Iron Overload in CKD and Effects on Various Tissues

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Disclosure of Interests

Alphabetical order:

Abbott: Grant, Speaker bureau
Affymax: Advisory Board
Amgen: Advisory Board, Speaker bureau
BBraun: Speaking engagemenet
DaVita: grant, medical directorship
Fresenius: Speaker bureau, Consultant
Genzyme: Consultant, proctorship
Keryx: Advisory boards
NKF: Grants, advisory boards
NIH: Study sections, grants
Otsuka: Speaker bureau, consultation
Rockwell: Advisory board
Shire: Speaker bureau, consultation
Vifor: consultation

We cope well with iron shortage…

- **The human body has many mechanisms to absorb, transfer, and store iron**

- **Iron Deficiency (ID) is the most common deficiency state in the world**

  Most common causes of ID in non-CKD:
  - Blood loss
  - Diet

  Most common causes of ID in CKD:
  - GI blood loss?
  - ESA use without iron?

- Iron Reserves: ~1000 mg of iron is stored as ***ferritin*** (1/3 of total body iron)
- Intestinal absorption of iron increases in response to deficiency

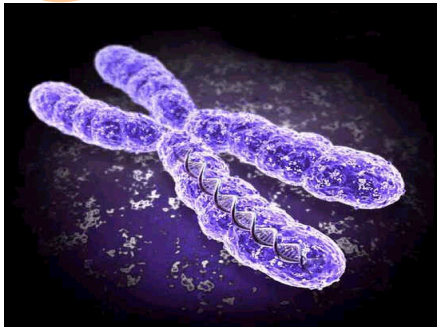
But we cope poorly with iron excess

- *Hepcidin system to "trap" iron … but it does not get rid of excess iron*
- Some iron is excreted by shedding of intestinal cells?
- There is no effective physiologic mechanism to "excrete" excessive iron

Spectrum of chronic iron overload

- Transfusional iron overload

- Genetic iron overload



- IV iron in CKD pts?

Blood transfusion can overwhelm the iron balance

- Normal daily iron flux:

1-2 mg

- Each unit of PRBC:

- IV iron to hemodialysis patients:

50-400 mg

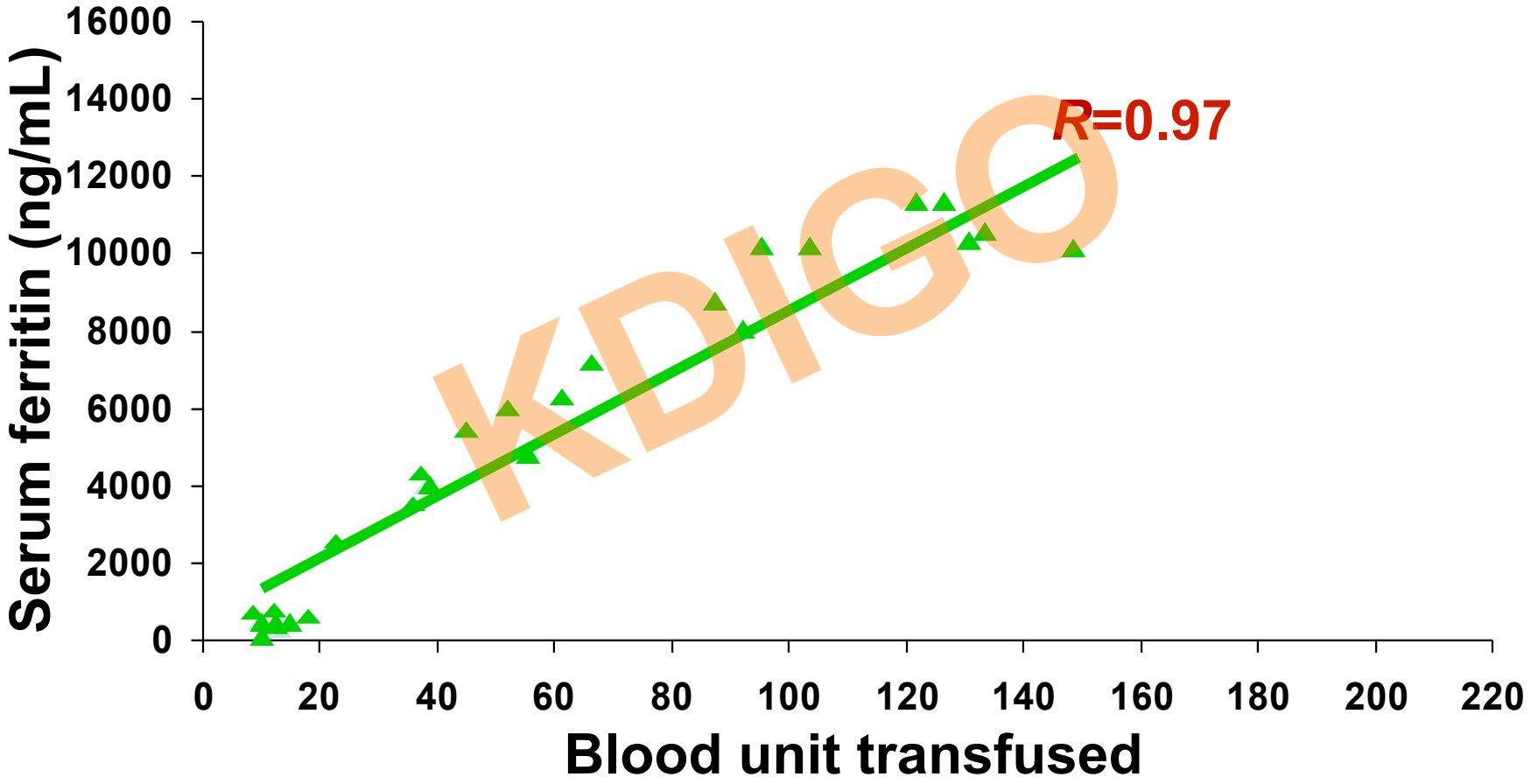
But… ESA therapy in ESRD pts likely has prevented and even cured iron overload, be it from PRBC transfusion or IV iron!

When does iron become a problem?

- Normally 2.5 – 3 grams of iron in the body.

- Tissue damage when total body iron is 7 – 15 grams
  - After 30-50 units of red blood cells (e.g. in Thalassemia)

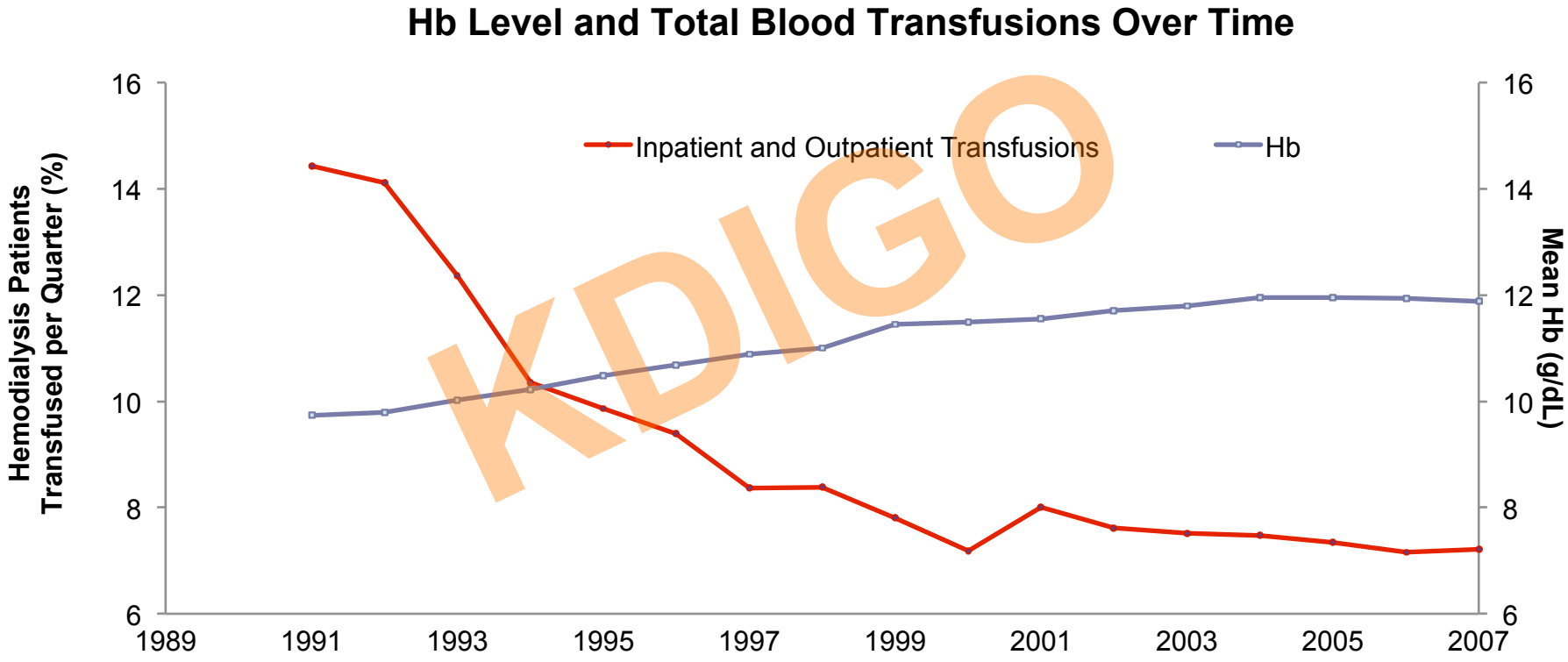
Correlation between serum ferritin levels and transfusion burden



Kattamis C et al. *The Management of Genetic Disorders* 1979;351–359

Transfusions Dramatically Decreased in Medicare Patients on Dialysis 1989-2007

1989: Recombinant Human Erythropoietin Introduced



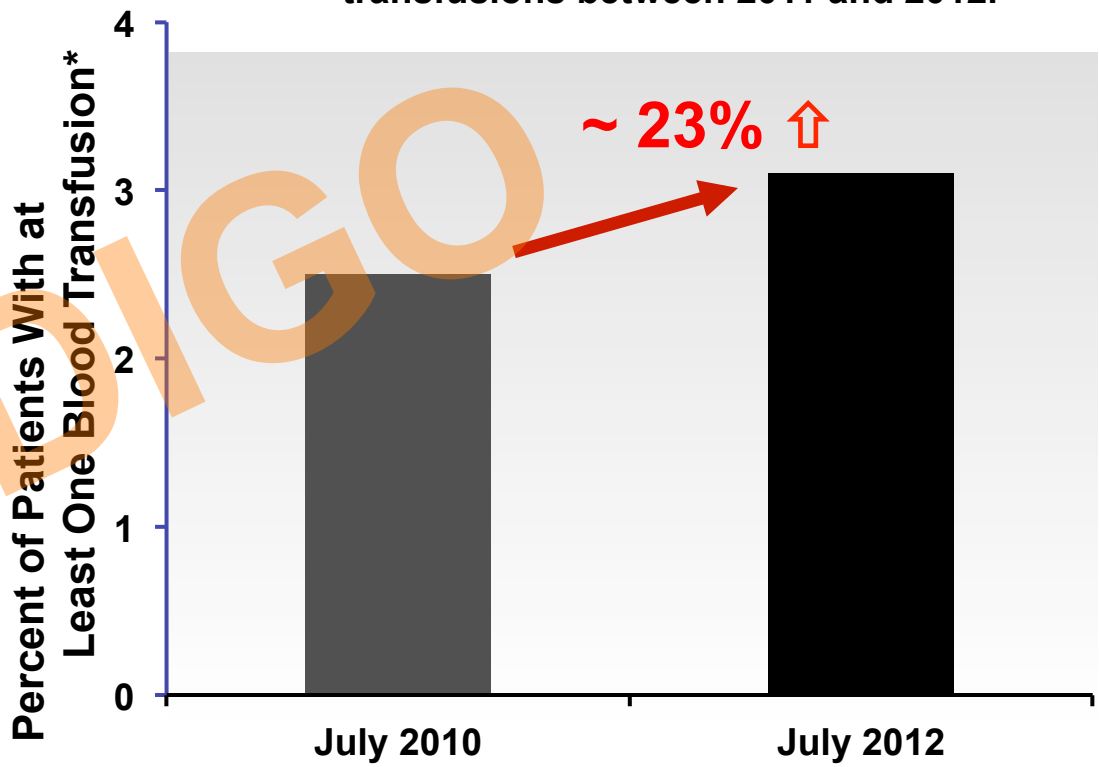
US Renal Data System. *USRDS 2009 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* 2009.

RBC Transfusion Rate in increased in dialysis patients since 2010

- **An analysis conducted by the CMS found that the average monthly blood transfusion rate increased 19% between 2010 and 2011.[1]**

USRDS = United States Renal Data System; CMS = Centers for Medicare & Medicaid Services.
*USRDS data are for period prevalent patients on dialysis in 2011 and 2012. Only patients with a dialysis claim during the month were included in the analysis.

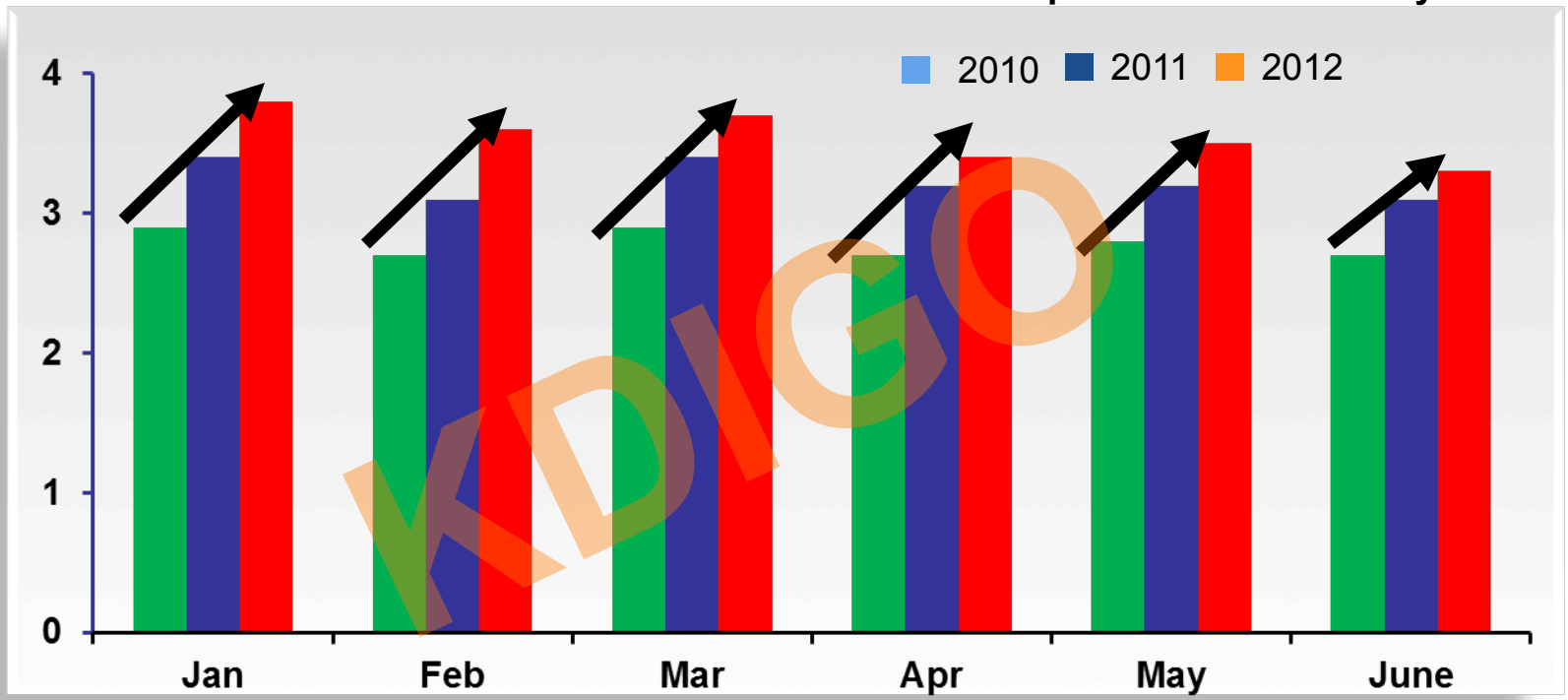
USRDS data demonstrated an increase in transfusions between 2011 and 2012.[2]



1. Centers for Medicare & Medicaid Services CMS-1352F. *Fed Regist.* November 9, 2012;77: 67450-67531. 42 CFR Parts 413 and 417.
2. Adapted from: US Renal Data System. *USRDS 2013 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* 2013.

RBC Transfusion Rates: 2010, 2011 and 2012 from USRDS Data

USRDS data demonstrated an increase in transfusions in patients on hemodialysis

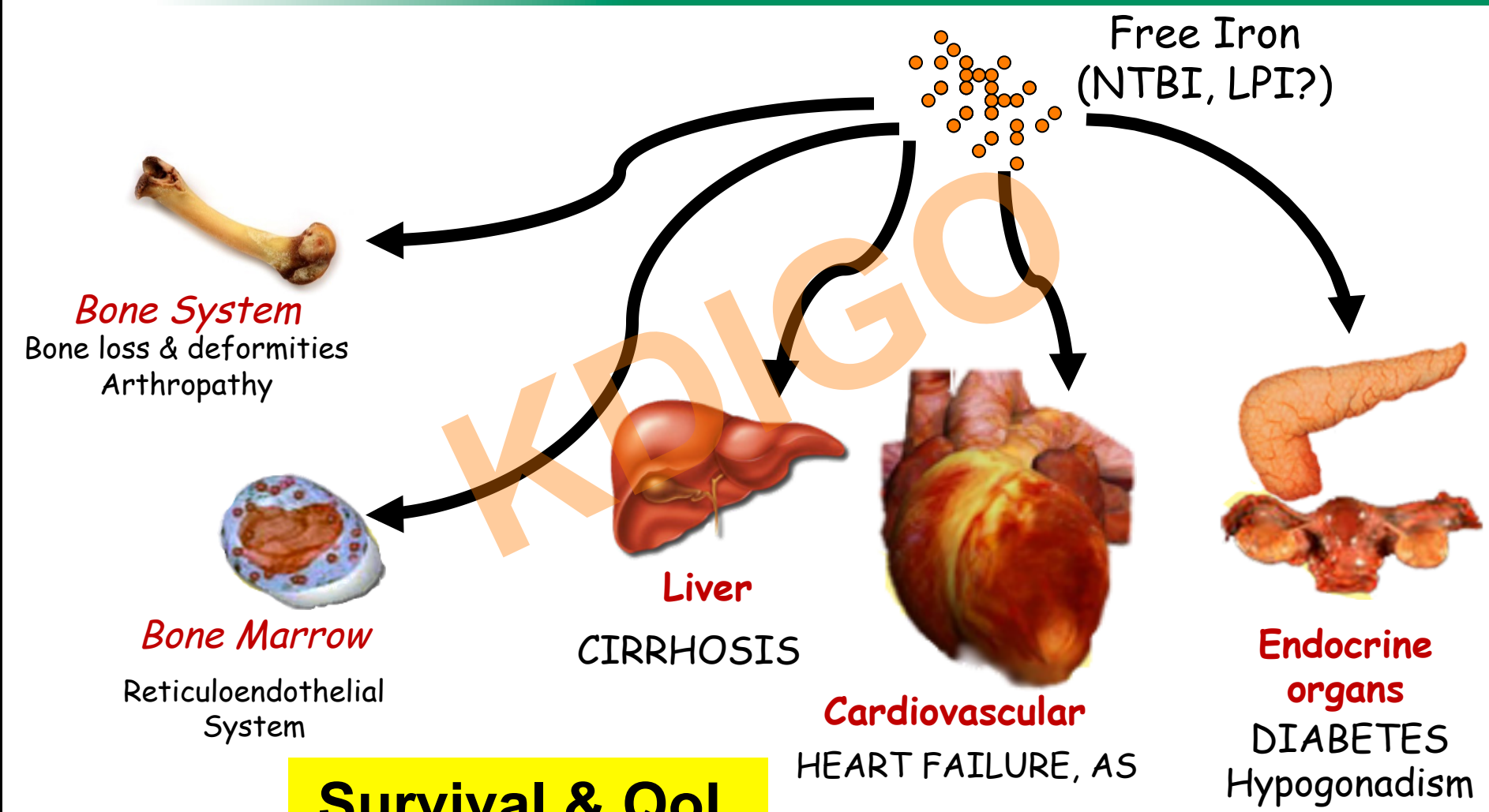


Monthly comparisons between 2010 and 2012 showed a 22% to 33% increase in the percent of patients receiving transfusions

USRDS = United States Renal Data Systems.
*USRDS data are for patients on dialysis with at least one transfusion event during the month.

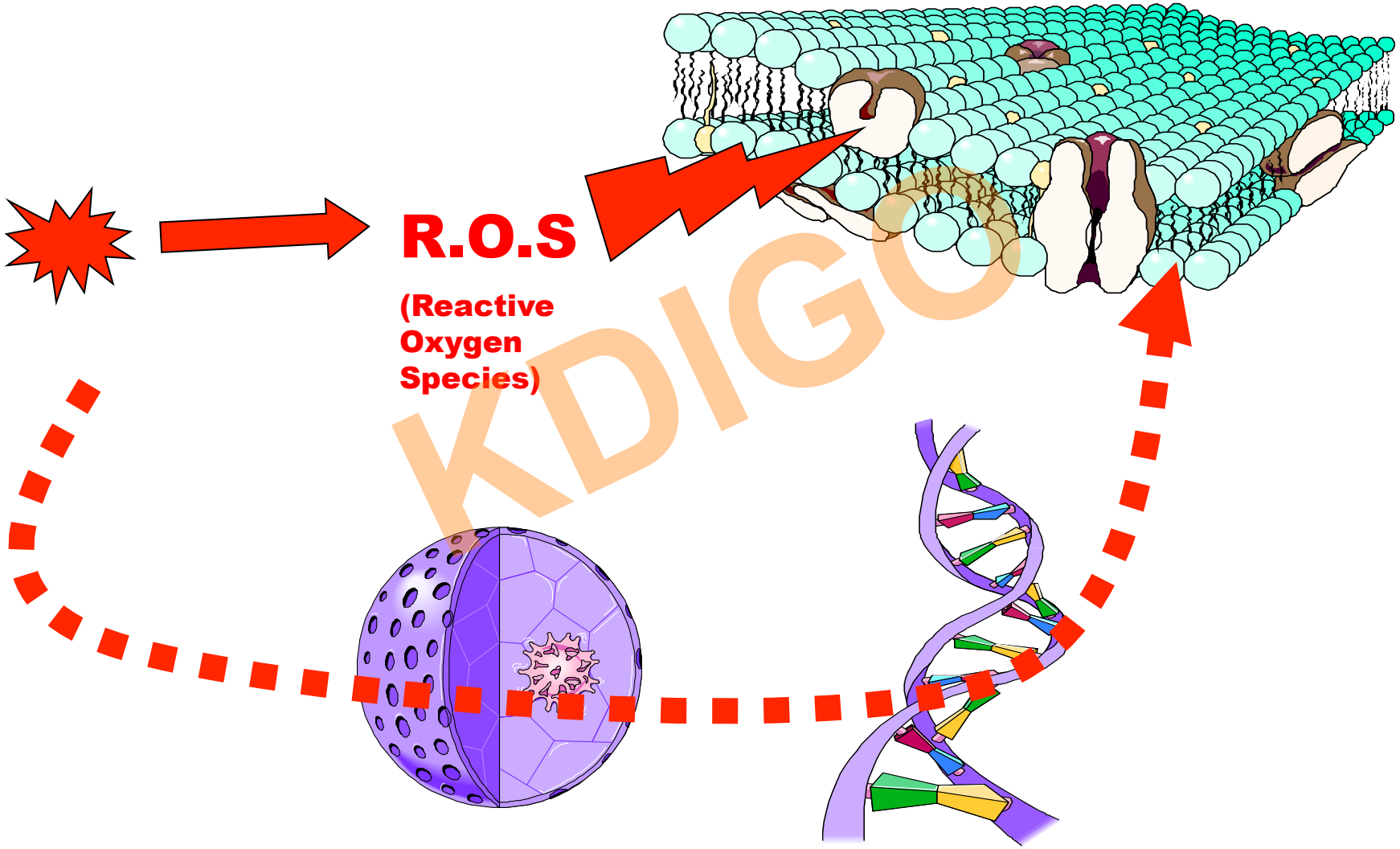
Adapted from: US Renal Data System. *USRDS 2013 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* 2013.

Iron Overload Effects on Various Tissues

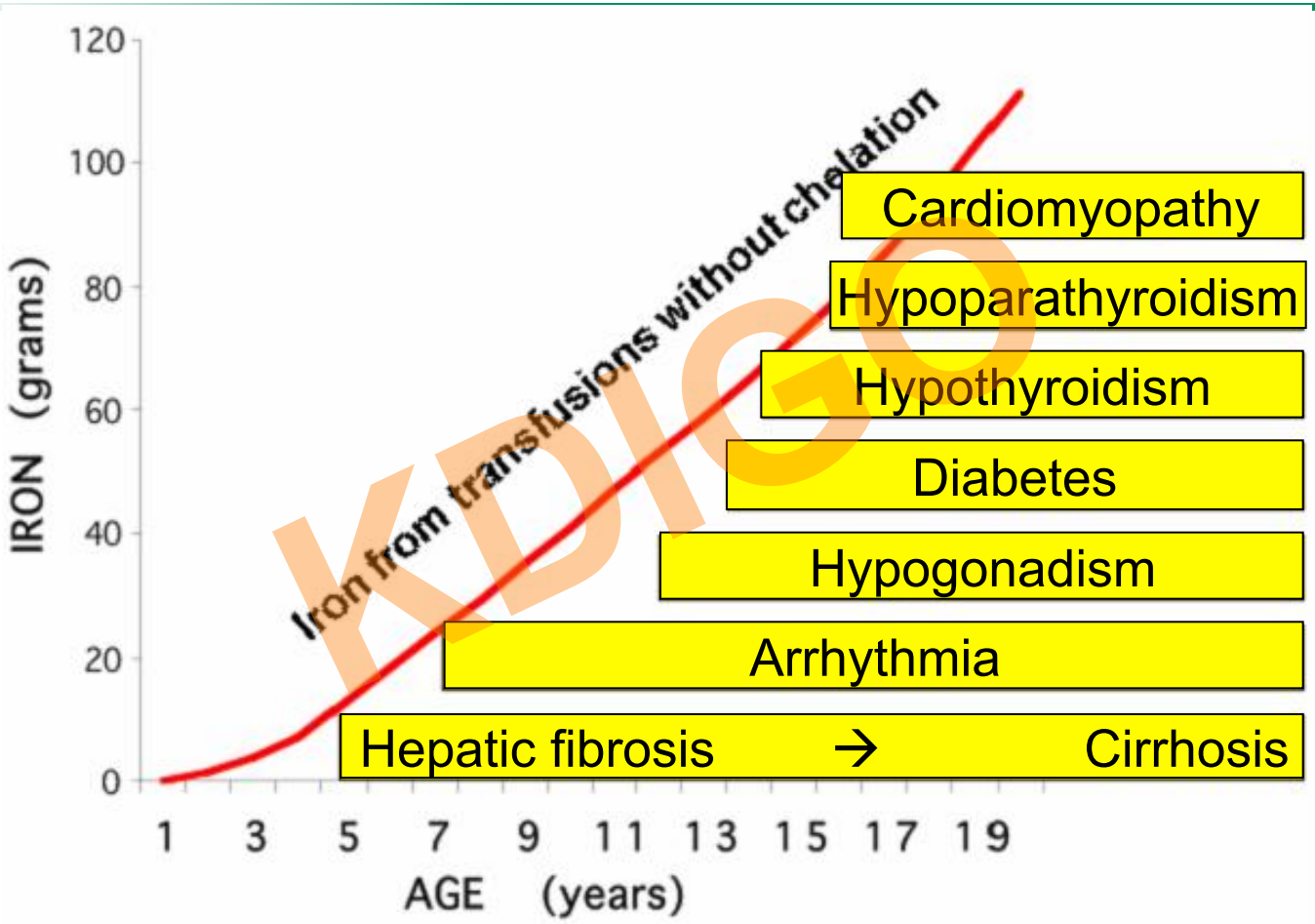


Survival & QoL

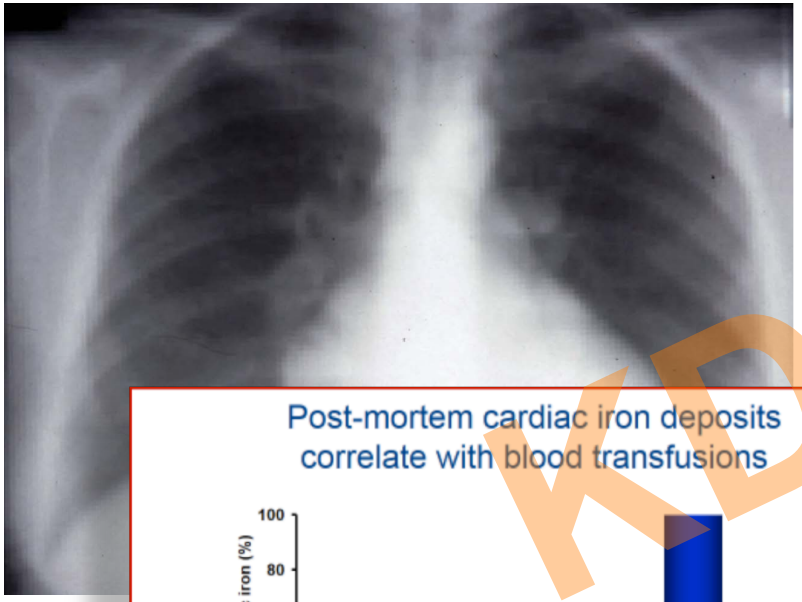
Dangerous iron species

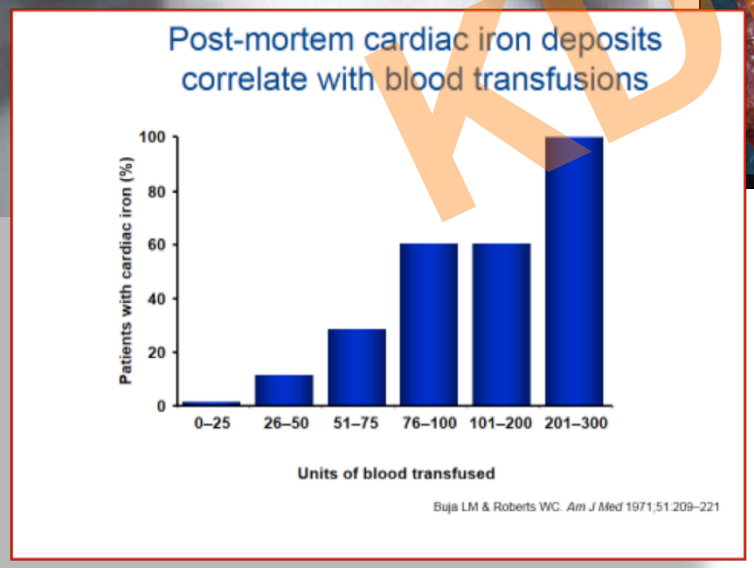


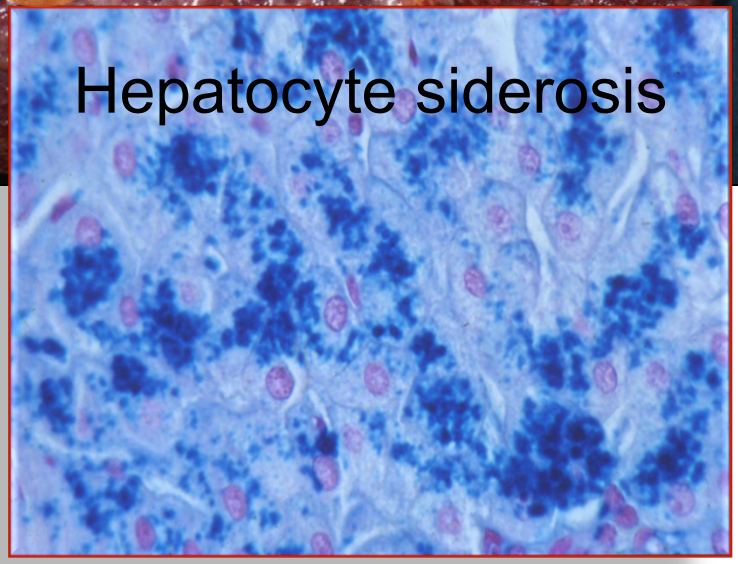
Lessons from thalassemia, sickle cell, MDS



Visceral targets of iron overload: liver and heart



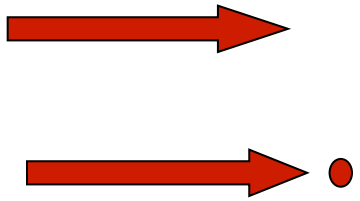




Impact of iron overload on endocrine glands

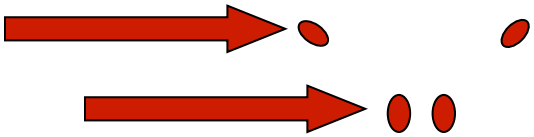
Lower height of pituitary gland

Argyropoulou MI, et al. Neuroradiology. 2001;43:1056-8



Hypogonadism (50% patients)

Clin Endocrinology (Oxf). 1995;42:581-6



Short stature

Raiola G, et al. J Pediatr Endocrinol Metab. 2003;16:259-66.

Iron overload causes insulin deficiency and insulin resistance and diabetes

- Iron overload causes apoptosis of beta cells which are exquisitely susceptible to oxidative stress due to their limited antioxidant capacity and high affinity for Fe uptake
- Even subtle increases in dietary iron content (red meat) and modest elevation of body iron pool are associated with insulin resistance, metabolic syndrome, and gestational diabetes
- Iron deficiency & reduction of body iron pool with bloodletting or blood donation ameliorates insulin resistance and improves glycemic control in type 2 diabetics
- Iron chelation therapy and blood donation reduce the risk of diabetes in normal subjects

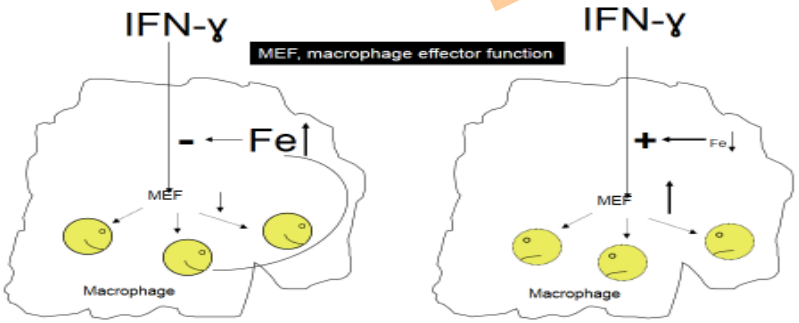
Vaziri et al, multiple publications

Iron overload & risk of infections

- **Infection is the second most common cause of mortality among ESRD patients**

- **Iron overload → increased susceptibility to infections in both ESRD and general populations.**
  - **Fe is essential for bacterial multiplication & iron availability is closely associated with bacterial virulence**
  - **Iron overload impairs immune function, thereby heightens susceptibility to and increases severity of infection**

Iron Loading of Macrophages and PMNs Impairs Their Ability to Kill Intracellular Pathogens by IFN-γ Mediated Pathways



II- Iron heightens growth and virulence of pathogens

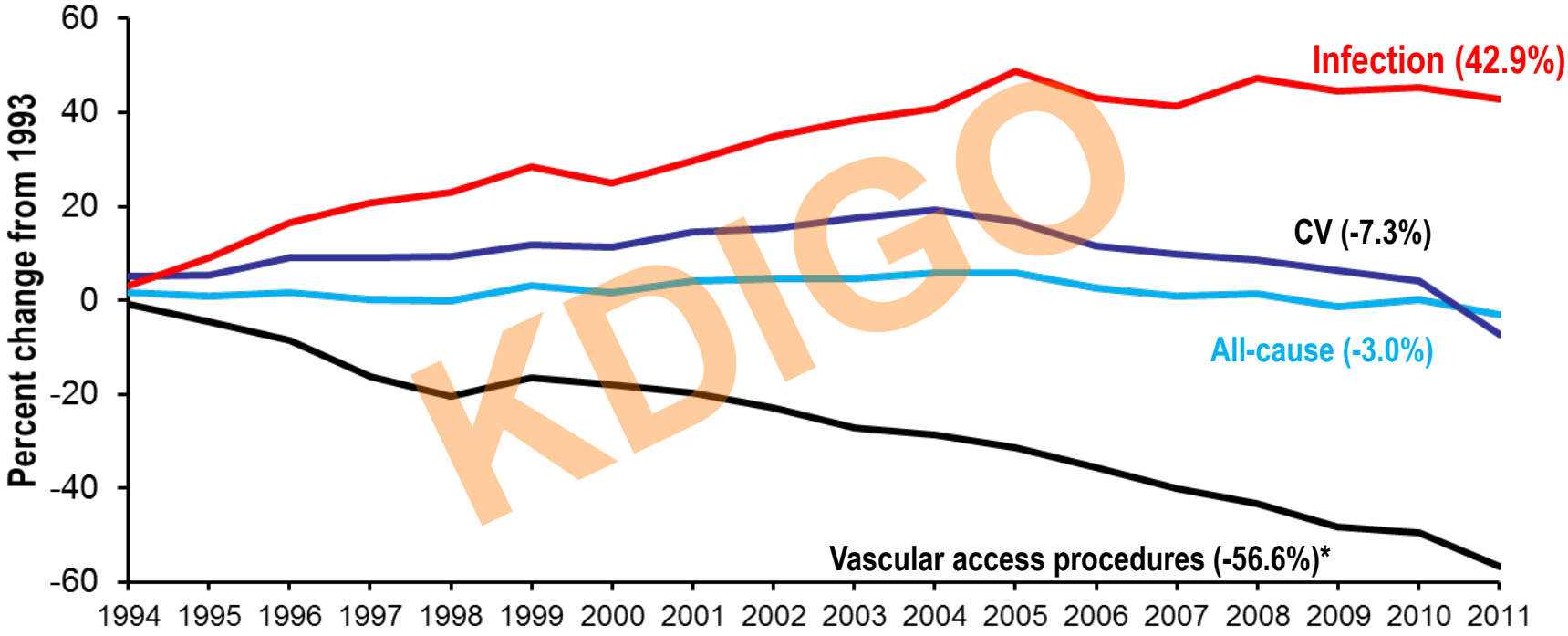
Vaziri et al, multiple publications

IRON & INFECTION in CKD
Iron overload impairs the Immune system

- **ESRD → immune deficiency → increased risk of infection**
- **IV iron → compound uremia-induced immune deficiency**
  - **IV iron → intracellular ROS → shortens survival of CD4+ lymphocyte**
  - **IV iron → impair phagocytic activity and microbial killing capability of neutrophils**
- **lymphocytes are poorly equipped to sequester iron in ferritin → excess iron delivered by hydrophilic chelates can be toxic for lymphocytes**
- **iron overload →**
  - **CD4+ T cell depletion**
  - **reduction of B cells, dendritic cells,**
  - **defective monocytes/neutrophils phagocytic capacity**
  - ***Vaziri et al, multiple publications***

Hospitalization Rates Due to Infection Have Increased in Hemodialysis Patients

USRDS analysis of period prevalent hemodialysis patients in 2011; rates adjusted for age, gender, race, & primary diagnosis; reference = ESRD patients in 2010

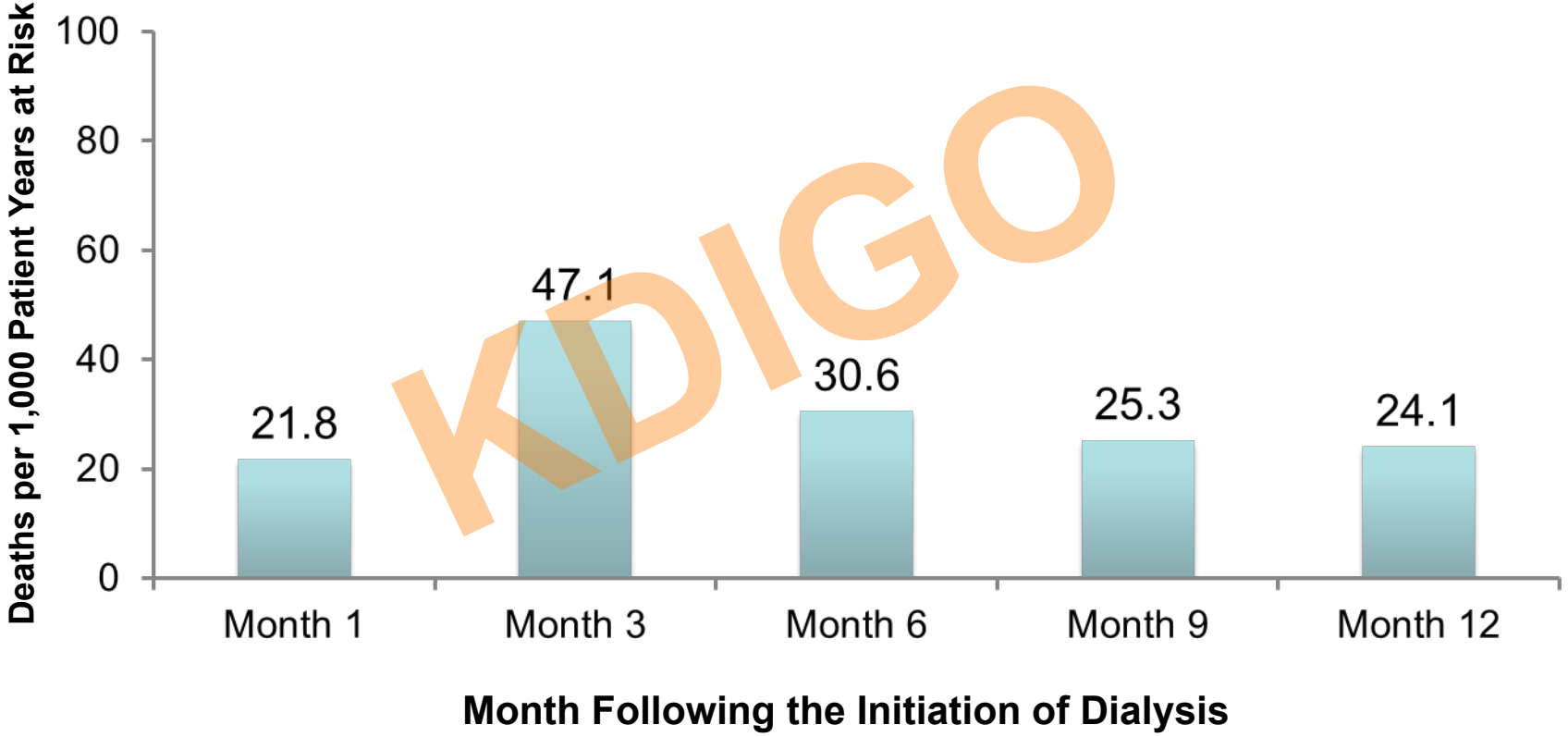


CV = cardiovascular.

Adapted from: US Renal Data System. *USRDS 2013 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* 2013.
US Renal Data System. *USRDS 2012 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* 2013.

Infection Is a Contributor to Mortality in the First Year of Dialysis

Adjusted cause-specific mortality in the first months of therapy: mortality due to infection in 2008



Incident hemodialysis patients; adjusted for age, gender, race, & primary diagnosis.
Incident hemodialysis patients, 2005, used as reference cohort.

Adapted from: US Renal Data System. *USRDS 2011 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* 2011.

Iron & carotid artery lesions

- **Carotid artery lesions in humans contain large amounts of iron, which strongly correlates with the plaque's cholesterol and oxidized protein contents.**

- **In patients with carotid atherosclerosis serum ferritin level correlates with the level of low molecular weight iron compounds and lipid peroxidation products in the carotid endarterectomy specimens.** ***(Vaziri et al, multiple publications)***

- **Interaction of iron and lipoproteins in the plaque promotes plaque instability by inducing foam cell apoptosis**

- **RCT of mild iron reduction therapy (phlebotomy Q 6 months) in elderly patients with peripheral vascular disease (the"FeAST" trial) showed that Fe reduction strategy is safe and that it can reduce CV and overall M&M if initiated early but not late in the course of the disease.**
  (Reduction of Iron Stores and Cardiovascular Outcomes in Patients With Peripheral Arterial Disease, A Randomized Controlled Trial, *JAMA. 2007*)

Common Carotid Artery IMT & Iron in Dialysis Patients

Drueke Study 2002: Cohort of 79 HD patients:

Cumulative iron dose was positively related to CCA-IMT (*P*=0.015) in patients <60 years

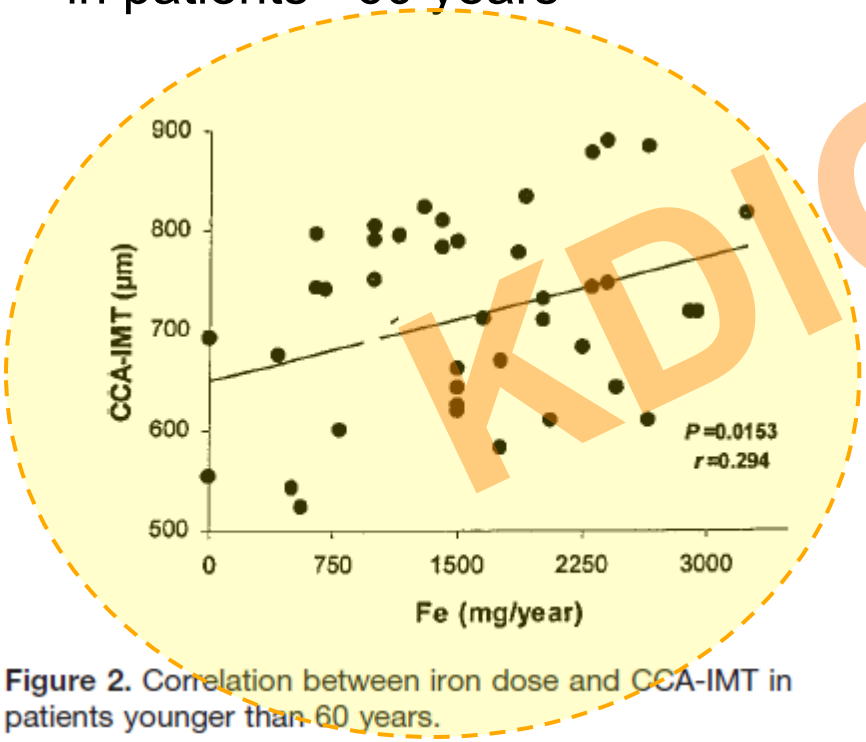
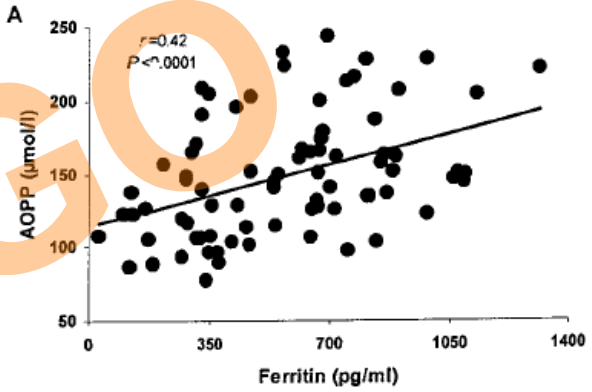
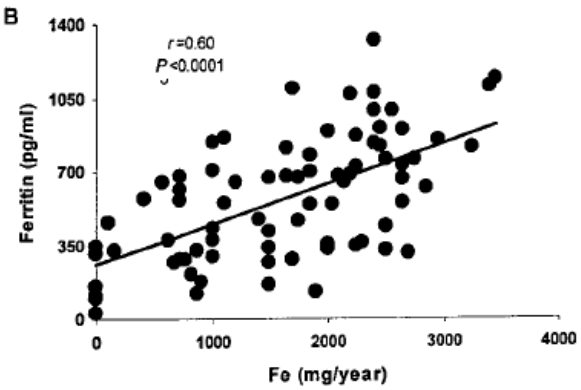


Figure 2. Correlation between iron dose and CCA-IMT in patients younger than 60 years.





Drueke et al, ***Circulation*** 2002

Potential role of iron in progression of renal disease

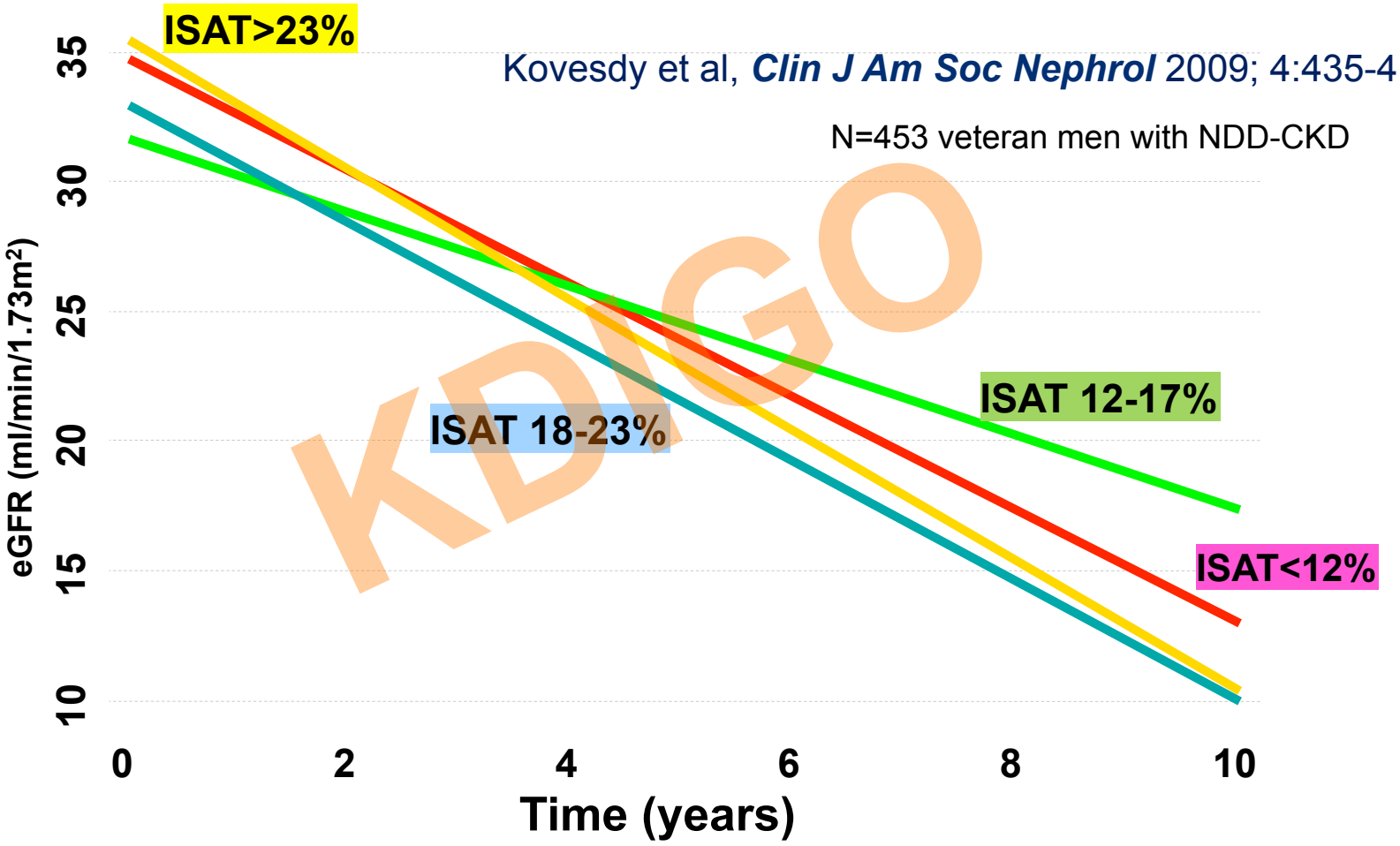
- **Catalytically active iron accumulates in the renal tissue in various models of AKI**
- **Iron chelation therapy attenuates renal injury and dysfunction in these models**
- **Proteinuria results in accumulation of iron in the proximal tubular epithelial cells (most likely through uptake of filtered iron-binding proteins) causing cell damage**
- **Iron chelation therapy or iron deficient diet ameliorate proteinuria and improve renal function and structure in animal models of anti-GBM glomerulonephritis, puromycin-induced minimal change disease, membranous nephropathy and immune complex glomerulonephritis induced**

- **the role of iron in AKI, progression of CKD and potential loss of residual renal function in CKD and ESRD patients treated with excessive amounts of IV iron.**

Shah SV, Rajapurkar MM.. *Hemoglobin,* 33(5):378–385, 2009

Vaziri et al, multiple publications

Potential role of iron in progression of renal disease

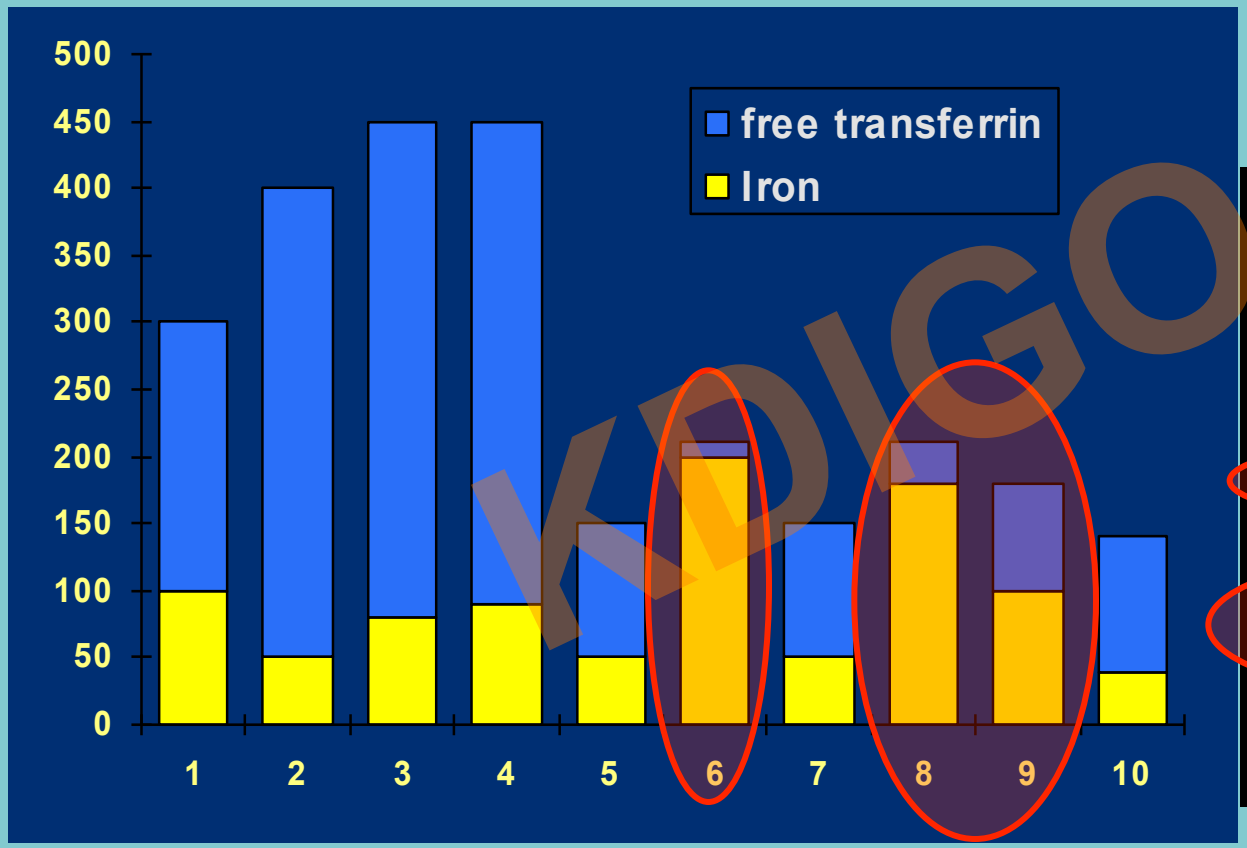


Diagnose of Iron Overload in CKD

Diagnosis of Iron Overload in CKD: How do we know if there's too much iron?

- Transferrin Saturation
- Serum ferritin concentration
  - Used in clinical practice globally
- Liver biopsy
  - Reference methodology ('gold standard')
- Magnetic resonance imaging (MRI)
  - Investigational, potential for broad access

TSAT in Different Disease States



1- normal
2- Iron deficiency
3- pregnancy
4- oral contraceptive
5- Inflammation
6- Hemochromatosis
7- Nephrotic syndrome
8- Porphyria
9- Thalasemia
10- Hypoproteinemia (malnutrition)

The transferrin saturation index is calculated according the equation:

Saturation (%) = serum iron / TIBC

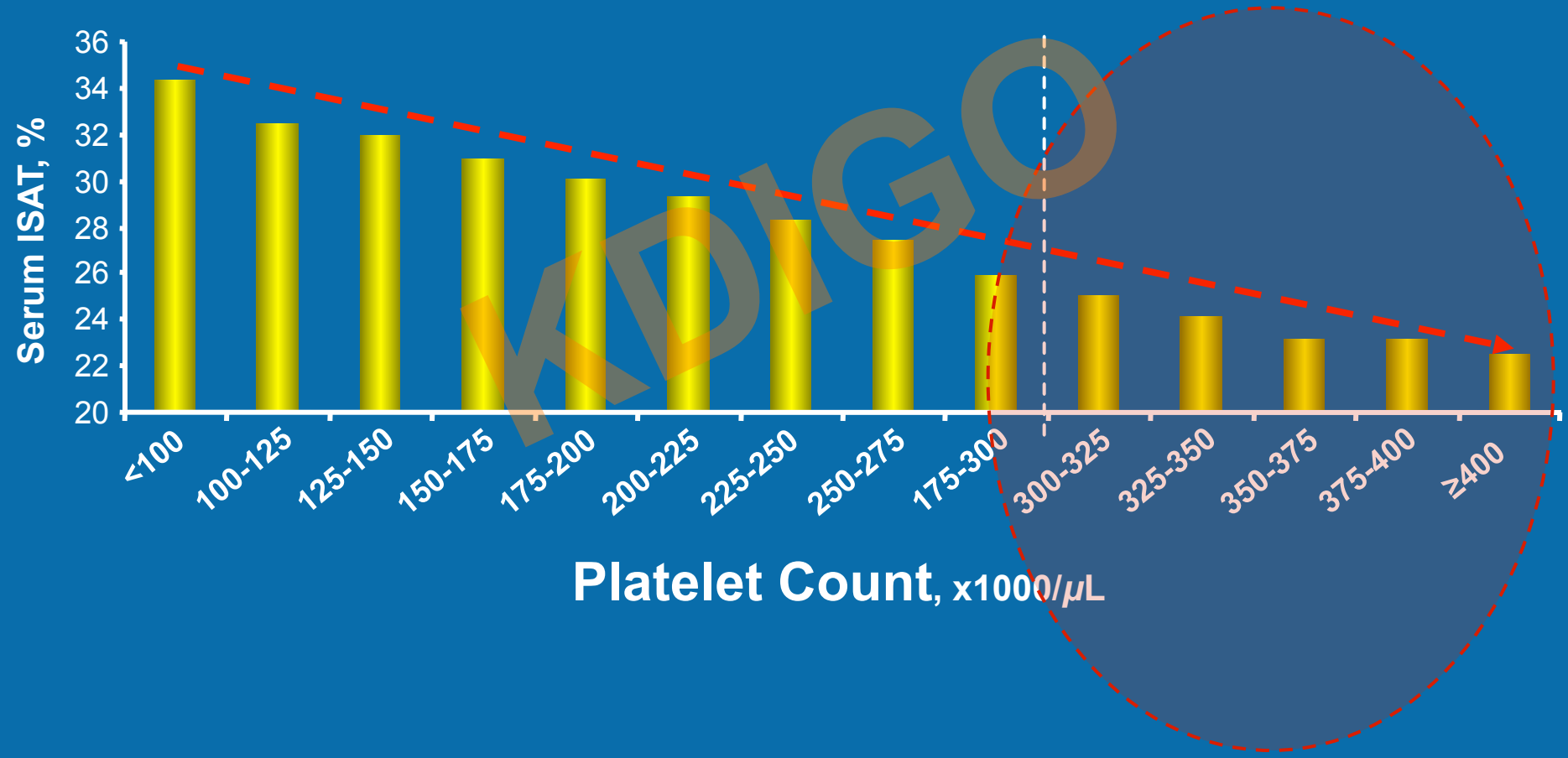
Limitations of TSAT in Diagnosing ID in Dialysis Patients

Malnutrition-inflammation, by lowering serum transferrin level, may interfere with the reliability of the transferrin saturation ratio as a diagnostic tool for iron deficiency in dialysis patients.

$$\uparrow \text{TSAT} = \frac{\text{Serum Iron}}{\downarrow \text{TIBC}}$$

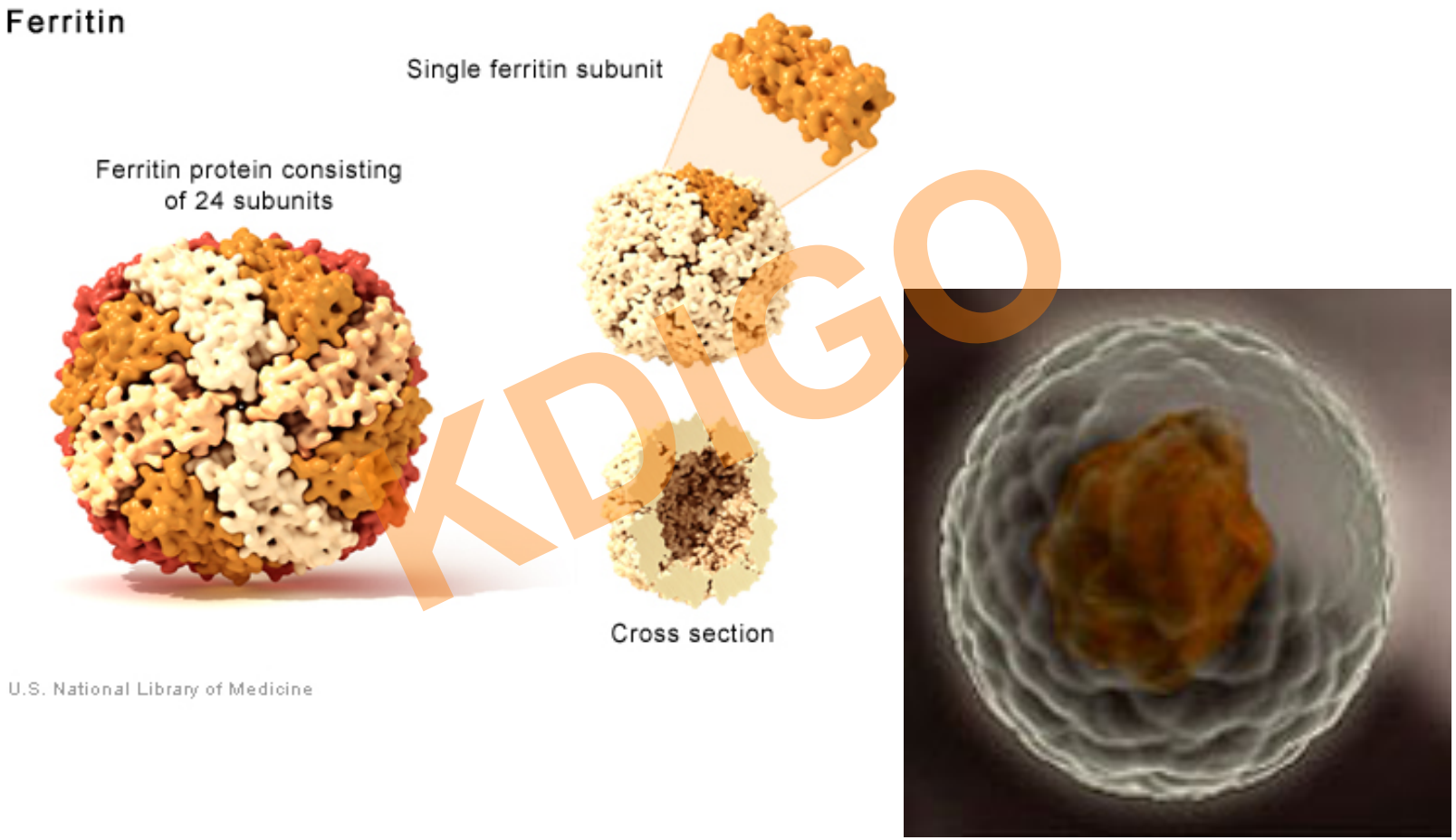
Low TSAT → High Platelet Counts

in 40,787 HD Patients

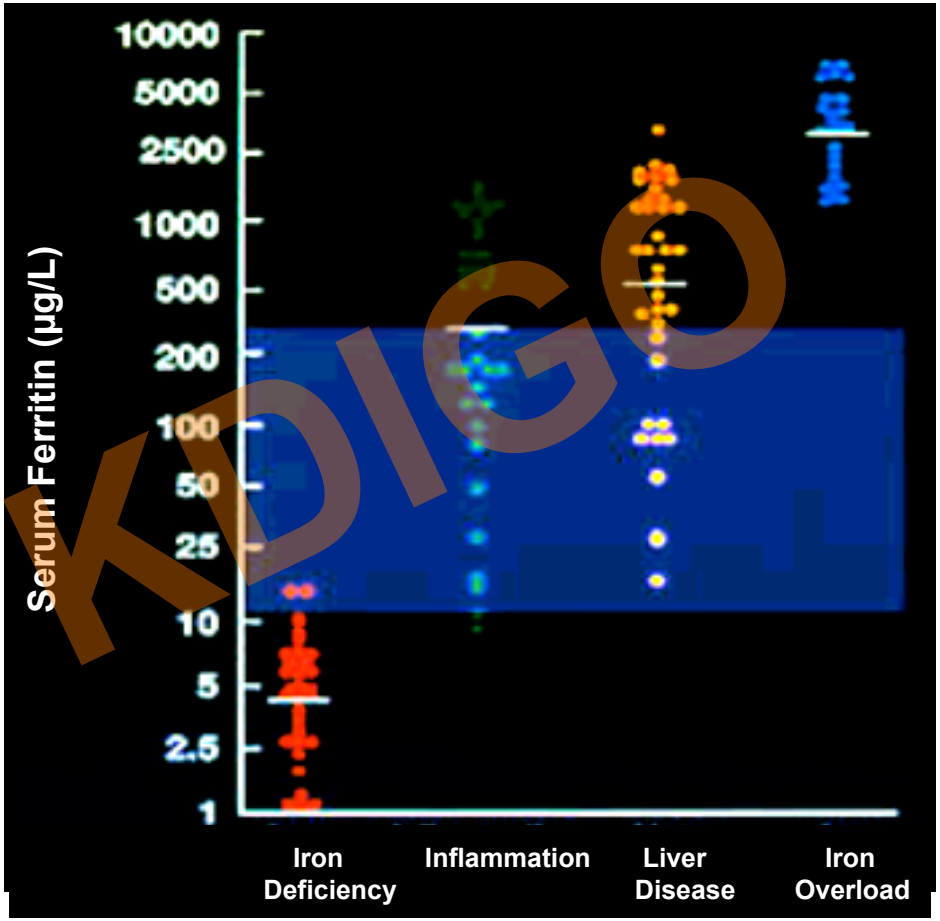


Streja et al. *AJKD* Oct 2008

Ferritin

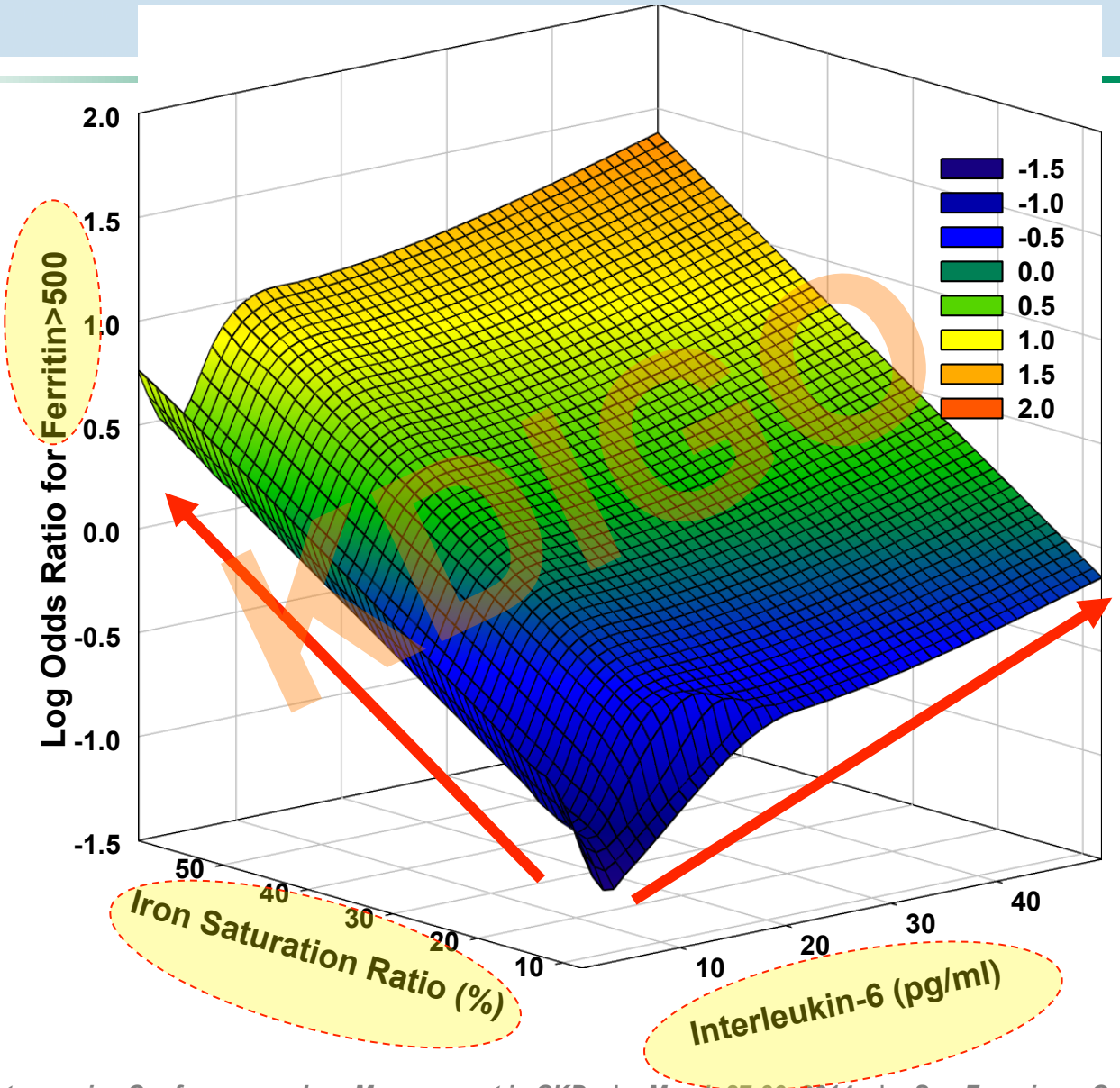


Serum Ferritin Alterations in Inflammation and Liver Disease



Lipschitz et al. ***N Eng J Med*** 290:1213-5; 1974

Ferritin>500 ng/ml = IL6 + TSAT



Rambod, Kovesdy & Kalantar-Zadeh. *Clin J Am Soc Nephrol* 2008; 3:1691-701

National Hemochromatosis Screening

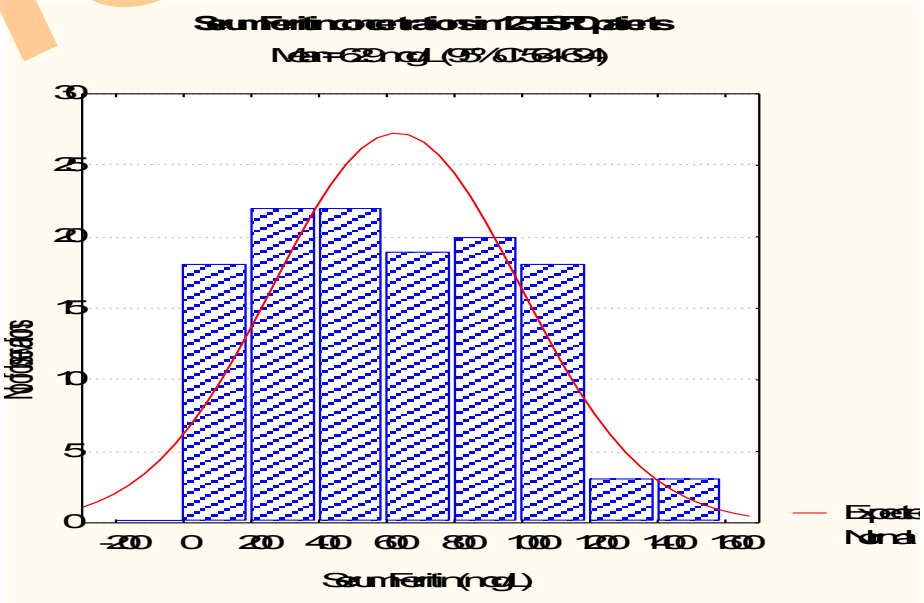
"Any Ferritin over 200-300 ng/ml is a suspected case of hemochromatosis!"

Powell et al; Diagnosis of hemochromatosis. *Ann Intern Med*. 129:925-31; 1998

But CKD Patients Are Different!

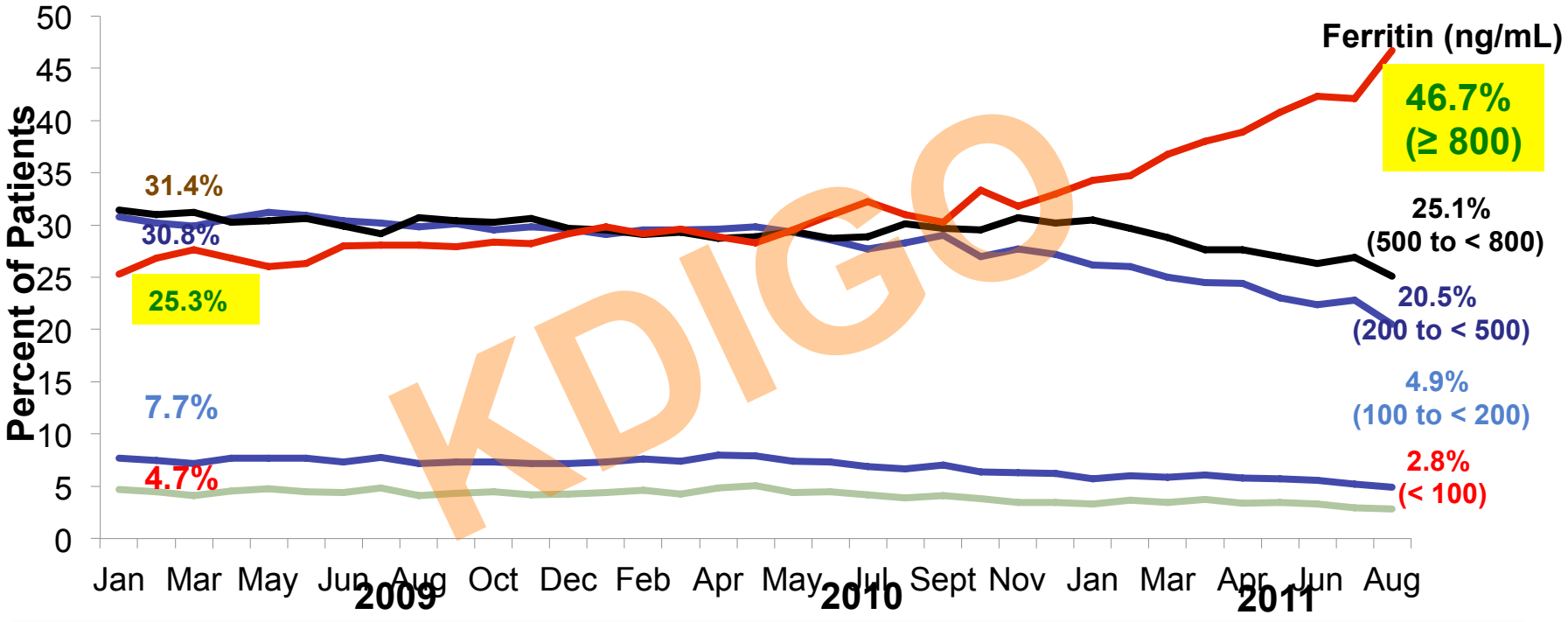
"...we suggest that the hemochromatosis criteria be modified for patients with ESRD."

Kalantar-Zadeh and Luft; Diagnosis of hemochromatosis. Ann Intern Med 131:311-312; 1999



Almost 50% of Patients In the United States Have Ferritin Levels > 800 ng/mL*

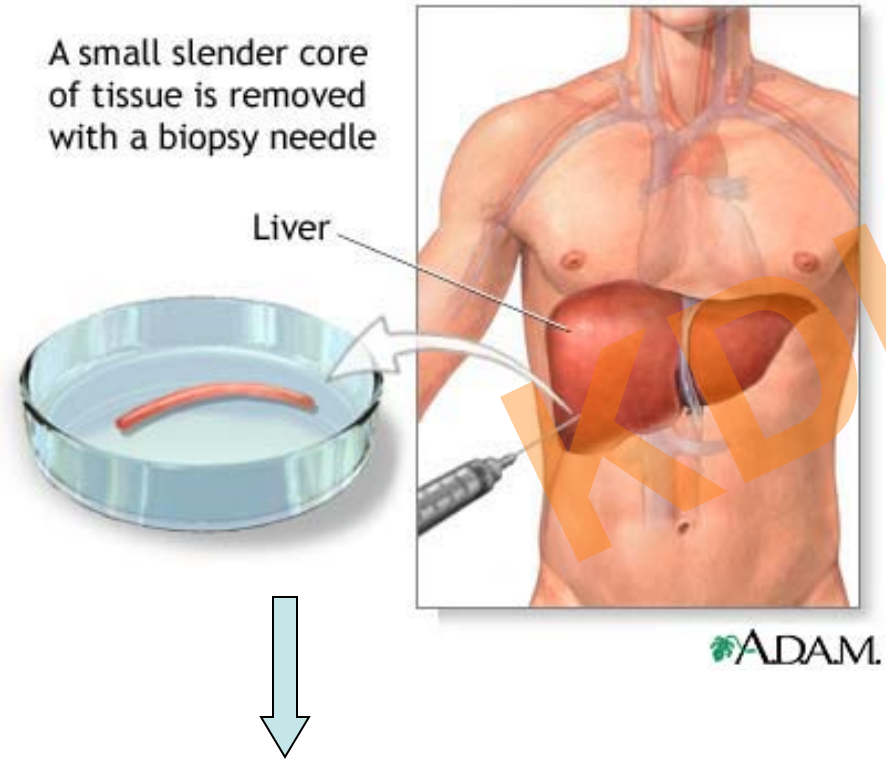
OutcomesPlus National Provider Database, January 2009 through August 2011



"…infectious hospitalizations, catheter use, and use of IV iron and other therapies have all increased during the same period, something which requires careful evaluation." USRDS

Data from "OutcomesPlus database (Amgen); August, 2011.
US Renal Data System. *USRDS 2008 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* 2008.

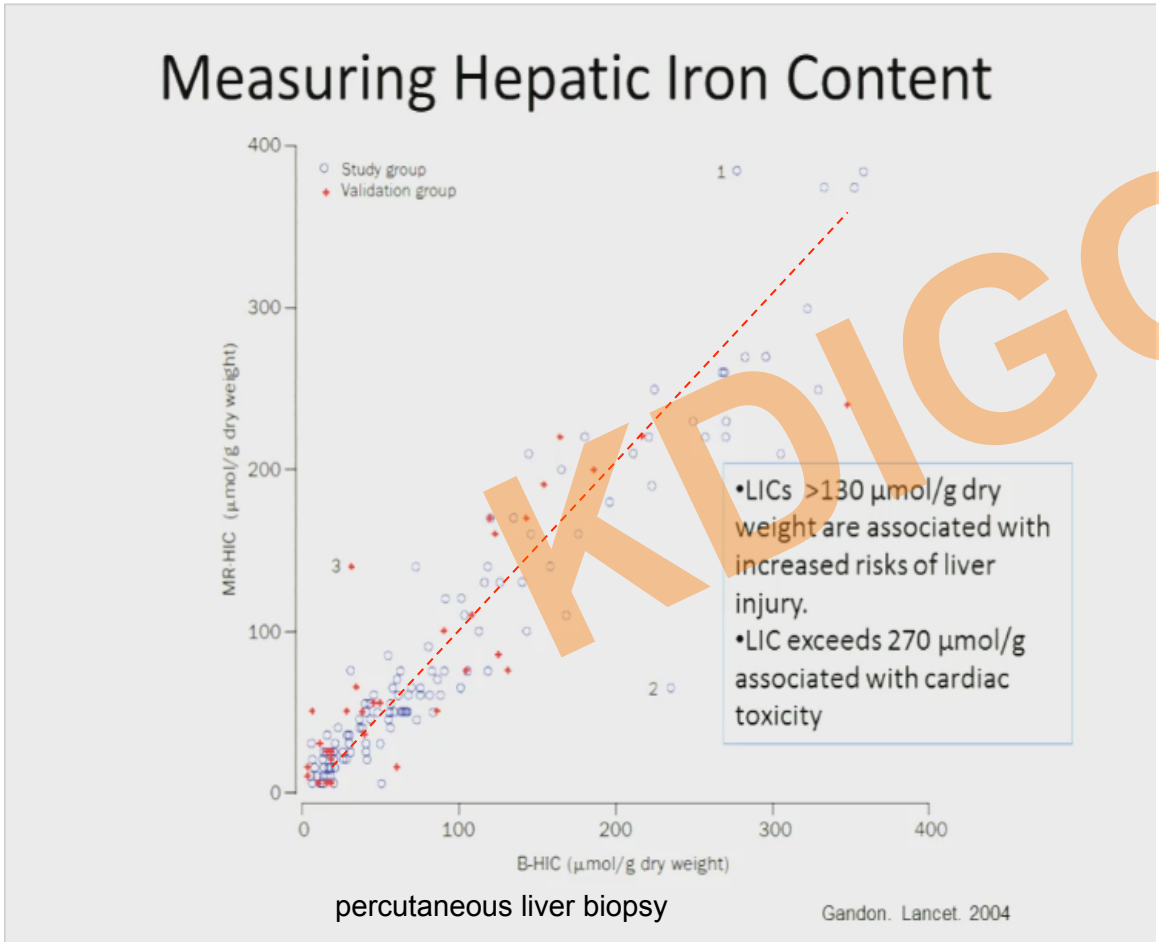
Gold Standards: Liver Biopsy and Bone Marrow biopsy to measure iron content



Direct measurement of iron content

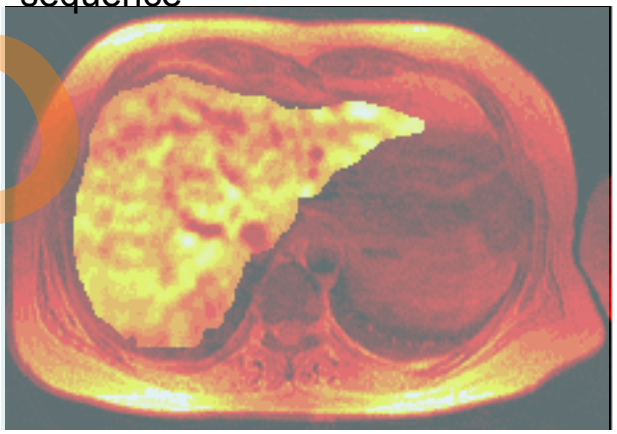
- The "Gold Standard"
- Invasive
- Potentially risky
- Not often used in hematology

Magnetic Resonance Imaging



percutaneous liver biopsy

percutaneous liver biopsy with biochem
of hepatic iron concentration (B-HIC) a
liver with various gradient-recalled-ech
sequence



Bright = high iron concentration; dark areas = low iron concentration

Gandon Y1 et al, Non-invasive assessment of hepatic iron stores by MRI. ***Lancet***. 2004; 31;363:357-62.

Current Day Evidence of Iron Overload

Hemodialysis-associated hemosiderosis in ESA era: MRI study

- Cross Sectional Analysis of 119 Chronic HD Pts
- 36 (30%) had "severe" iron overload of the liver(MRI) > 200 µmol/g

	Positive Control	High Iron HD
Ferritin (µg/L)	524 (335-828)	2688 (1220–6820)
Liver Iron (µmol/g)	210 (70-280)	250 (210-340)
Hepcidin* (ng/mL)	ND	162.70 (5.29-1036)
Cardiac iron	ND	ND

* Enzyme imumoassay, Peninsula Laboratories, USA; normal range: (1.71-175.9 ng/mL)

Rostoker et al, Am J Med. 2012;125:991-999

(adapted from presentation by J. Zaritsky, ASN 2013)

Current Day Evidence of Iron Overload

Evidence for tissue iron overload in long-term hemodialysis patients and the impact of withdrawing parenteral iron.

- Targeted 21 with a serum ferritin >1000 µg/L
  - Ferritin 2688 ± 1489 µg/L
  - Hepcidin 60.15 ± 29.54 nM*
- Liver iron (via MRI)
  - 10% (n=2) had normal values (70 µmol/g)
  - 40% (n=8 had mild (80– 90 µmol/g)
  - 25% (n=5) had moderate (90–95 µmol/g)
  - 30% (n=6) had severe (>95 µmol/g)
- NONE had iron overload in the heart

* mass spectrometry-based method; normal range: (10.61 ± 6.44 nM)

Ghoti et al, Eur J Haematol. 2012 89:87-93.

adapted from presentation by J. Zaritsky, ASN 2013)

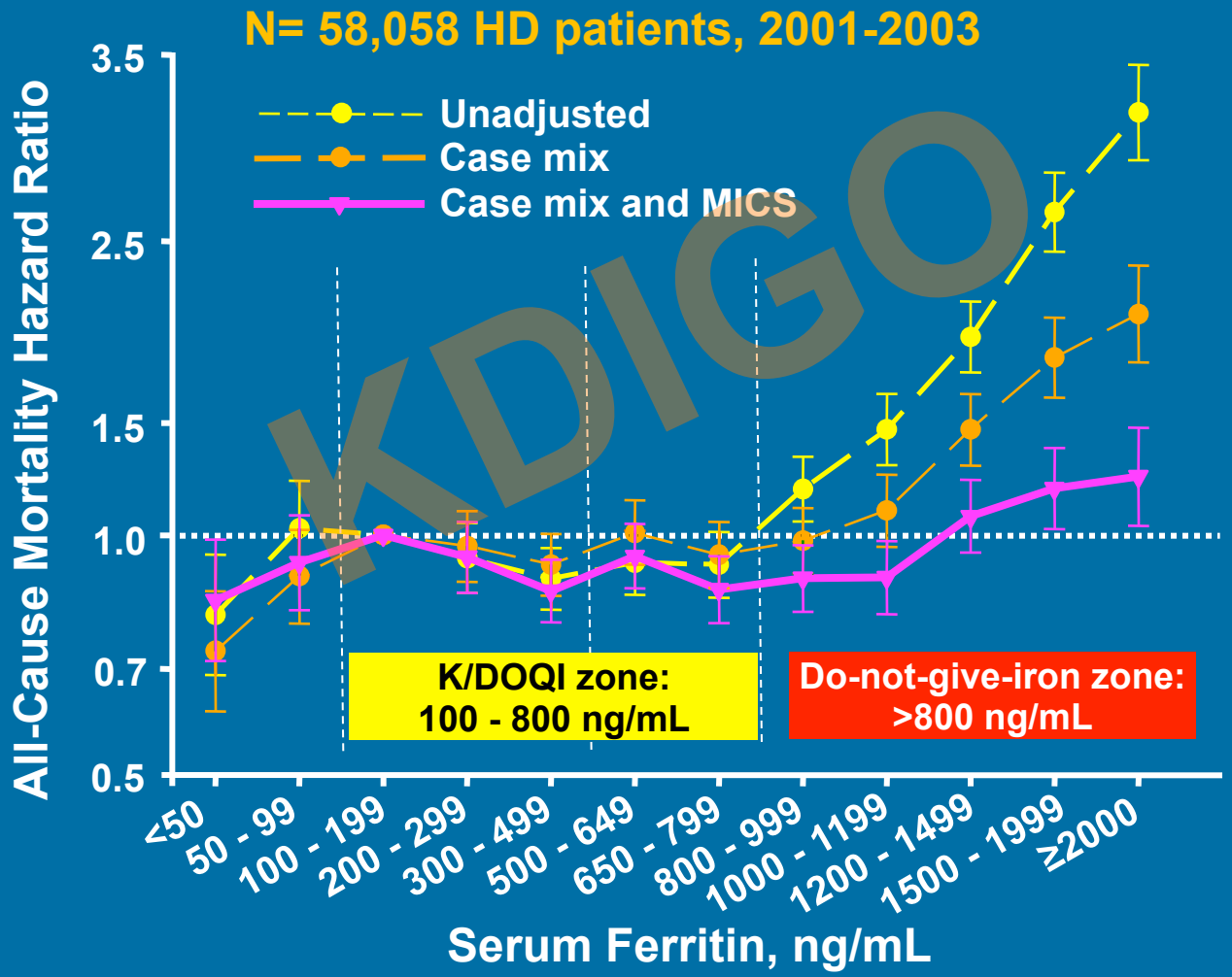
Iron Overload and Survival in CKD

Risk of Death by Serum Ferritin Level in CKD-5D

Is there an association between serum
FERRITIN
and
DEATH
in dialysis patients?

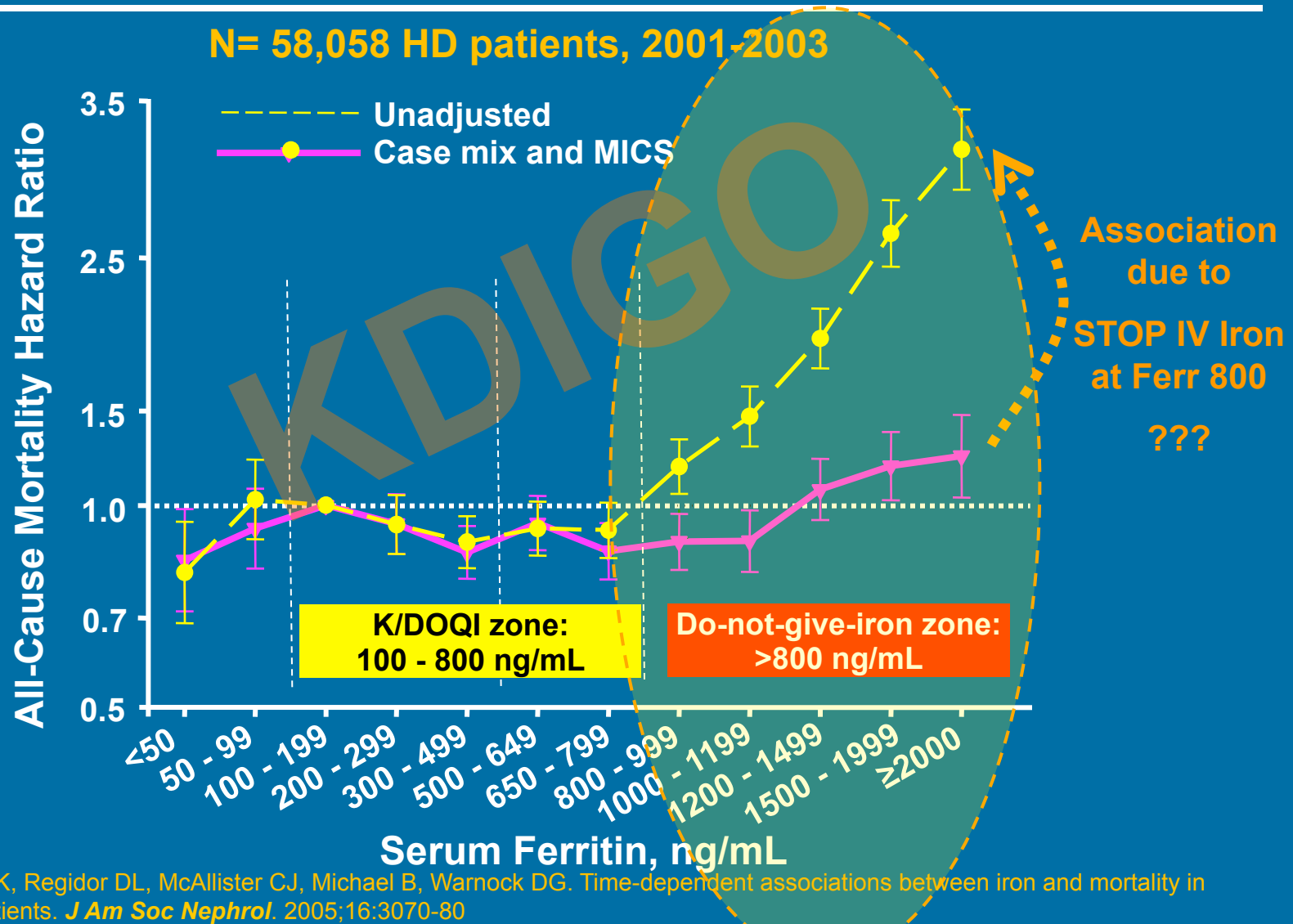
Risk of Death by Serum Ferritin Level

(time-dependent Cox model)



Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. ***J Am Soc Nephrol***. 2005;16:3070-80

Risk of Death by Serum Ferritin Level
(time-dependent Cox model)

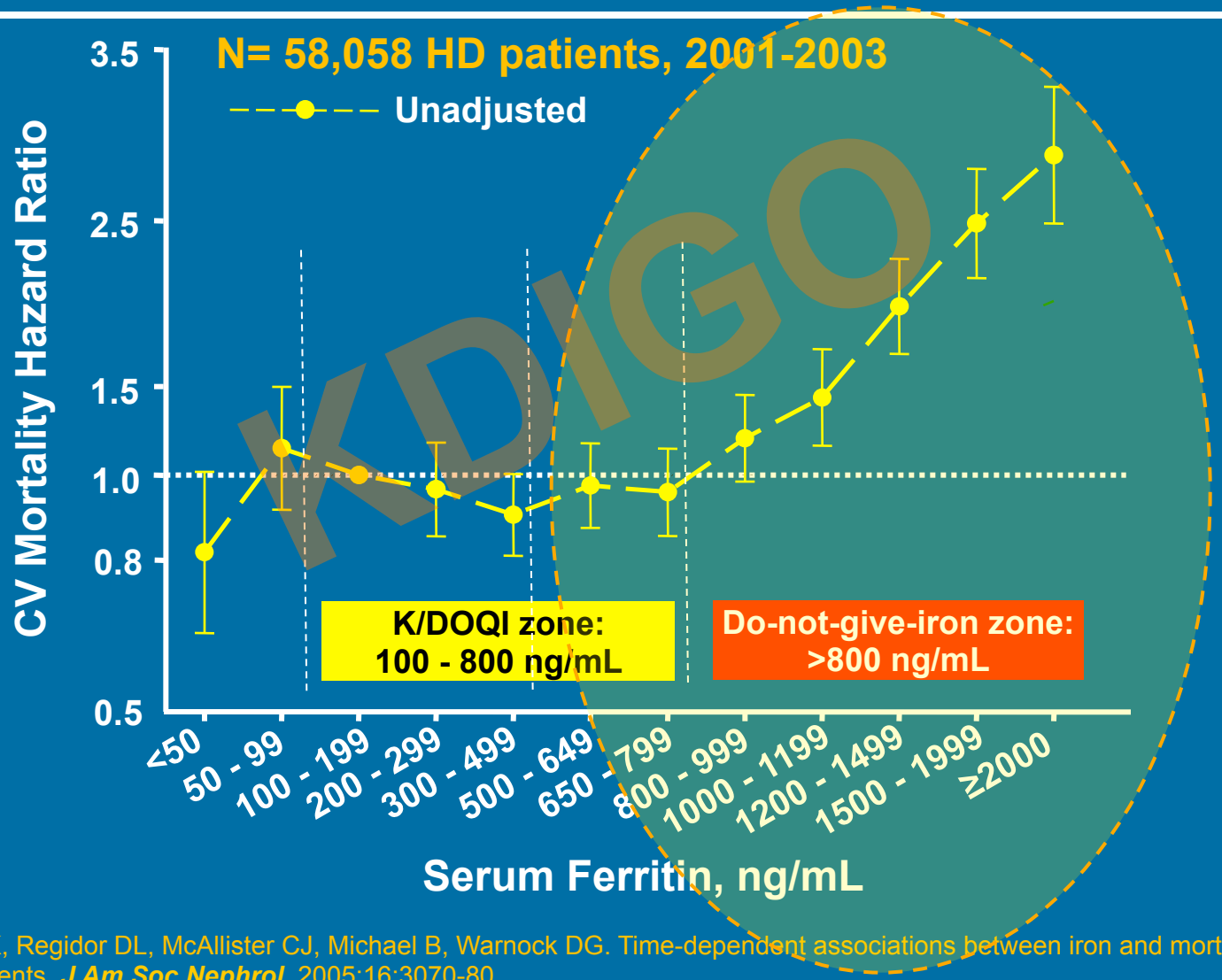


Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. ***J Am Soc Nephrol***. 2005;16:3070-80

Risk of Death by Serum Ferritin Level in HD

What about the association between serum
FERRITIN
and
CARDIO-VASCULAR
DEATH?

Risk of Death by Serum Ferritin Level *(Cardiovascular Death)*



Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. ***J Am Soc Nephrol***. 2005;16:3070-80

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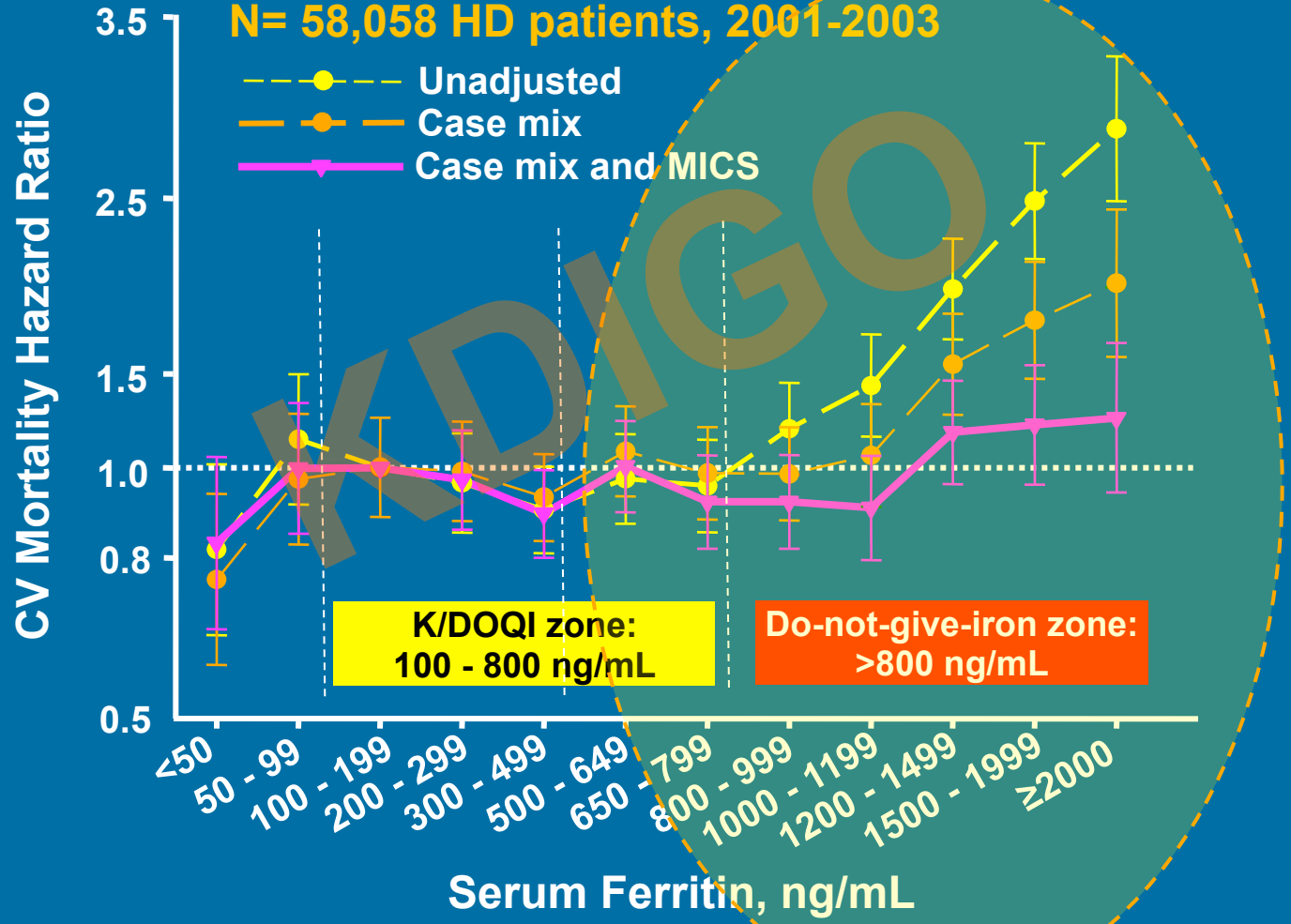
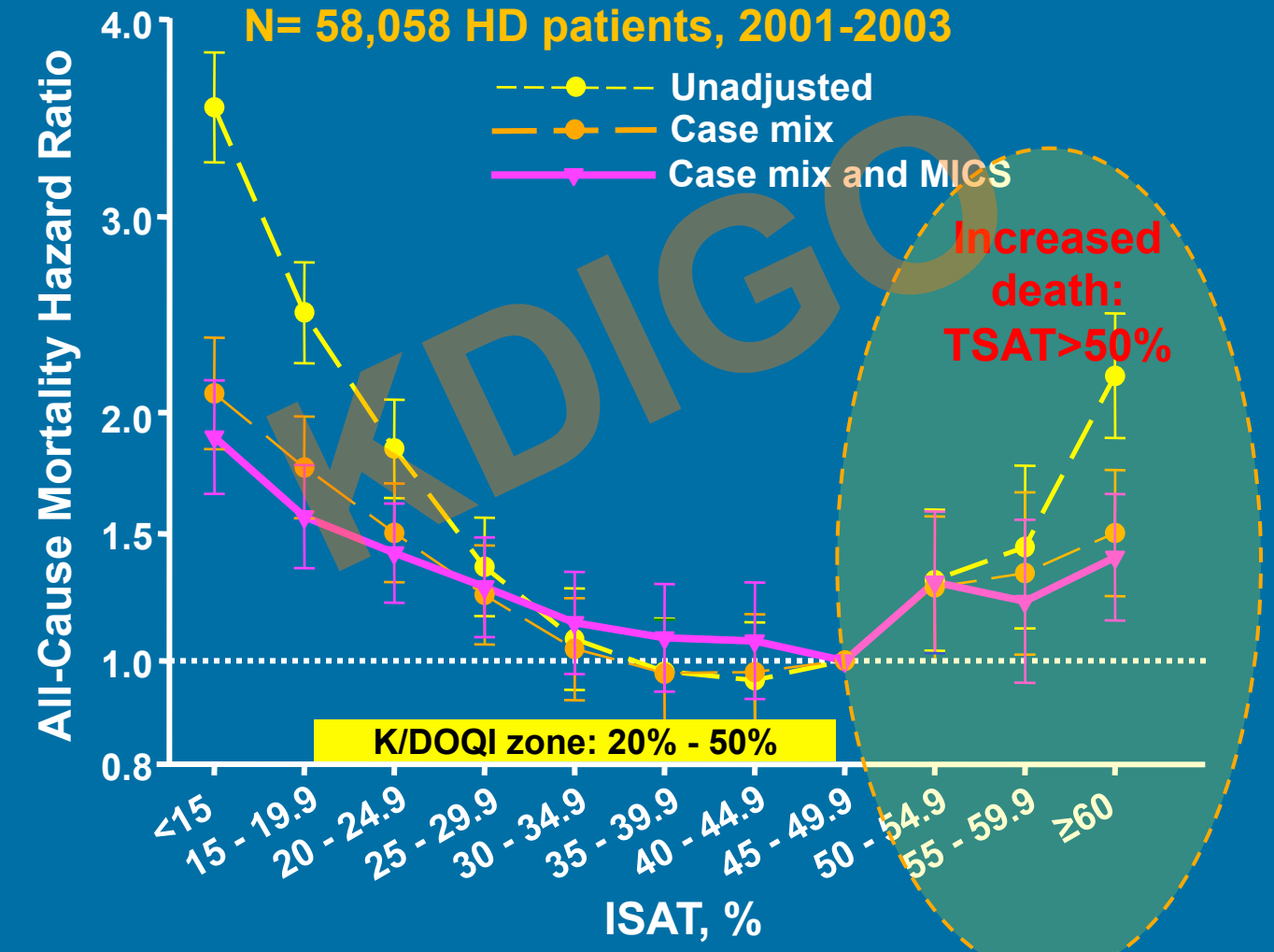


Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. ***J Am Soc Nephrol***. 2005;16:3070-80

Risk of Death by TSAT in HD patients (time-dependent Cox model)

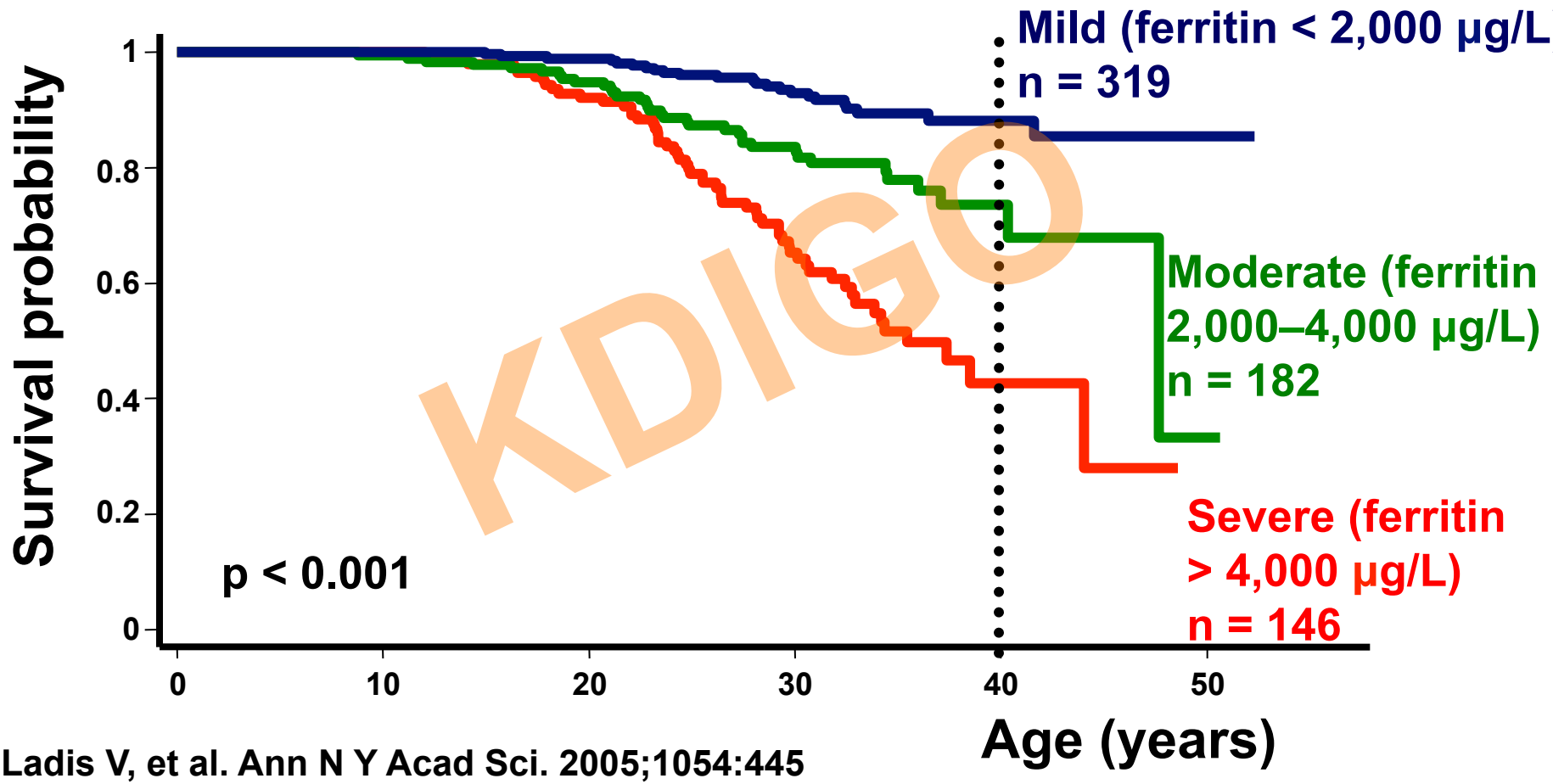
What about the association between serum TSAT and DEATH?

Risk of Death by Transferrin Saturation Ratio (time-dependent Cox model)



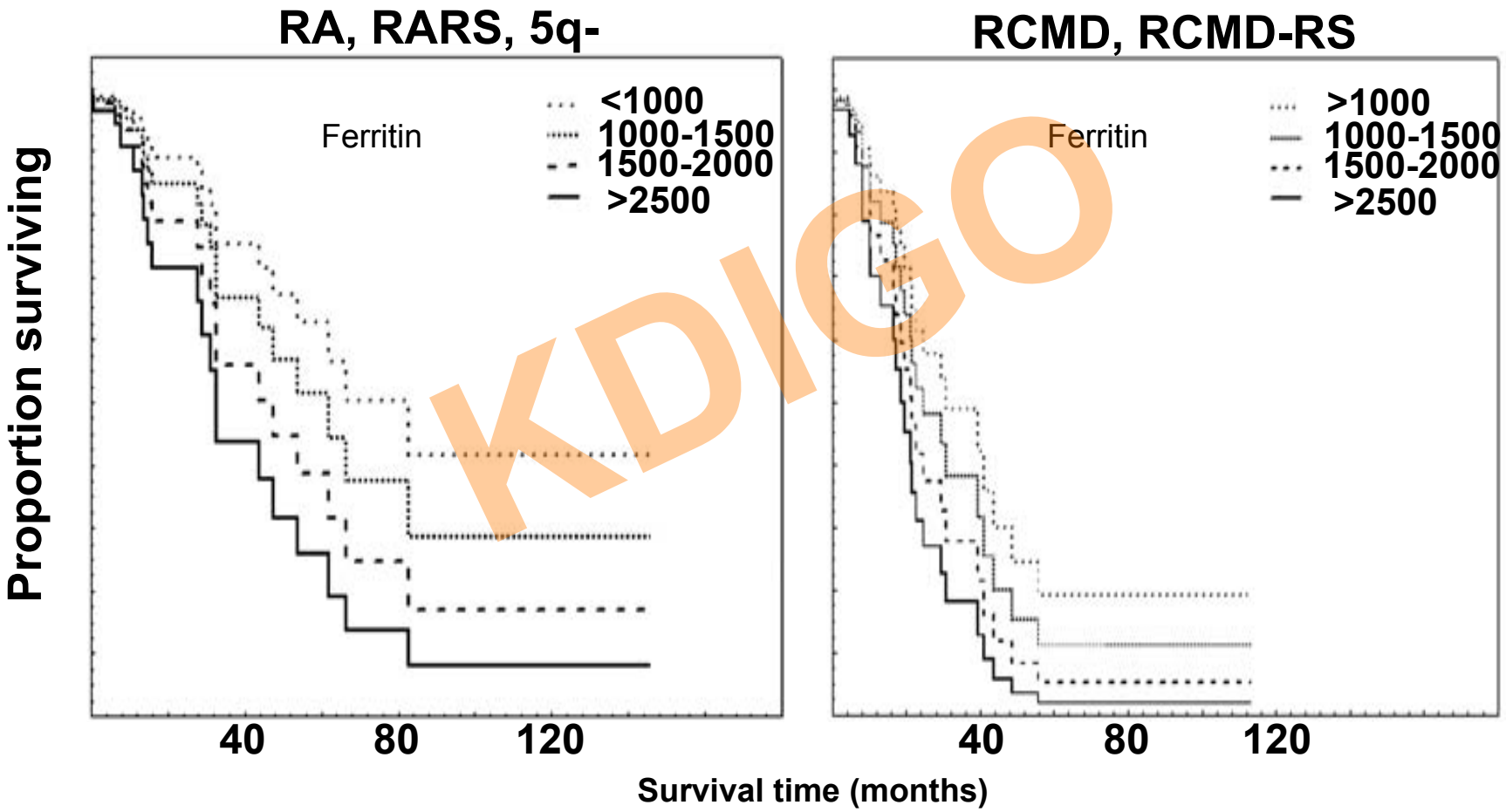
Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. ***J Am Soc Nephrol***. 2005;16:3070-80

Effect of iron overload on survival in β-thalassaemia



Ladis V, et al. Ann N Y Acad Sci. 2005;1054:445

Iron overload impairs survival in MDS



Malcovati, Haematologica, 2006

Administered IV Iron and SURVIVAL in 58,058 HD Patients

- 3 different IV irons were administered 2001-2003:
  (1) Iron gluconate
  (2) Iron sucrose
  (3) Iron dextran

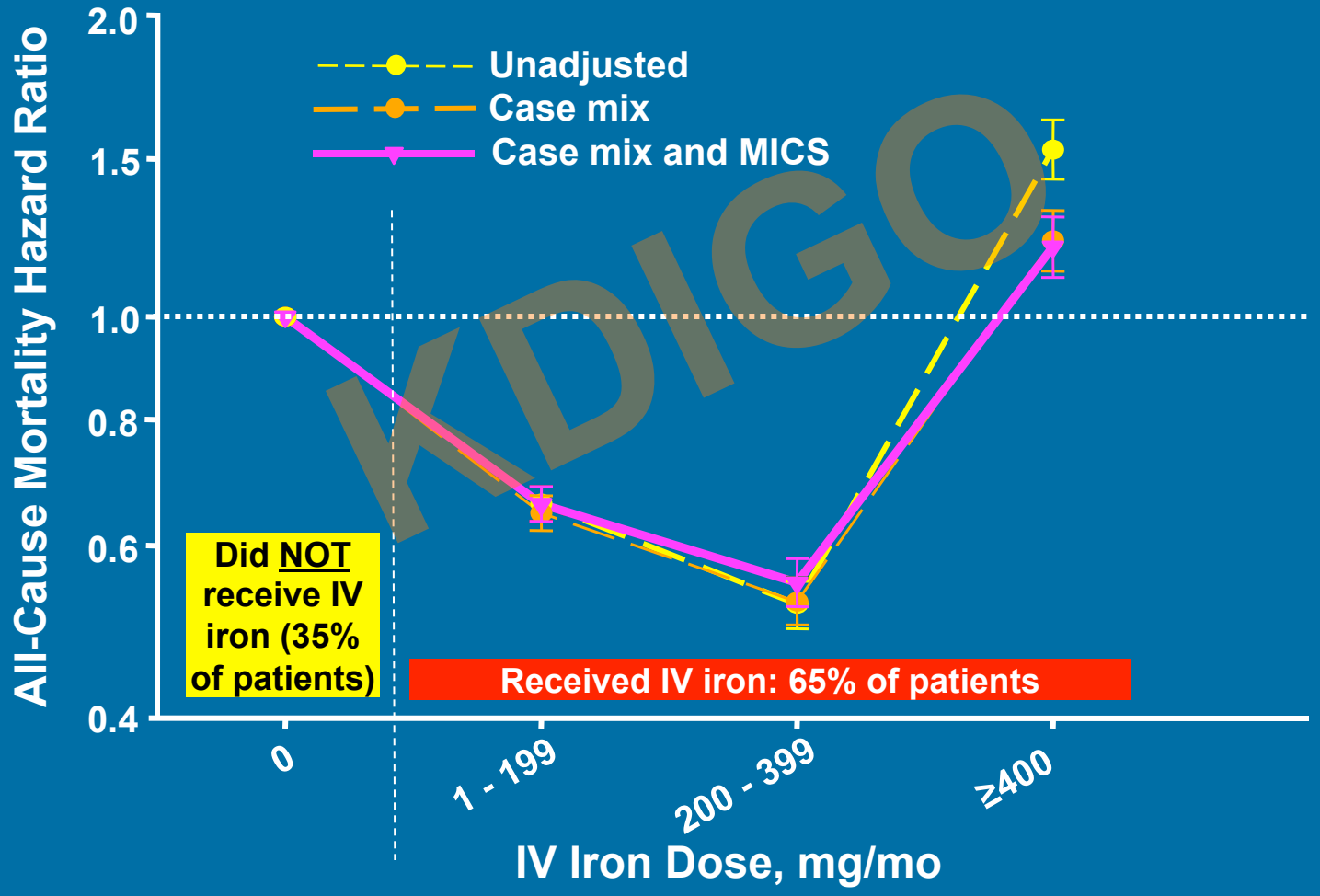
- All 3 forms of IV iron were merged into one single variable and 4 groups of HD patients were created:

  (1) Those who did not receive any IV iron during the entire 13 weeks of baseline calendar quarter
  (2) IV iron 1 - <200 mg/month
  (3) IV iron 200 - <400 mg/month
  (4) IV iron 400 mg/month or greater

Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. ***J Am Soc Nephrol***. 2005;16:3070-80

Risk of Death by IV Iron Dose

N=58,058 HD patients, 2001-2003



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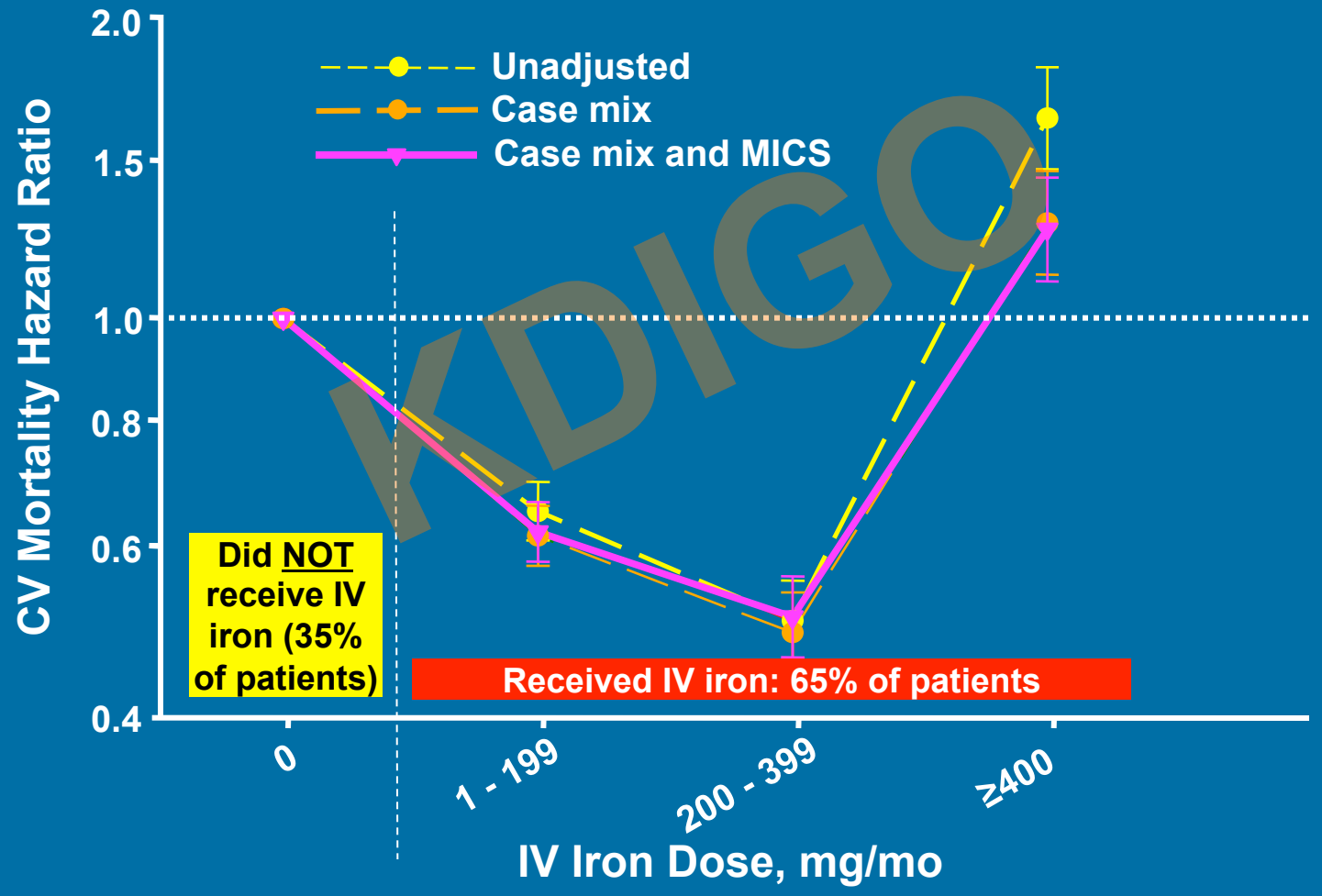

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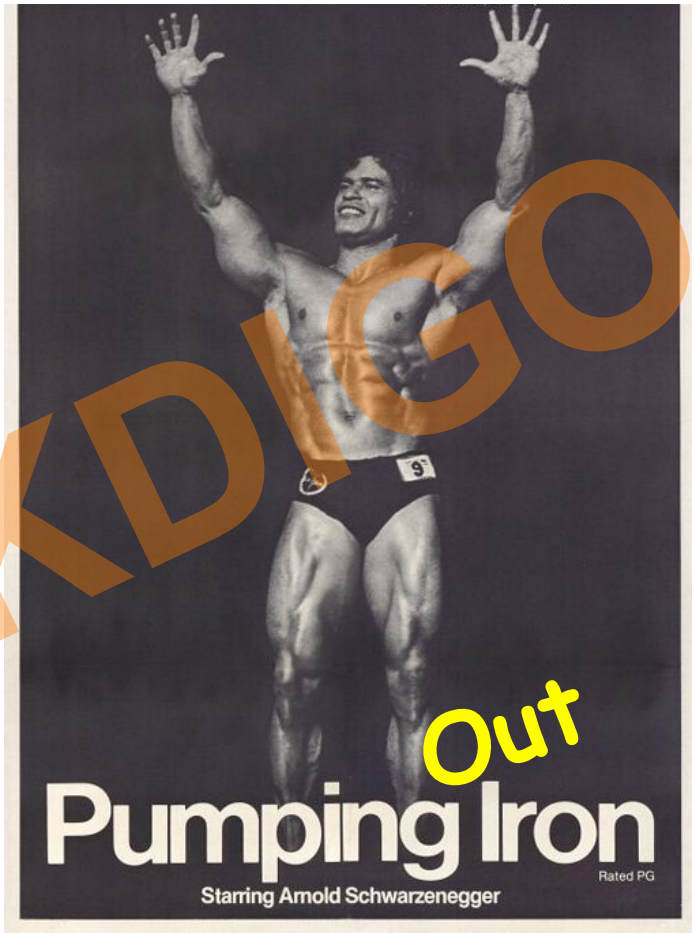
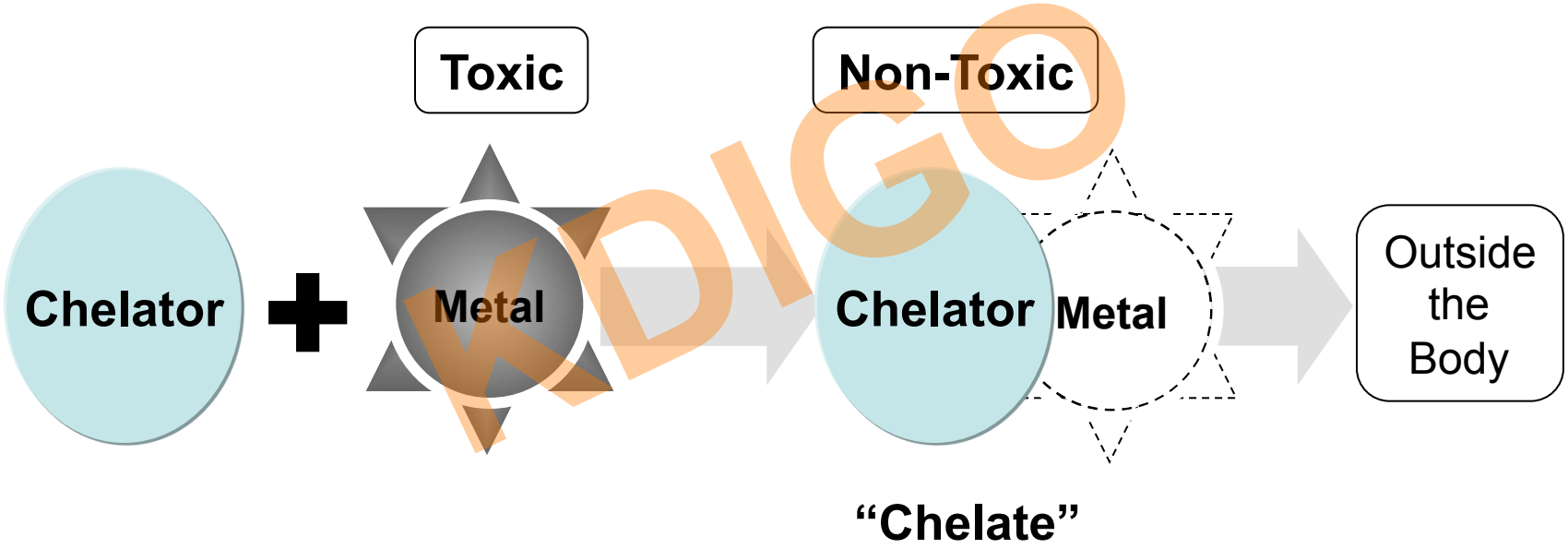
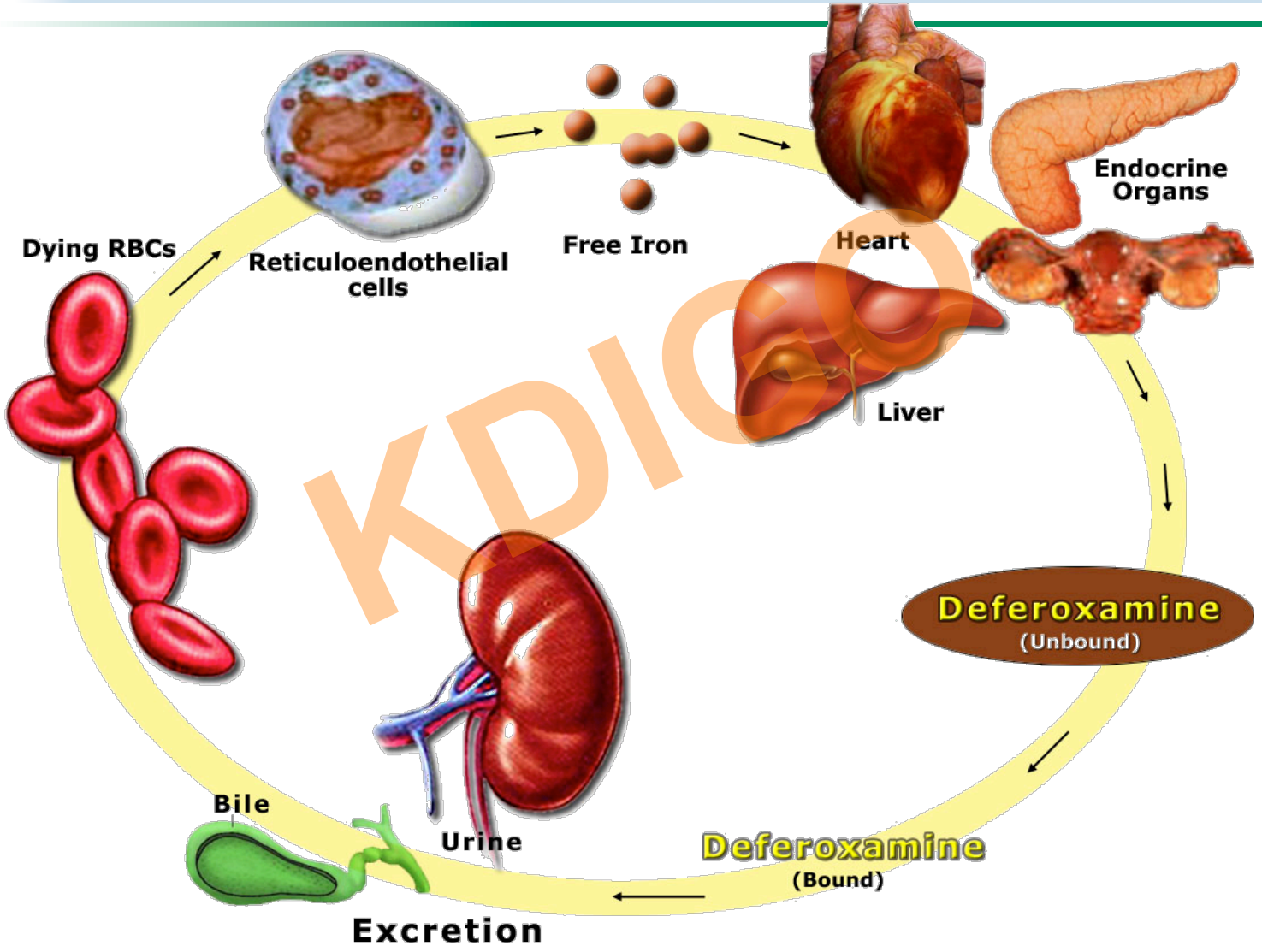
Iron chelation



What is Chelation Therapy?



Deferoxamine: Mode of Action

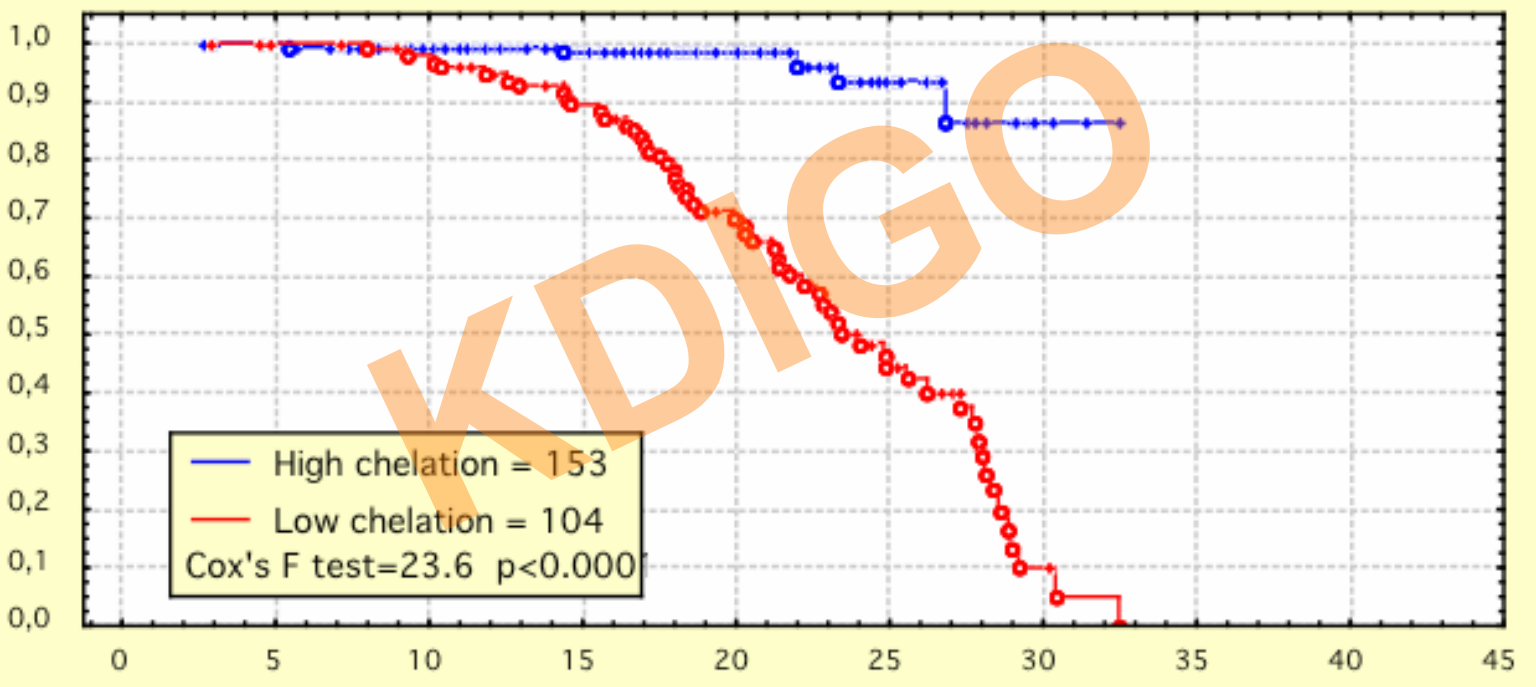


Iron chelation and deferoxamine

- Chelation works by attaching a drug to iron, which allows the body to excrete it.
- Deferoxamine Rx is challenging…
  - Inconvenient and uncomfortable to take
  - Many unfavorable side effects
- …but it is effective
  - Enormous extension of lifespan in thalassaemia.

Deferoxamine works!

Survival of patients with thalassaemia



No similar data are available for iron chelation in CKD

Challenges of Deferoxamine

- Subcutaneous/Intravenous route of administration
  - Expensive
  - Cumbersome
  - Uncomfortable
- Rapid metabolism (30 minute half-life) necessitates prolonged infusion (12-15 hours)
- Complications due to iron overload still occur due to poor compliance with therapy

Common Side Effects of Deferoxamine

- Local reactions
  - Erythema (localized redness)
  - Induration (localized swelling)
  - Pruritus (itchiness)
- Ophthalmologic
  - Reduced visual acuity
  - Impaired color vision
  - Night blindness
  - Increased by presence of diabetes
- Hearing loss
- Zinc deficiency

Summary: Iron Overload in CKD

- Iron overload caused by transfusions or IV iron may lead to damage to the liver, heart, endocrine organs, bones, etc. CKD confounding effect is not clear?
- In the non-CKD population, the problems may begin after 30 units of PRBC (or even earlier). No contemporary data available in post-ESA era?
- In CKD, the use of ESA may have mitigated or even cured hemochromatosis?
- Higher TSAT associated with faster CKD progression?
- Serum ferritin level (>1200 ng/ml) and liver MRI may be used to estimate iron overload in CKD pts including HD pts?
- Therapy (?chelation therapy) including IV iron withdrawal (while ESA RX is maintained) should be offered to iron overloaded CKD patients e.g. ferritin above 2,000 ng/ml range?

Why too much iron is a bad thing