La Correzione dell'Anemia nella DKD: Ferro, ESA e…?

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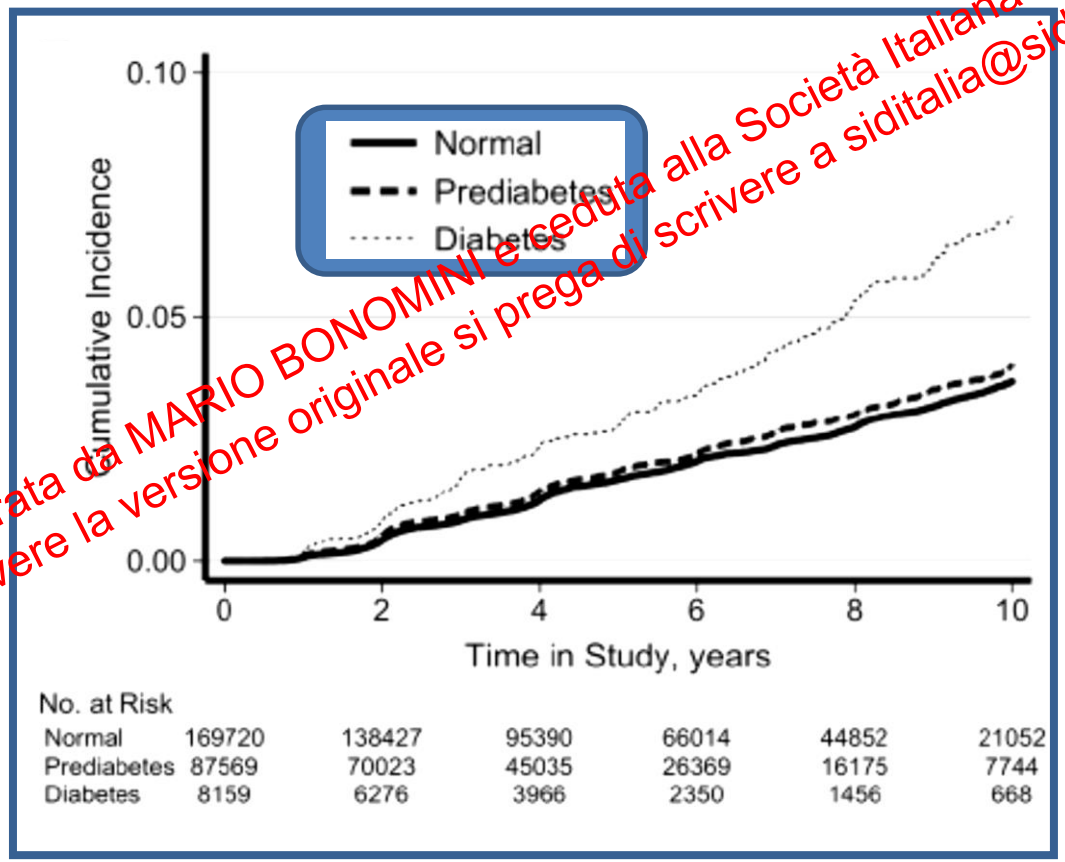
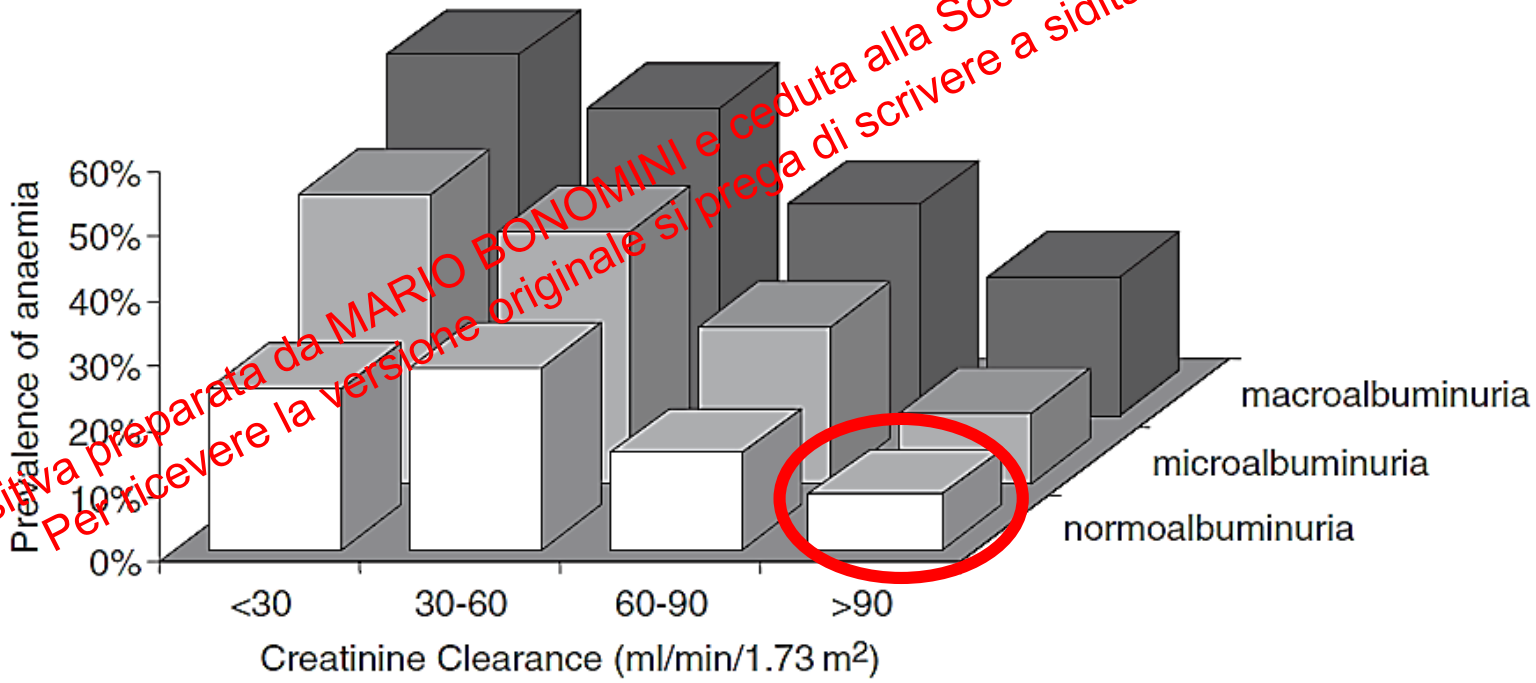
Risk factors for incident anemia of chronic diseases: A cohort study



Lee et al., PLoS ONE 2019

The burden of anemia in type 2 diabetes and the role of nephropathy: a cross-sectional audit



Thomas et al., Nephrol Dial Transplant 2004

Possible mechanisms of anemia in diabetes

Reduced Production of Erythropoietin	Other contributors
Microvascular damage	Reduced red cell half survival
Chronic hypoxia	Haematinic deficiency
Oxidative stress	Reduced iron availability
Systemic inflammation	Occult blood loss
Autonomic neuropathy	Drug therapy
Increased salt reabsorption	Celiac disease (type 1)
Hyperfiltration	Induction of EPO release inhibitors
Urinary erythropoietin loss	

Thomas et al., Curr Diabetes Rev 2005

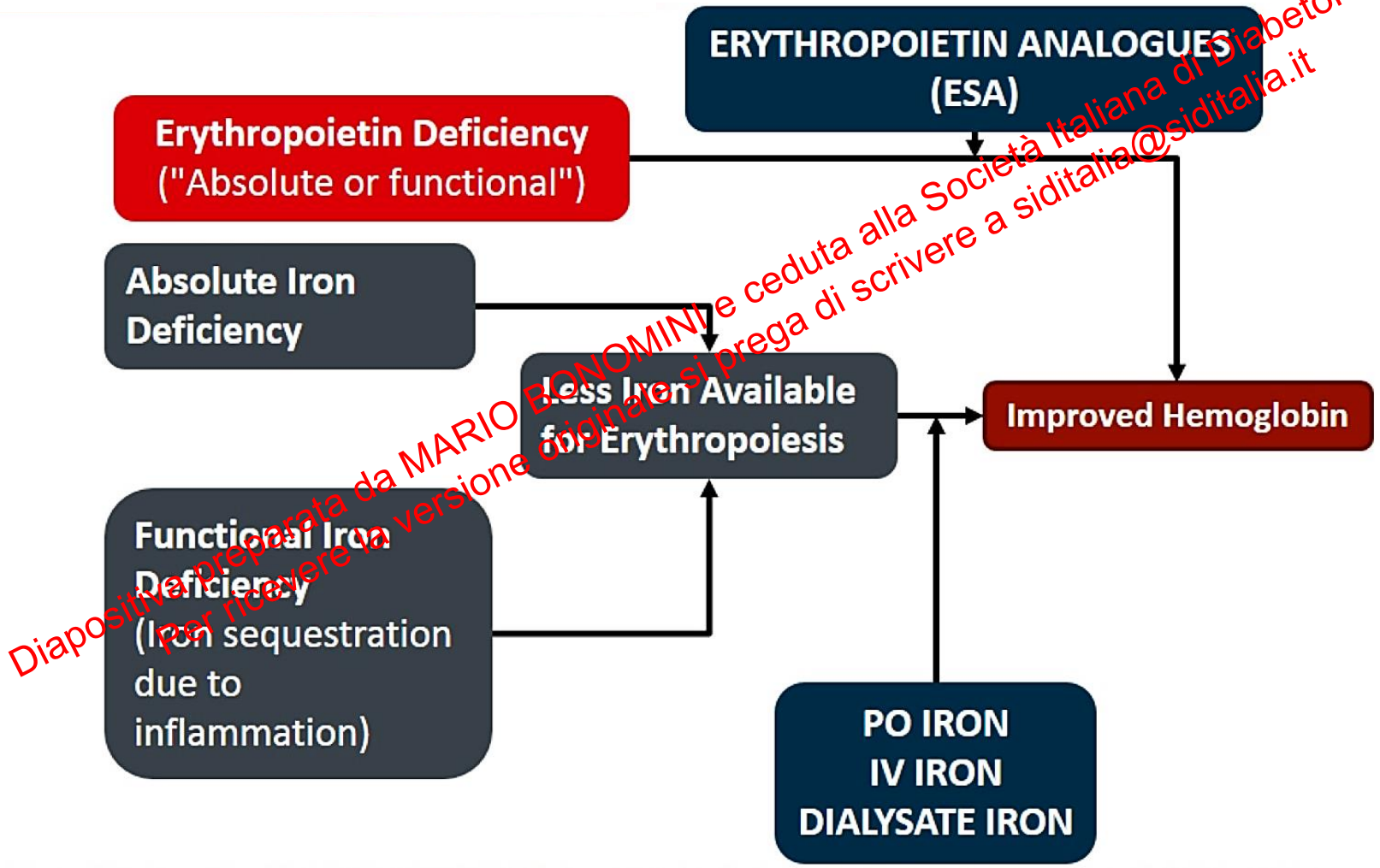
Anemia in diabetic patients with chronic kidney disease – prevalence and predictors

Table 3 Mean haemoglobin values and prevalence of anaemia (K/DOQI definition) in various stages of chronic kidney disease (CKD)

CKD stage	Diabetes status	*n* (%)	Hb (g/l) (mean±SD)	*p* (Hb)	eGFR (ml/min) (mean±SD)	*p* (eGFR)	Anaemia prevalence *n* (%)	*p* (anaemia prevalence)
CKD 1 and 2 (*n*=172)	Diabetic	76 (44%)	131±17	<0.002	82±17	NS	13 (17%)	<0.01
	Non-diabetic	96 (56%)	140±15		83±16		4 (4%)	
CKD 3 (*n*=156)	Diabetic	65 (42%)	121±17	<0.0001	43±9	NS	33 (51%)	<0.0001
	Non-diabetic	91 (58%)	135±17		44±9		12 (13%)	
CKD 4 and 5 (*n*=140)	Diabetic	63 (45%)	115±17	<0.001	19±7	NS	37 (59%)	<0.05
	Non-diabetic	77 (55%)	124±13		19±7		28 (36%)	

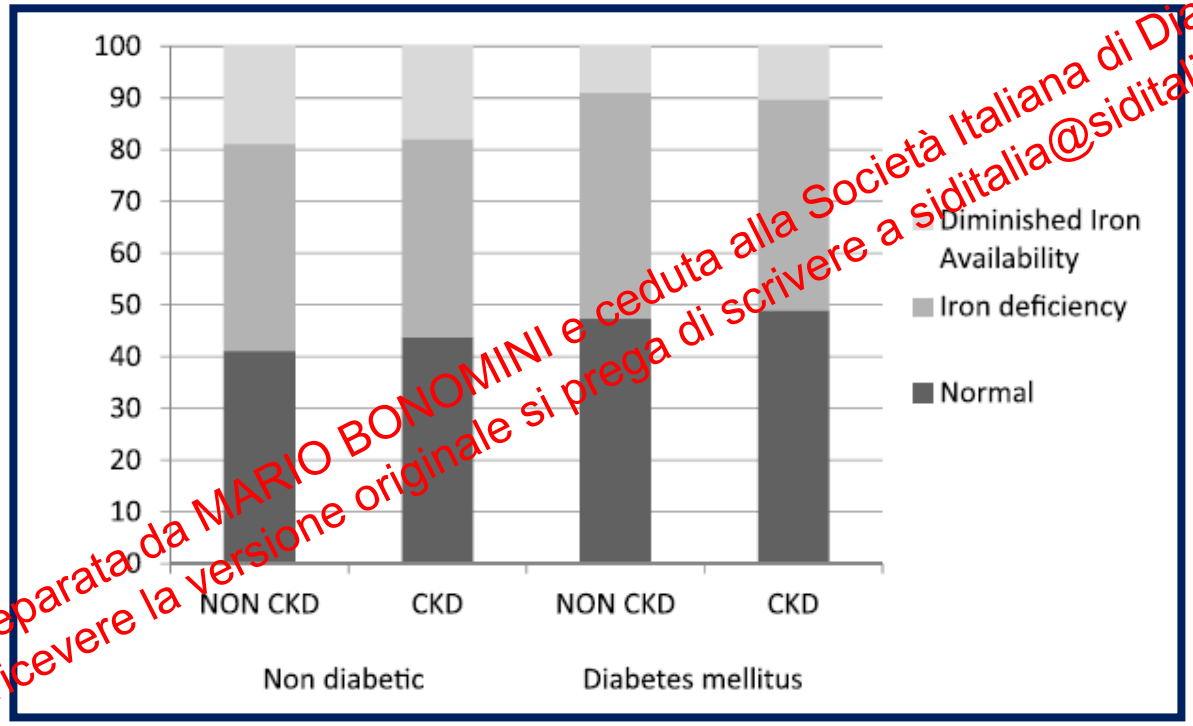
Al-Khoury et al., Diabetologia 2006

Available treatments for anemia associated with DKD



Yilmaz et al., Blood Purif 2011; Auerbach et al., Best Pract Res Clin Anaesthesiol 2013

Iron deficiency in chronic kidney disease patients with diabetes mellitus



Prevalence of iron deficiency was more frequent in diabetic patients than in non-diabetic subjects (p=0.048). Among CKD diabetic patients the prevalence of iron deficiency was higher than in non-diabetic CKD ones (p=0.040).

Robles et al., Diabetes Metab Syndr 2018

Target Iron Indices

	Target Ferritin, ng/mL	Target TSAT, %
CKD	> 100	> 20
ESRD	200-1200	30-50

KDIGO Anemia Work Group, Kidney Int 2012

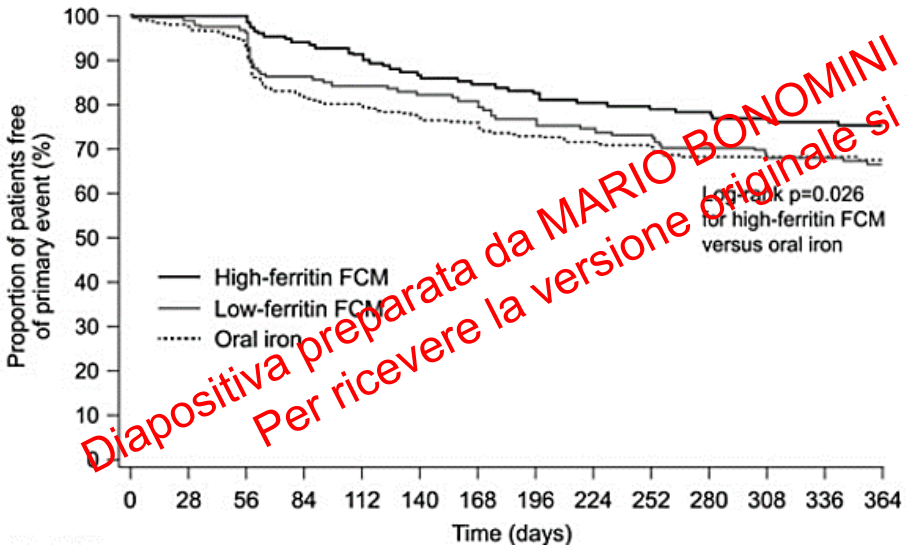
Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis

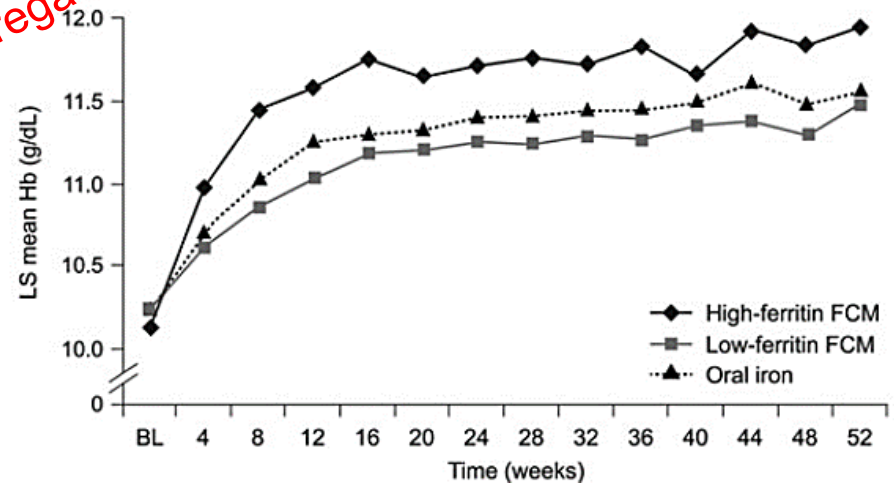
Results: 24 trials were identified, 13 including 2,369 patients with CKD stages 3 to 5 and 11 including 818 patients with CKD stage 5D. Patients treated with IV iron were more likely to reach an Hb response > 1 g/dL (risk ratios [RRs] of 1.61 [95% CI, 1.39-1.87] for CKD stages 3-5 and 2.14 [95% CI, 1.68-2.72] for CKD stage 5D). Safety analysis showed similar rates of mortality and serious and any adverse effects. IV iron replacement was associated with higher risk for hypotension (RR, 3.71; 95% CI, 1.74-7.94) and fewer gastrointestinal adverse events (RR, 0.43; 95% CI, 0.28-0.67).

Conclusions: Our results agree with current recommendations for IV iron replacement for patients with CKD stage 5D and support increased use of IV iron for patients with CKD stages 3 to 5.

Shepshelovich et al., AJKD 2016

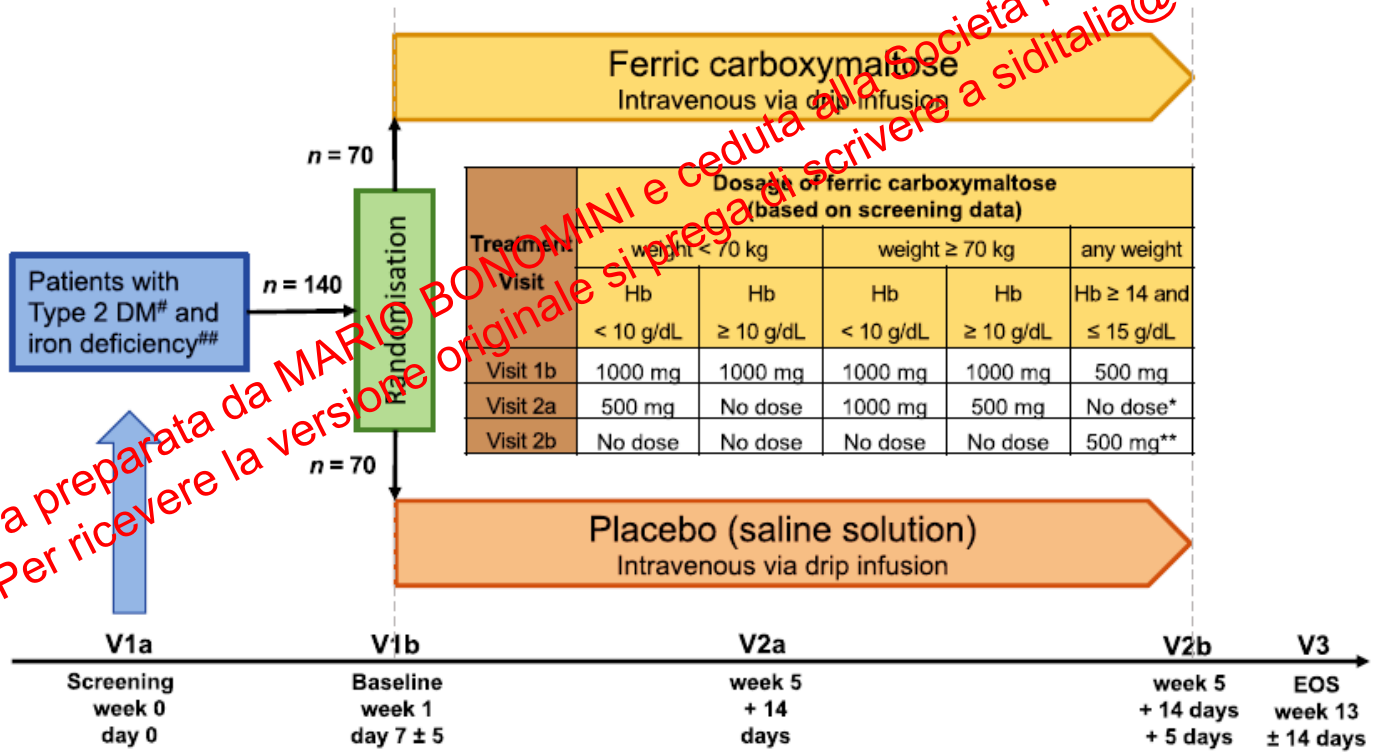
FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia





MacDougall et al., NDT 2014

Intravenous Ferric Carboxymaltose in Patients with Type 2 Diabetes Mellitus and Iron Deficiency: CLEVER Trial Study Design and Protocol



Treatment: Visit	Dosage of ferric carboxymaltose (based on screening data)				
	weight < 70 kg		weight ≥ 70 kg		any weight
	Hb < 10 g/dL	Hb ≥ 10 g/dL	Hb < 10 g/dL	Hb ≥ 10 g/dL	Hb ≥ 14 and ≤ 15 g/dL
Visit 1b	1000 mg	1000 mg	1000 mg	1000 mg	500 mg
Visit 2a	500 mg	No dose	1000 mg	500 mg	No dose*
Visit 2b	No dose	No dose	No dose	No dose	500 mg**

Schindler et al., Diabetes Ther 2019

Novel Oral Iron Therapies for Iron Deficiency Anemia in Chronic Kidney Disease

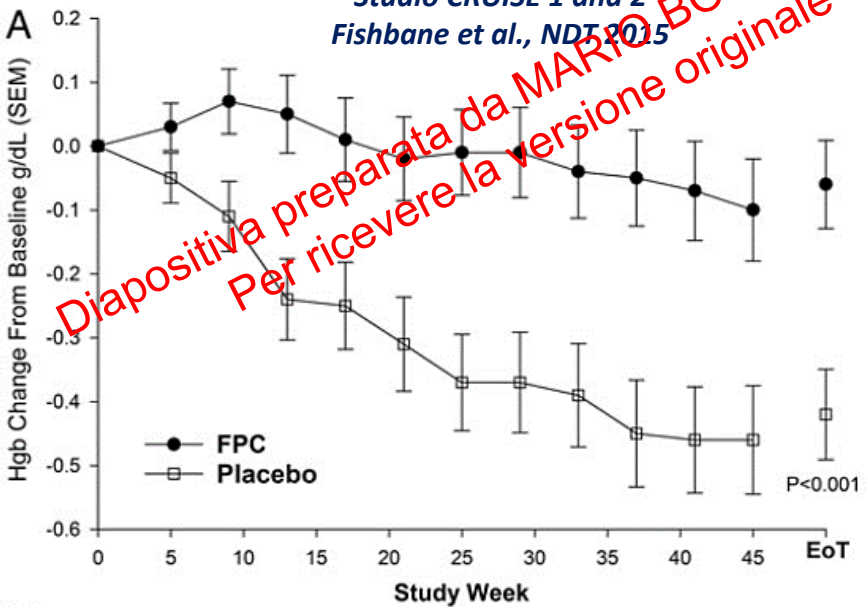
Pablo E. Pergola, Steven Fishbane, and Tomas Ganz

Adv Chronic Kidney Dis. 2019;26(4):272-291

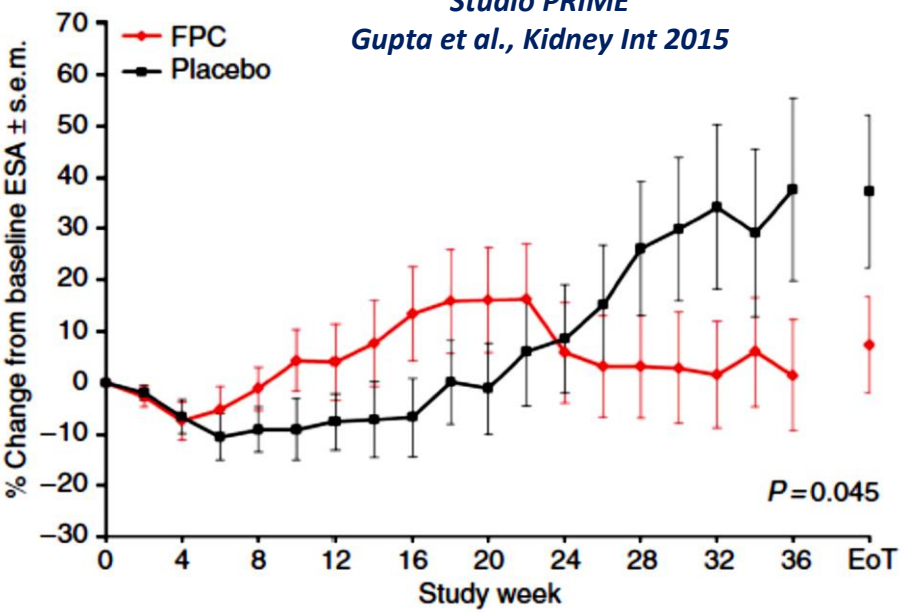
Ferric Pyrophosphate Citrate

New water soluble IV iron
Added to bicarbonate dialysate
Transfers across dialyzer membrane
Donates iron directly to transferrin
Delivers iron directly to bone marrow

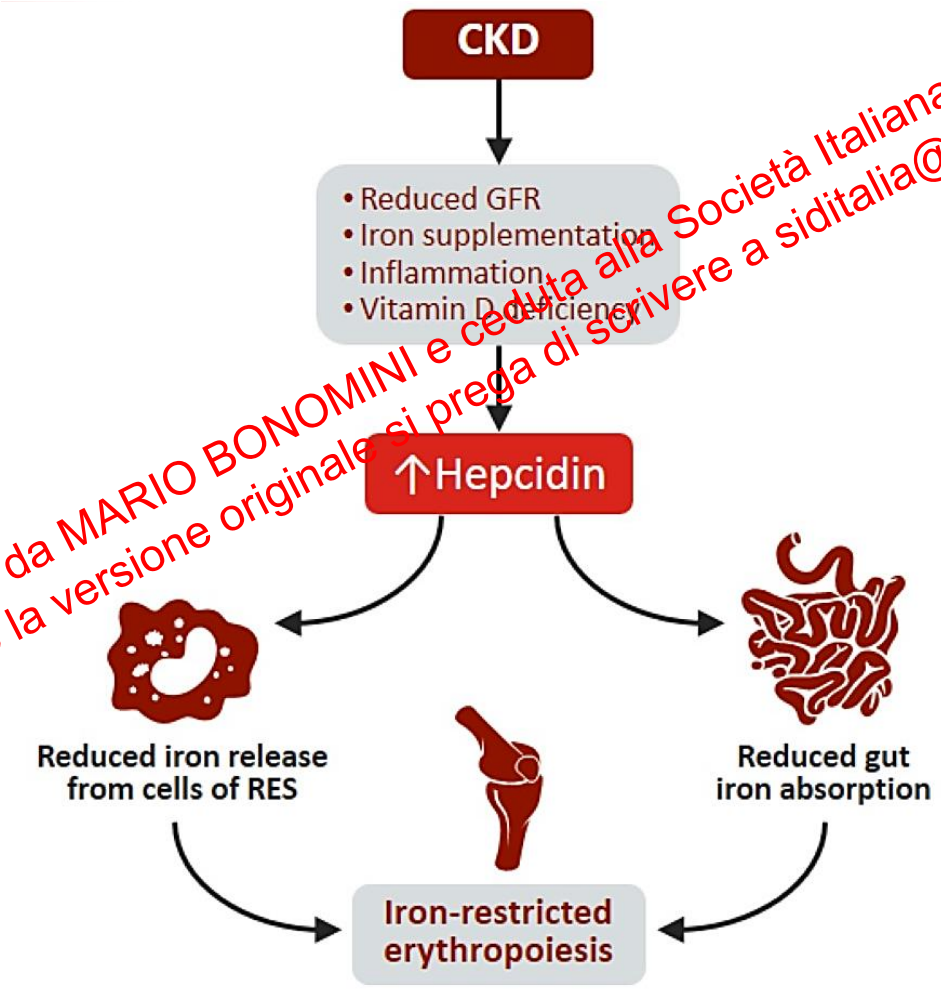
Studio CRUISE 1 and 2
Fishbane et al., NDT 2015



Studio PRIME
Gupta et al., Kidney Int 2015



Dysregulated iron homeostasis in CKD



Panwar et al., Semin Nephrol 2016

Compounds affecting iron-hepcidin axis under development

	COMPOUND	TARGET
HEPCIDIN AGONISTS	Hepcidin Mimetics	Ferroportin
	Stimulation of Hepcidin production	Tmprss6
	Ferroportin inhibitors	Ferroportin
HEPCIDIN ANTAGONISTS	Anti-hepcidin antibodies	Anti-hepcidin antibody
	Hepcidin binding spiegelmers	Chelates serum hepcidin
	Hepcidin binding anticalins	Hepcidin inhibitors
	BMP sequestration	BMP receptor type 1 inhibitors
	BMP receptor inhibitors	BMP pathway
	IL-6 signaling inhibitors	IL-6 pathway
	Erythroferrone	Erythroferrone

Malyszko et al., Expert Opin Ther Targets 2019

Terapia dell'anemia renale con ESA

- ✓ Successo della Medicina Clinica degli anni '90
- ✓ Soppressa necessità di terapia trasfusionale cronica
- ✓ Miglioramento sintomatologia, qualità di vita e capacità fisica

Red flags raised with ESA use

Four randomized controlled trials of hemoglobin-raising in chronic kidney disease

	NHCT[52]	CHOIR[53]	CREATE[54]	TREAT[55]
Population	Patients with chronic heart failure and end-stage renal disease on dialysis	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease with diabetes
Hemoglobin target	10 vs 14 g/dL	13.5 vs 11.3 g/dL	> 13 vs 11 g/dL	> 13 vs 9 g/dL
Target achieved?	No	No	Yes	No
Primary outcomes	Time to death or first myocardial infarction	Composite of death, myocardial infarction, hospitalization for chronic heart failure, stroke	Time to first cardiovascular event	Composite of death or a cardiovascular event and death or end-stage renal disease
Risks with higher hemoglobin level	Trend toward increased risk of primary outcome resulted in early study interruption	Increased risk of primary outcome	Trend toward risk increase that was nonsignificant: no benefits	No risk increase or reduction
Other results	Higher rate of thrombosis in high-target group		Improved quality of life	Higher rate of stroke

Nakhoul et al., Cleve Clin J Med 2016

Target Hemoglobin

FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease [6-24-2011]

•For patients with CKD, consider starting ESA treatment when the hemoglobin level is less than 10 g/dL. This advice does not define how far below 10 g/dL is appropriate for an individual to initiate. This advice also does not recommend that the goal is to achieve a hemoglobin of 10 g/dL or a hemoglobin above 10 g/dL.

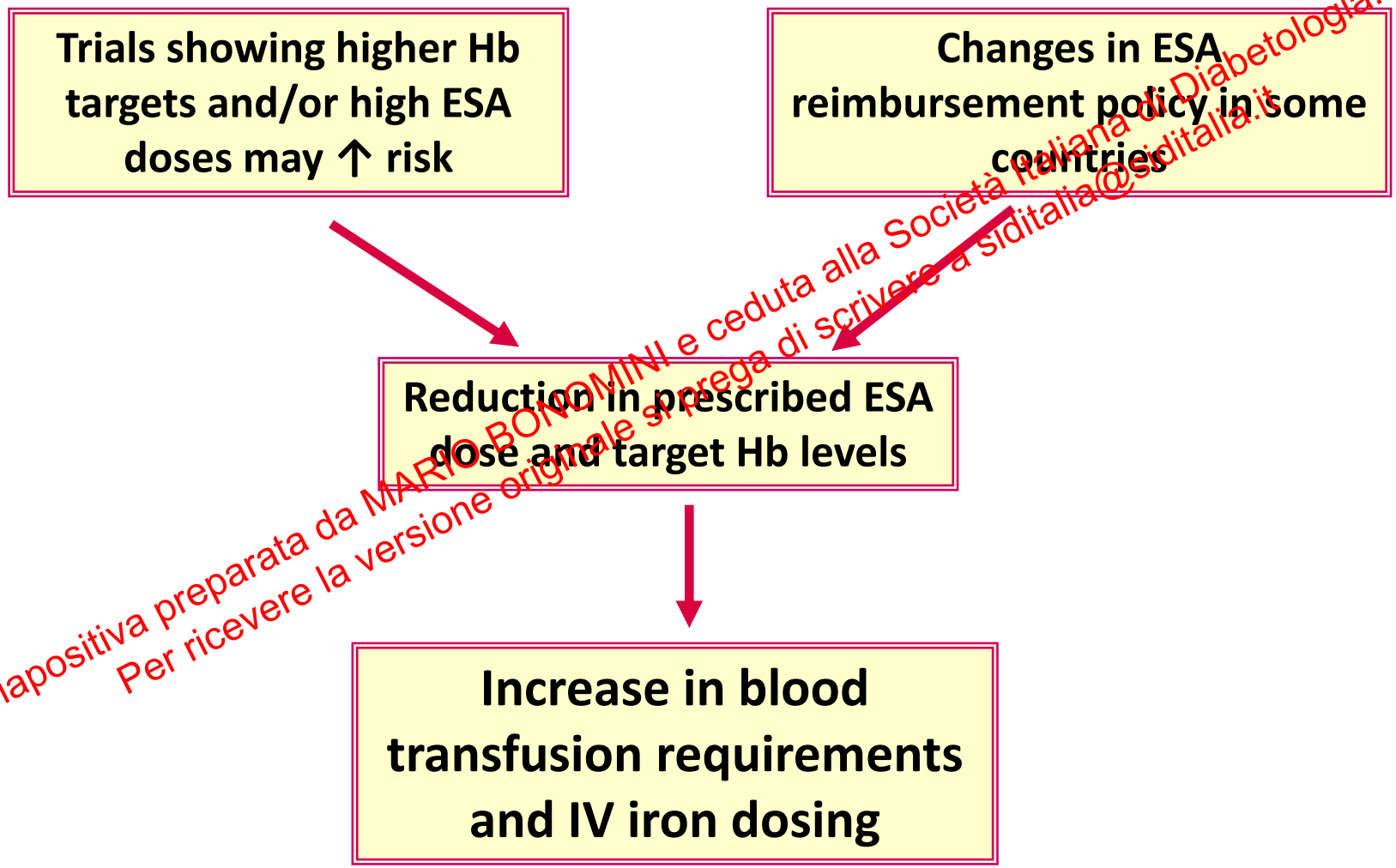
	Target Hb, g/dL
CKD	> 10
ESRD	10-11.5

KDIGO Anemia Work Group, Kidney Int 2012

Typically maintain the aspirational Hb range between 100 and 120 g/litre for adults, young people and children aged 2 years and older

NICE National Institute for Health and Care Excellence

2015



Bonomini et al., AJKD 2016

Strategies under development to stimulate erythropoiesis

Not Directly Targeting the EPO Receptor

- HIF stabilizers
  - FG-4592 (Roxadustat)
  - AKB-6548
  - GSK1278863
  - BAY 85-3934 (Molidustat)
  - JTZ-951
  - DS-1093a
- Activin traps
  - Sotatercept (ACE-011)
  - Luspatercept (ACE-536)
  - LY2157299

Targeting the EPO Receptor

- EPO mimetic peptides
  - Centocor molecules: CNTO 528, CNTO 530, CNTO 531
  - Affogen GmbH: AGEM400(HES)
  - Peginesatide[a]
- EPO fusion proteins
  - EPO-EPO dimers
  - EPO-CPT
  - EPO-$(CPT)_3$
  - Albumin-EPO
  - EPO-hyFc (Genexine GX-E2)
- Antibody agonists to EPO receptor
  - Mouse monoclonal IgG
  - Ab12 molecule
  - Ab12.6 (Abbott Laboratories ABT-007) molecule
- EPO gene therapy (TARGT EPO)
- Dimerization of EPO receptor intracellular domain with a CID

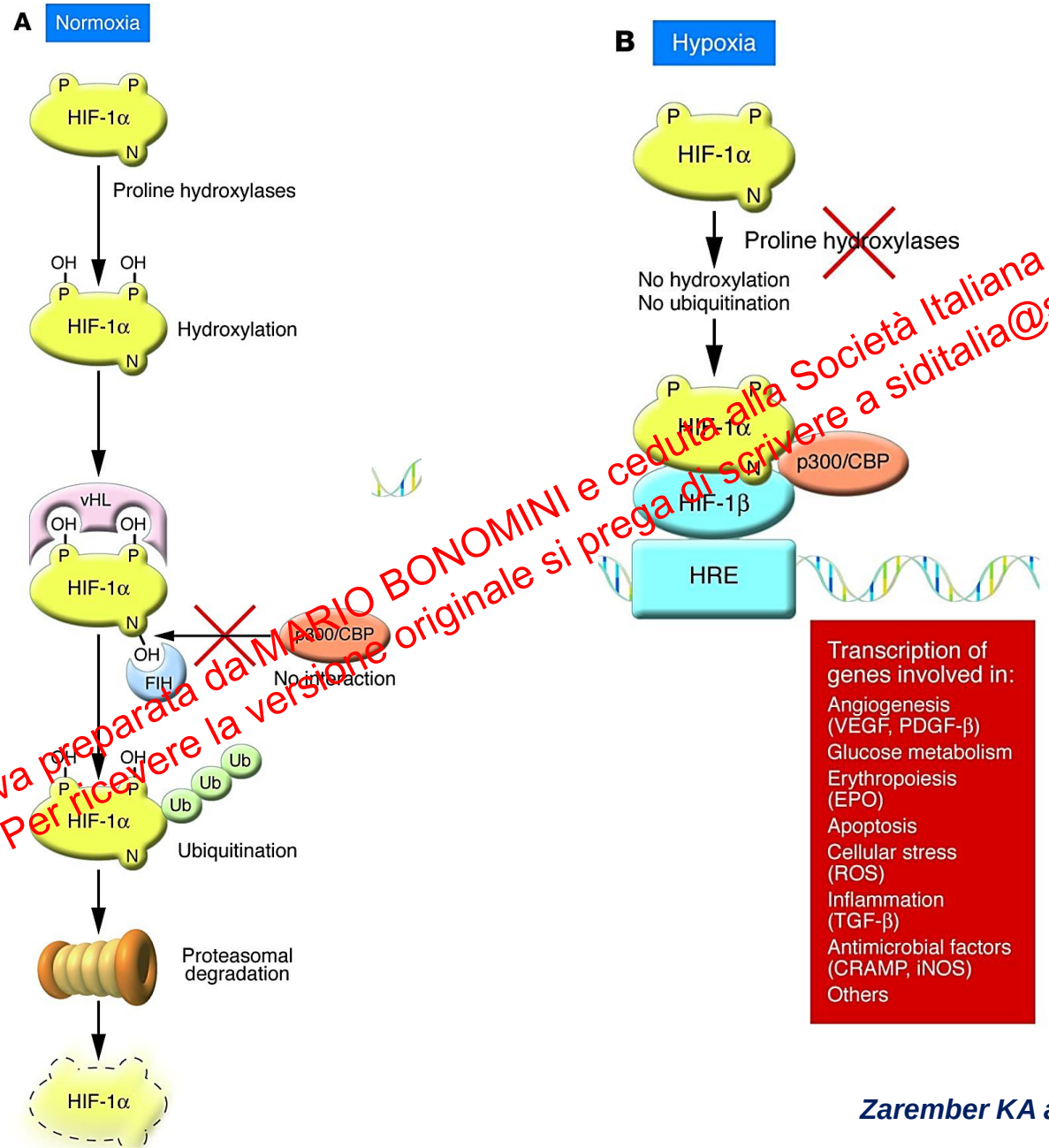
- **Stabilizzatori HIF**: inibitori competitivi prolil idrossilasi attivi per via orale

Bonomini et al., AJKD 2016

HIF stabilizers – data on clinical trials

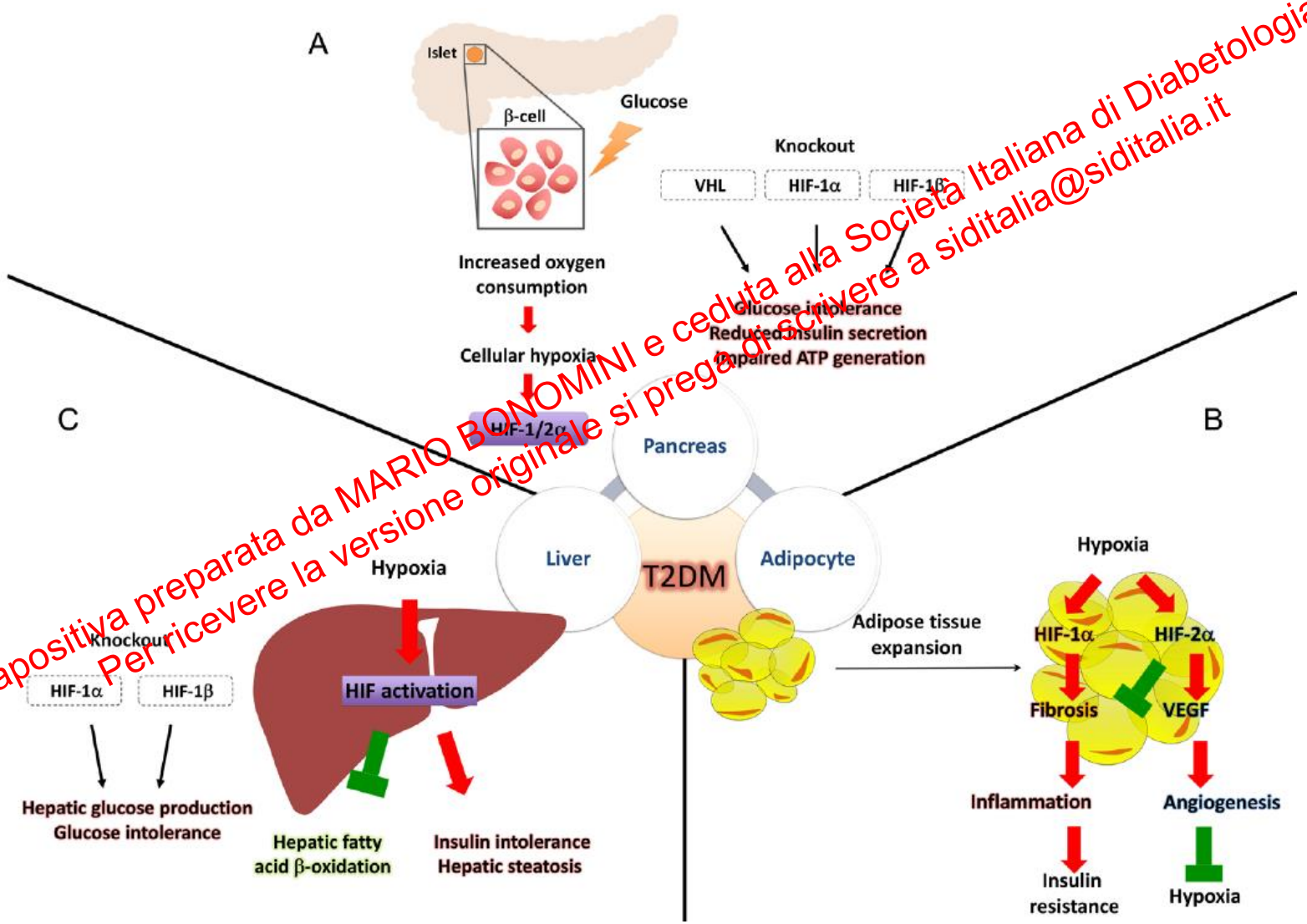
Compound	Company	Indication	Clinical trials	Target
Roxadustat	Fibrogen, Astellas, Astra Zeneca	Renal anemia	Phase 3 end	Stabilization of HIF Upregulation of EPO receptor in the bone marrow
Vadodustat	Akebia Therapeutics	Renal anemia	Phase 3 ongong	Stabilization of HIF Upregulation of EPO receptor in the bone marrow
Daprodustat	Glaxo Smith Kline	Renal anemia	Phase 3 ongoing	Stabilization of HIF Upregulation of EPO receptor in the bone marrow
Molidustat	Bayer Pharmaceuticals	Renal anemia	Phase 3 ongoing	Stabilization of HIF Upregulation of EPO receptor in the bone marrow
Enarodustat JTZ-951	Akros Pharmaceuticals	Renal anemia	Phase 3	Stabilization of HIF Upregulation of EPO receptor in the bone marrow
DS 1093a	Daiichi Sankyo	Renal anemia	Phase 1 completes	Stabilization of HIF Upregulation of EPO receptor in the bone marrow

Malyszko et al., Expert Opin Ther Targets 2019



Zarember KA and Malech HL, JCI 2005

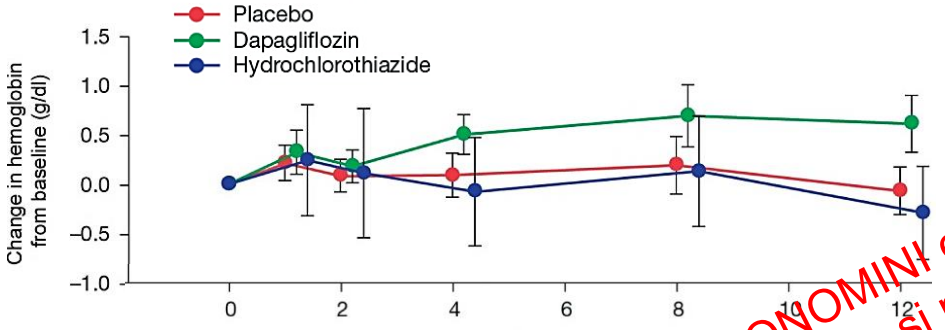
Regulation and function of HIF in endocrine organs associated with type 2 diabetes mellitus

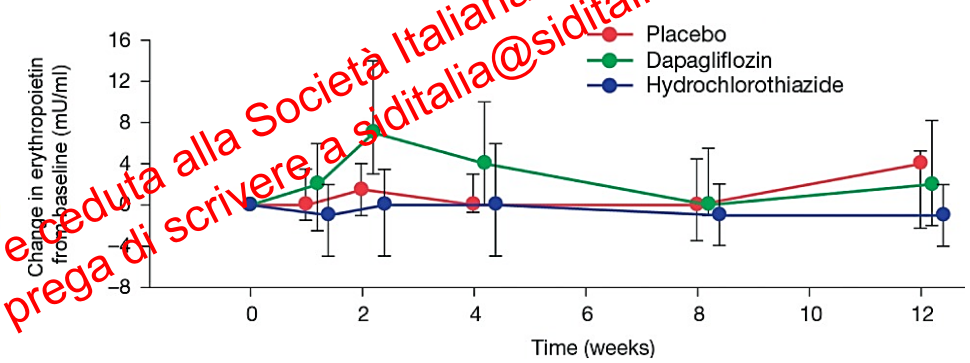


Lee H-C et al., J Endocrinol 2017

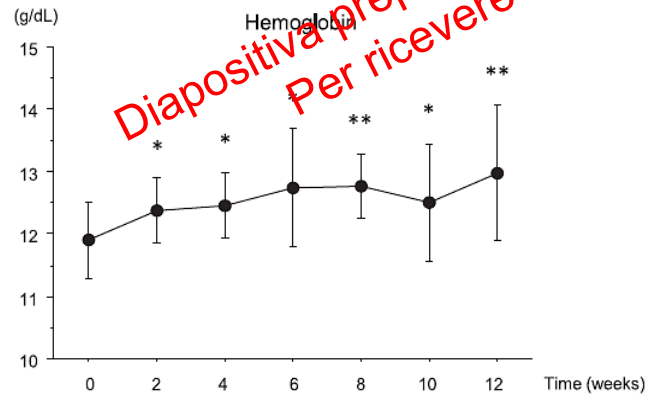
SGLT2 inhibitors in renal anemia

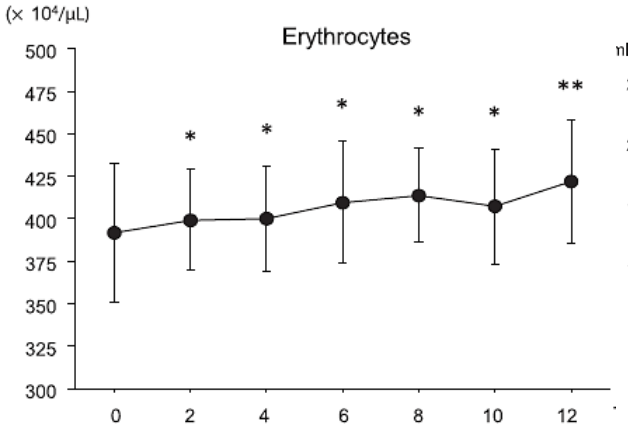
Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes *Lambers Heerspink et al., Diabetes Obes Metab 2013*

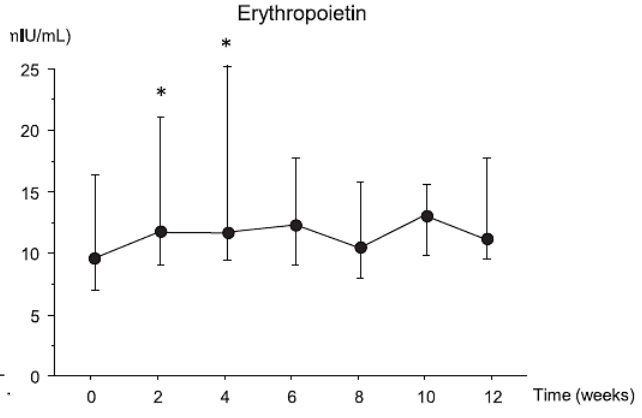




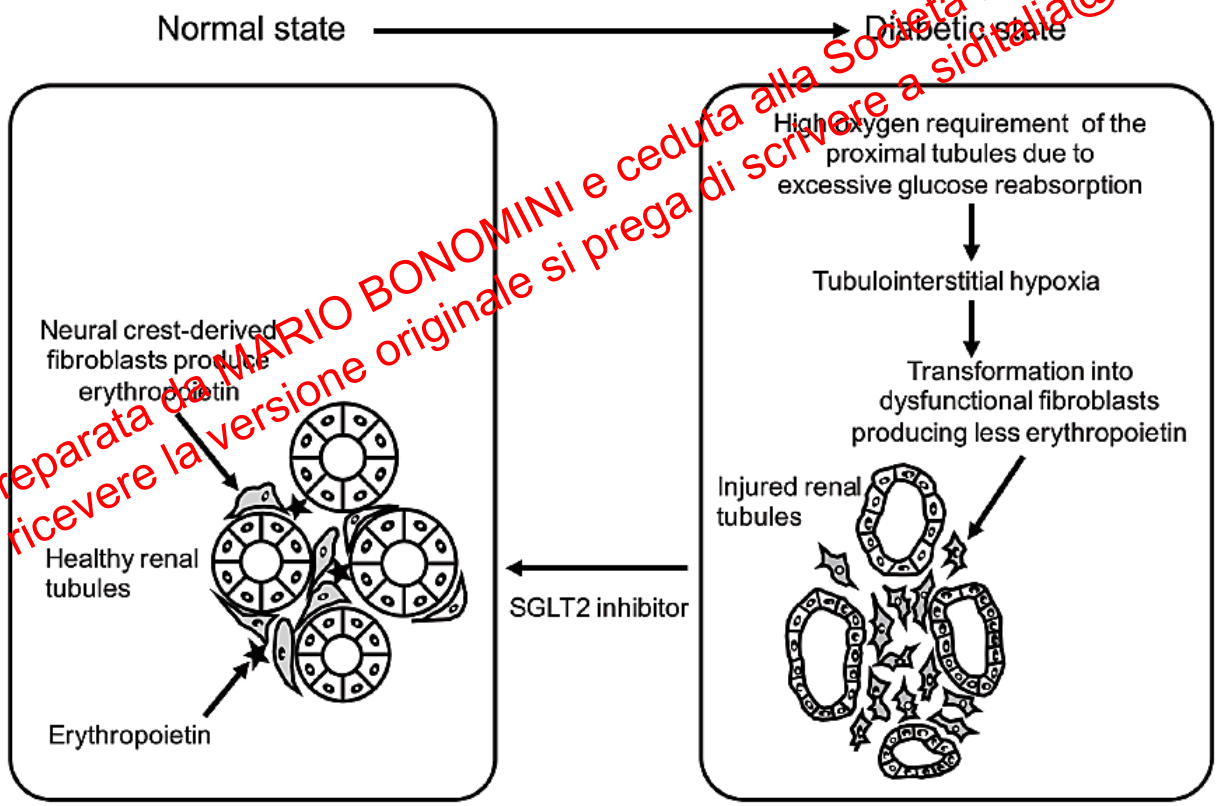
Canagliflozin improves erythropoiesis in diabetes patients with anemia of chronic kidney disease *Maruyama et al., Diabetes Technol Ther 2019*







Increased Hematocrit During Sodium-Glucose Cotransporter 2 Inhibitor Therapy Indicates Recovery of Tubulointerstitial Function in Diabetic Kidneys



Sano et al., J Clin Med Res 2016

Table 2—Univariable mediation analysis of risk of CV death with empagliflozin versus placebo: time-dependent covariate analysis adjusting for the change from baseline in each variable

	HR for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.615 (0.491, 0.770)	
Adjusted for		
HbA_{1c}	0.624 (0.496, 0.785)	3.0
FPG	0.665 (0.529, 0.837)	16.1
SBP	0.593 (0.473, 0.743)	−7.5
DBP	0.614 (0.490, 0.769)	−0.3
Heart rate	0.621 (0.495, 0.780)	2.0
LDL-C	0.596 (0.473, 0.748)	−6.5
HDL-C	0.638 (0.506, 0.799)	6.9
logTG	0.604 (0.482, 0.758)	−3.7
FFAs	0.586 (0.463, 0.741)	−9.9
logUACR	0.649 (0.518, 0.815)	11.1
eGFR (MDRD)	0.631 (0.504, 0.790)	5.3
eGFR (CKD-EPI)	0.632 (0.505, 0.791)	5.6
Weight	0.579 (0.461, 0.727)	−12.4
BMI	0.578 (0.460, 0.726)	−12.8
WC	0.598 (0.477, 0.750)	−5.8
Hematocrit	0.791 (0.626, 1.000)	51.8
Hemoglobin	0.780 (0.619, 0.983)	48.9
Albumin	0.696 (0.555, 0.873)	25.5
Uric acid	0.693 (0.553, 0.869)	24.6

Inzucchi et al., Diabetes Care 2018

Anemia nella DKD

- Complicanza frequente, spesso precoce
- Cause principali: insufficiente produzione di EPO e deficit di ferro (assoluto e/o funzionale)
- Approccio terapeutico attuale come nella CKD non diabetica
- Gli studi in corso e le derivanti informazioni su efficienza e sicurezza di nuovi agenti in grado di migliorare l'eritropoiesi, anche mediante nuovi meccanismi d'azione, potrebbero consentirne una migliore e più semplice gestione