite
- Emocromatosi tipo 2 (HJ, Hepc)
- HSCT
- Sickle cell disease
- Emocromatosi tipo 3 (TfR2)
- Talassemia intermedia
- Emocromatosi tipo I (HFE)
- Membranopatie eritrocitarie
- MDS trasfusione-indipendenti

RICERCA SISTEMATICA

GIUDIZIO CLINICO

CONCLUSIONI: 2. Diagnosi con RM T2*

**45 year old male
with idiopathic CM**



**Iron
Overload**

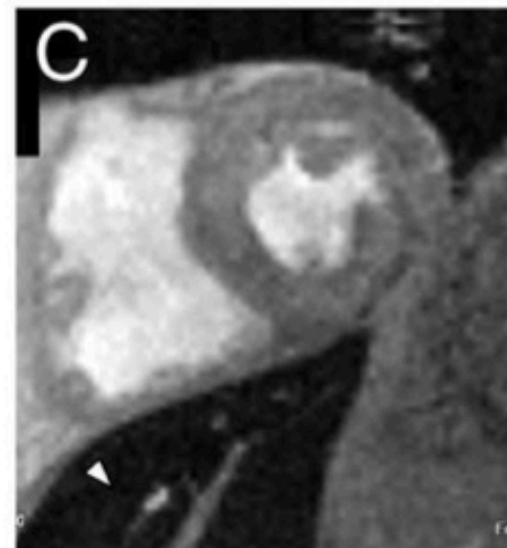
**Heart (-)
Liver (-)**

**35 year old female
with sickle cell anemia**



**Heart (+)
Liver (+)**

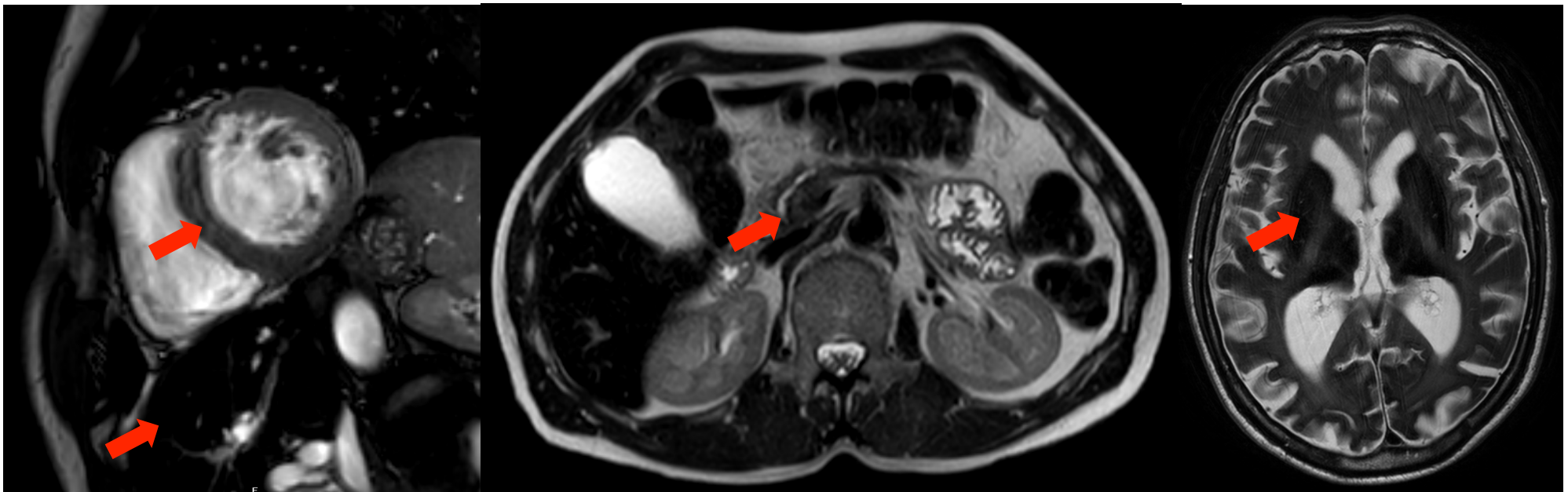
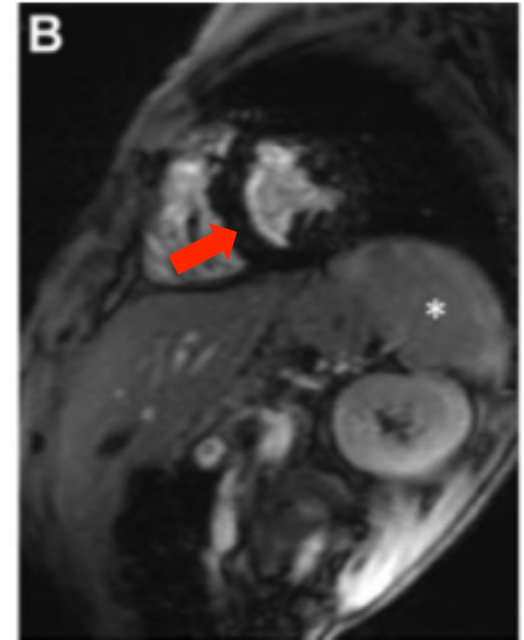
**45 year old male
with HH**



**Heart (-)
Liver (+)**

CONCLUSIONI: 3. Miti da sfatare?

- Ci può essere accumulo cardiaco solo quando il fegato è “pieno di ferro”
- Ci può essere accumulo cardiaco solo con TSat elevata



CONCLUSIONI: 4. Terapia e auspici futuri

- Terapia è in genere con ferrochelante/i (tipo/dose dipende dalla severità dell'accumulo)
- Ruolo potenziale ma non ancora certo dei calcio antagonisti
- Necessità di linee guida per la diagnosi e di trial clinici per raccomandazioni terapeutiche

**Grazie per
l'attenzione
!!!**





<http://www.gimferverona.org>



The Verona Interdisciplinary group on Iron Disorders



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