IRON AND OUTCOMES IN CKD

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Iron: Why is it Important?

- Most abundant element on Earth: 35% of Earth's mass!
- Essential trace element used by almost all living organisms.
  - Catalyst of oxidative reactions
  - Transport of soluble gases
    - Essential component of hemoglobin

Iron: Why is it Important?

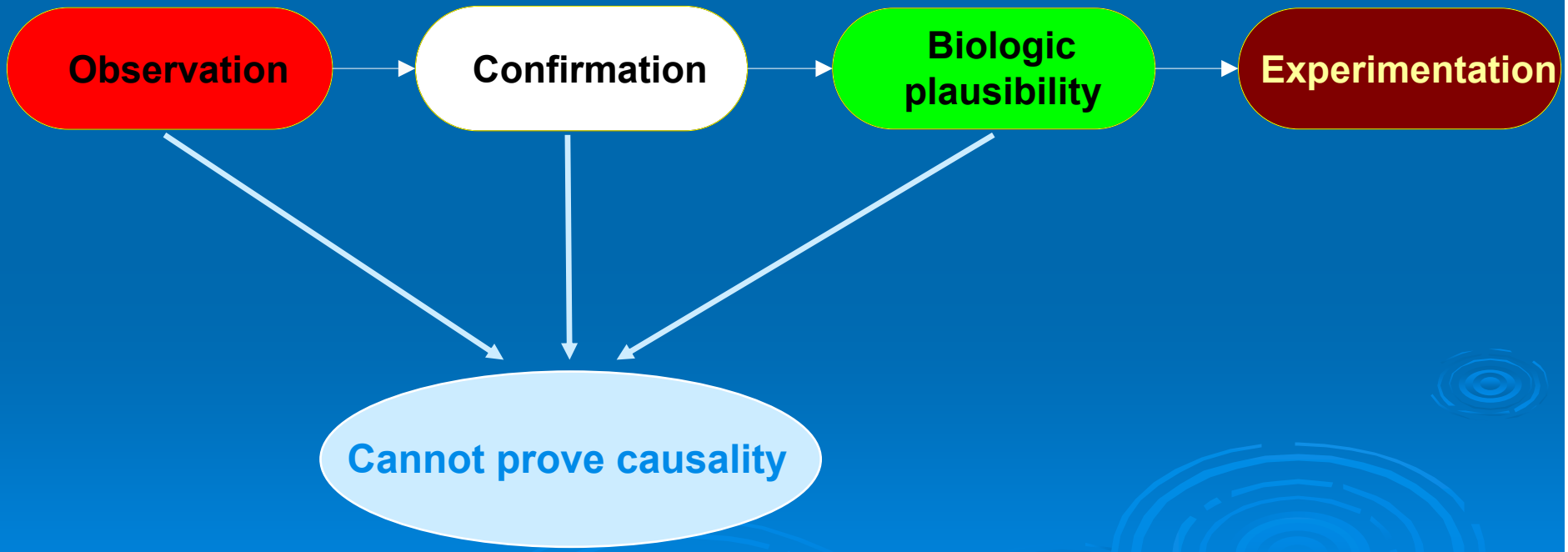
- The practical answer: It is needed for blood production.
  - Especially when treating patients with ESAs
- But what are the long term consequences of iron imbalance (deficiency, overload)?
- Can long term clinical outcomes be improved by treating iron imbalance?

Iron Markers

- Bone Marrow Iron (semi-quantitative)
- Liver Iron: Biopsy or via Superconducting Quantum Interference Device (SQUID)
- Ferritin
- Transferrin Saturation (iron saturation)
- Serum Iron
- Reticulocyte Hemoglobin Content (CHr)
- Percentage of Hypochromic Red Cells (PHRC)
- Soluble Transferrin Receptor (sTfR)
- Erythrocyte Zinc Protoporphyrin
- Hepcidin

Kalantar-Zadeh et al, CJASN 2006

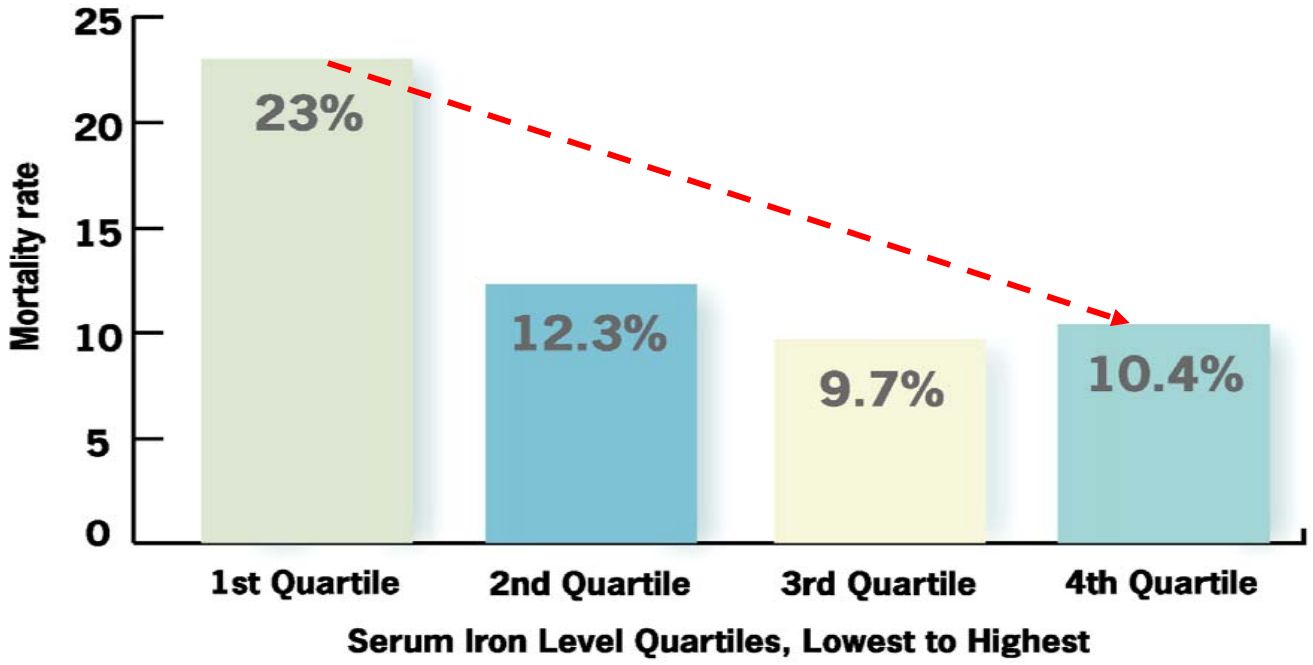
The Path of Discovery



↓ Serum Iron → ↑ Mortality

Mortality Doubles When Iron Is Low

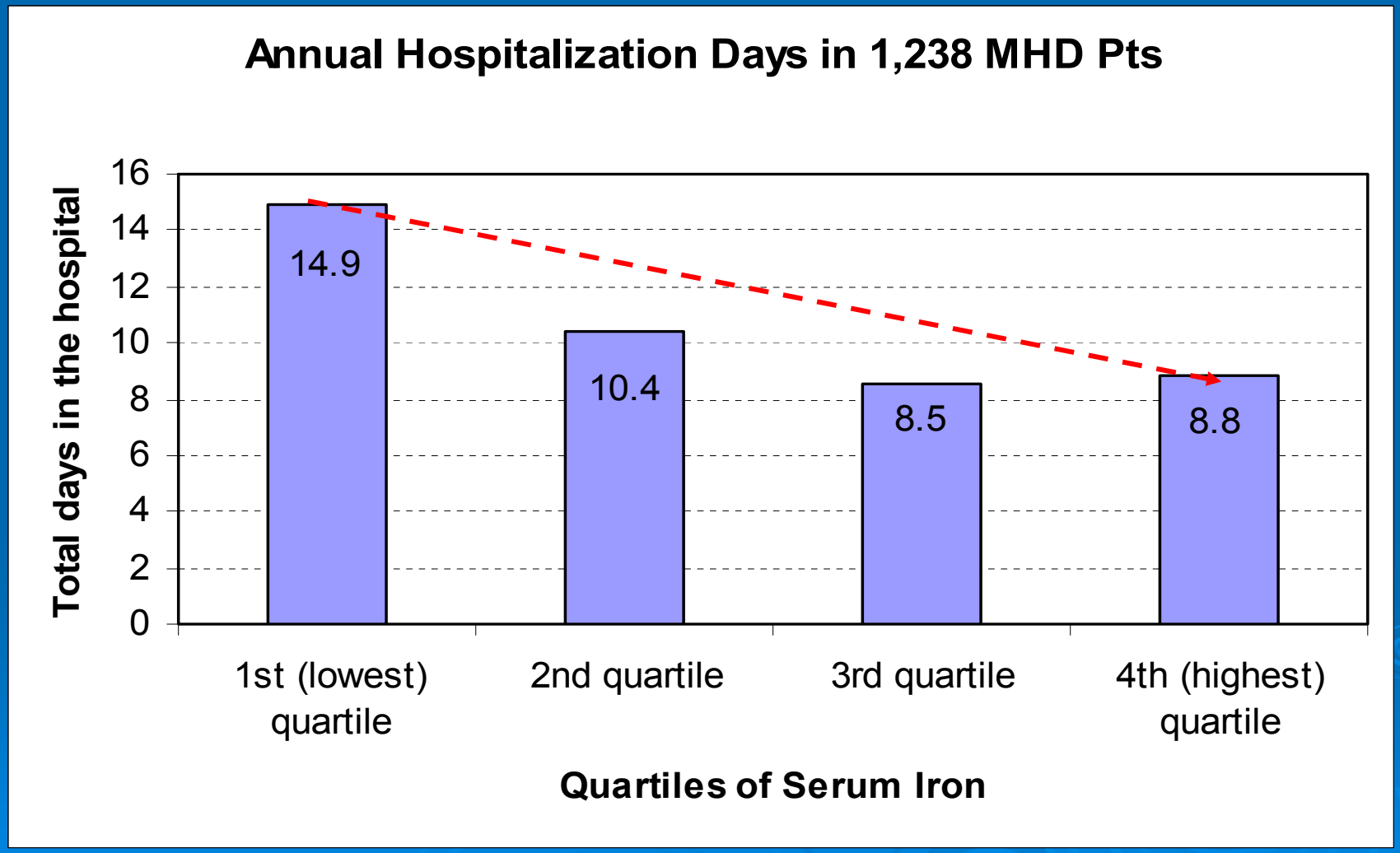
Among patients on maintenance hemodialysis, those in the lowest quartile of serum iron level had a mortality rate about twice that of the other quartiles.



Source: Kalantar-Zadeh K, McAllister CJ, Lehn RS, et al. A low serum iron level is a predictor of poor outcome in hemodialysis patients. *Am J Kidney Dis.* 2004;43:671-684.

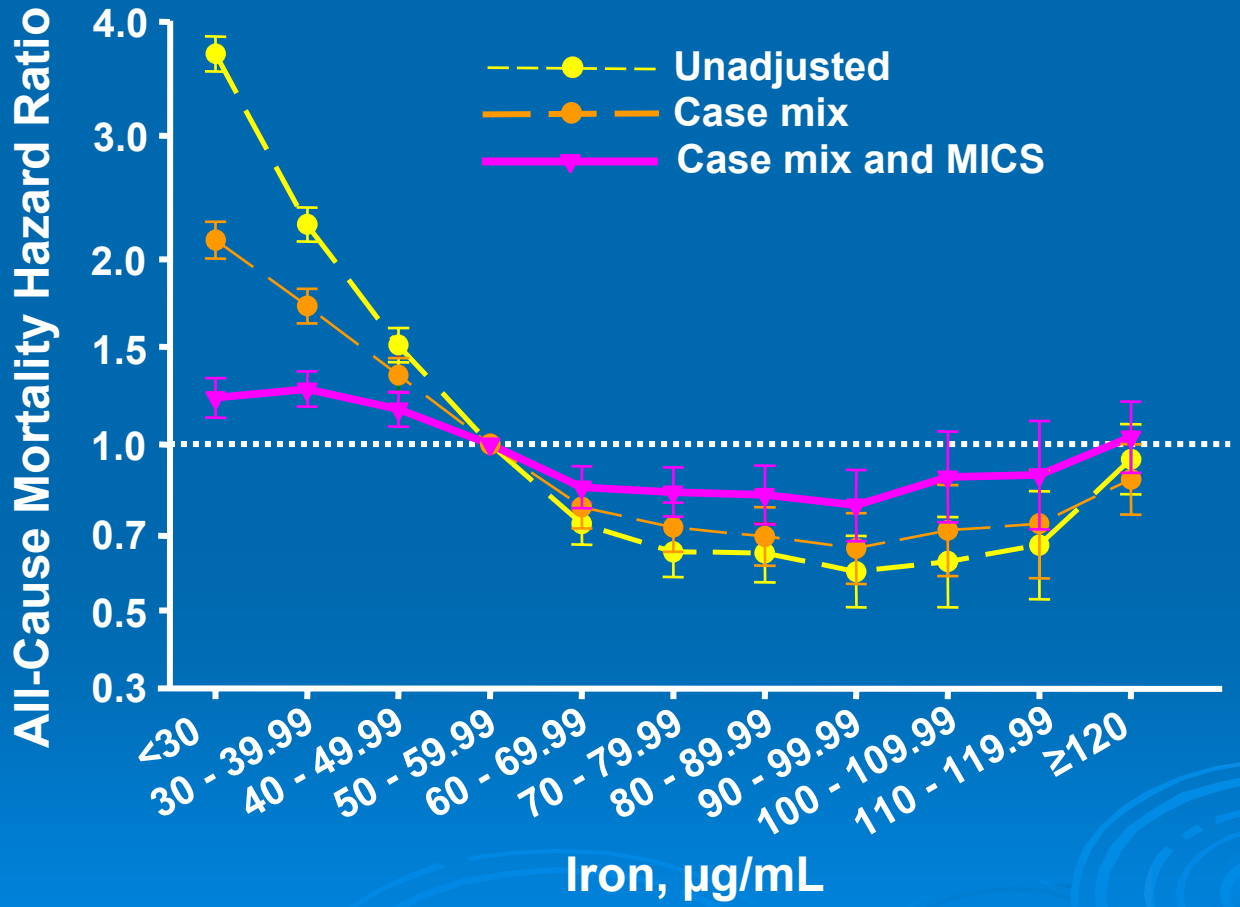
Kalantar-Zadeh et al. AJKD 2004 [6]

↓ Serum Iron → ↑ Hospitalization



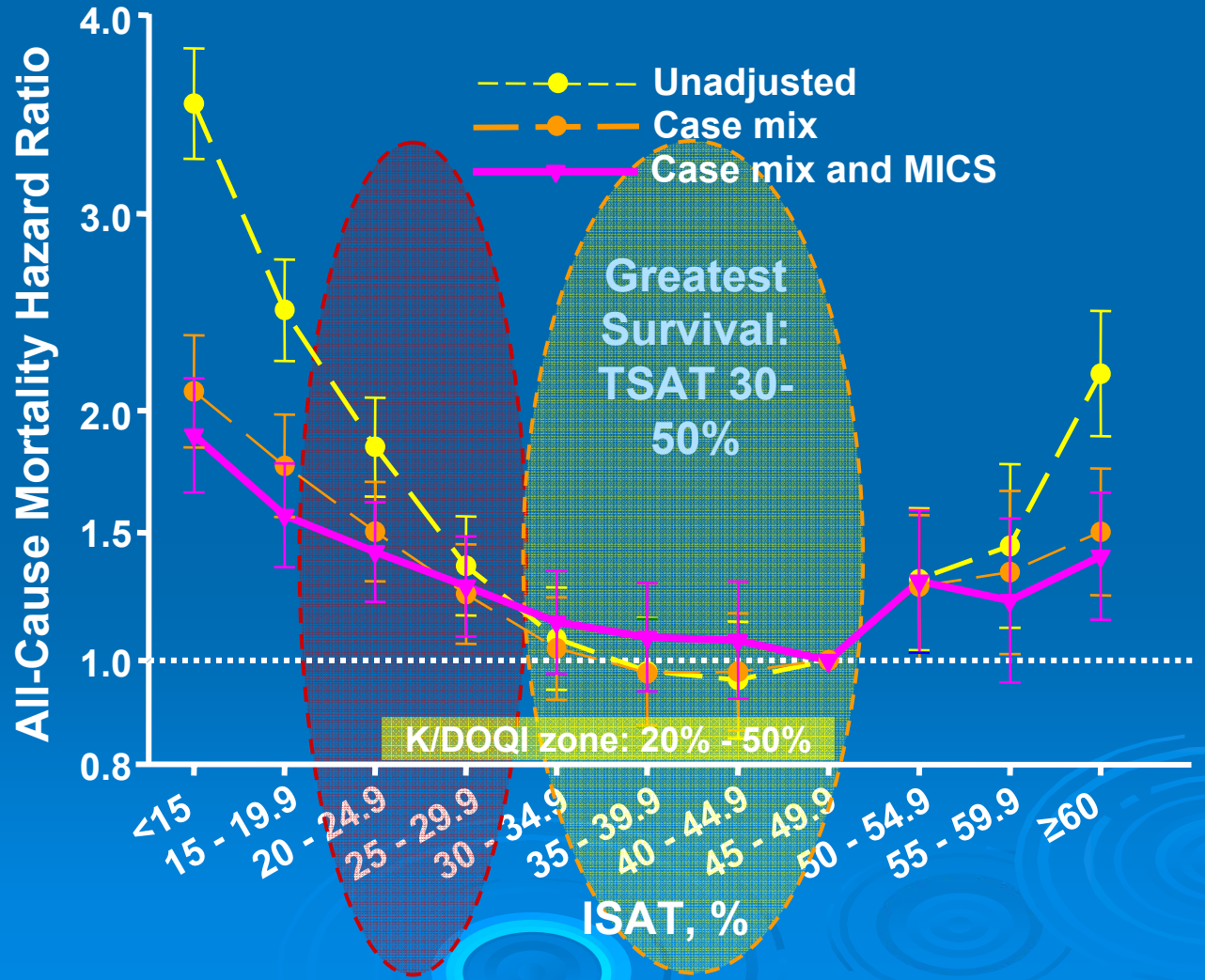
Kalantar-Zadeh et al. AJKD 2004

Risk of Death by Iron Levels (time-dependent Cox model)



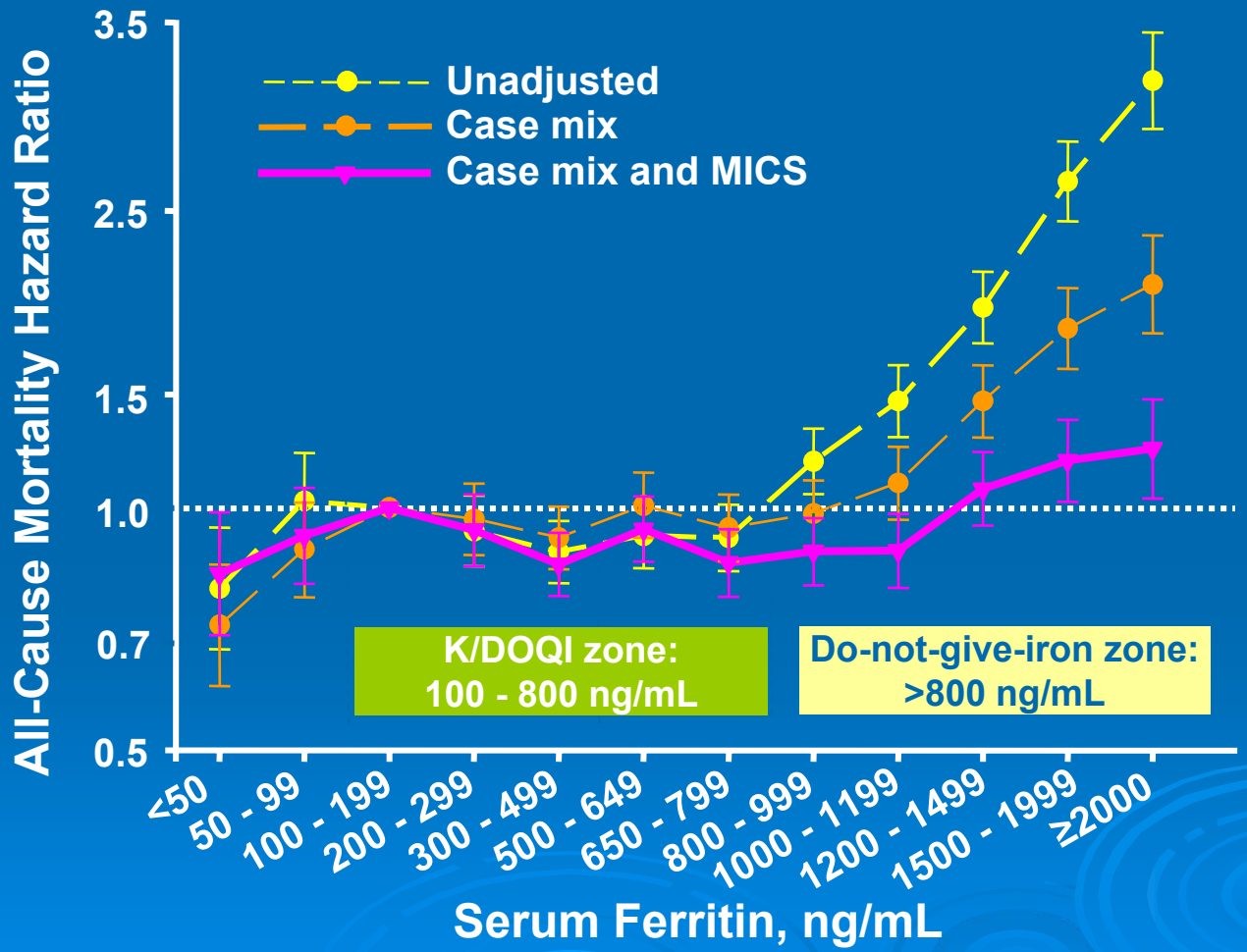
Kalantar-Zadeh et al. J Am Soc Nephrol. 2005

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



Kalantar-Zadeh et al. J Am Soc Nephrol. 2005

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



Kalantar-Zadeh et al. J Am Soc Nephrol. 2005[10]

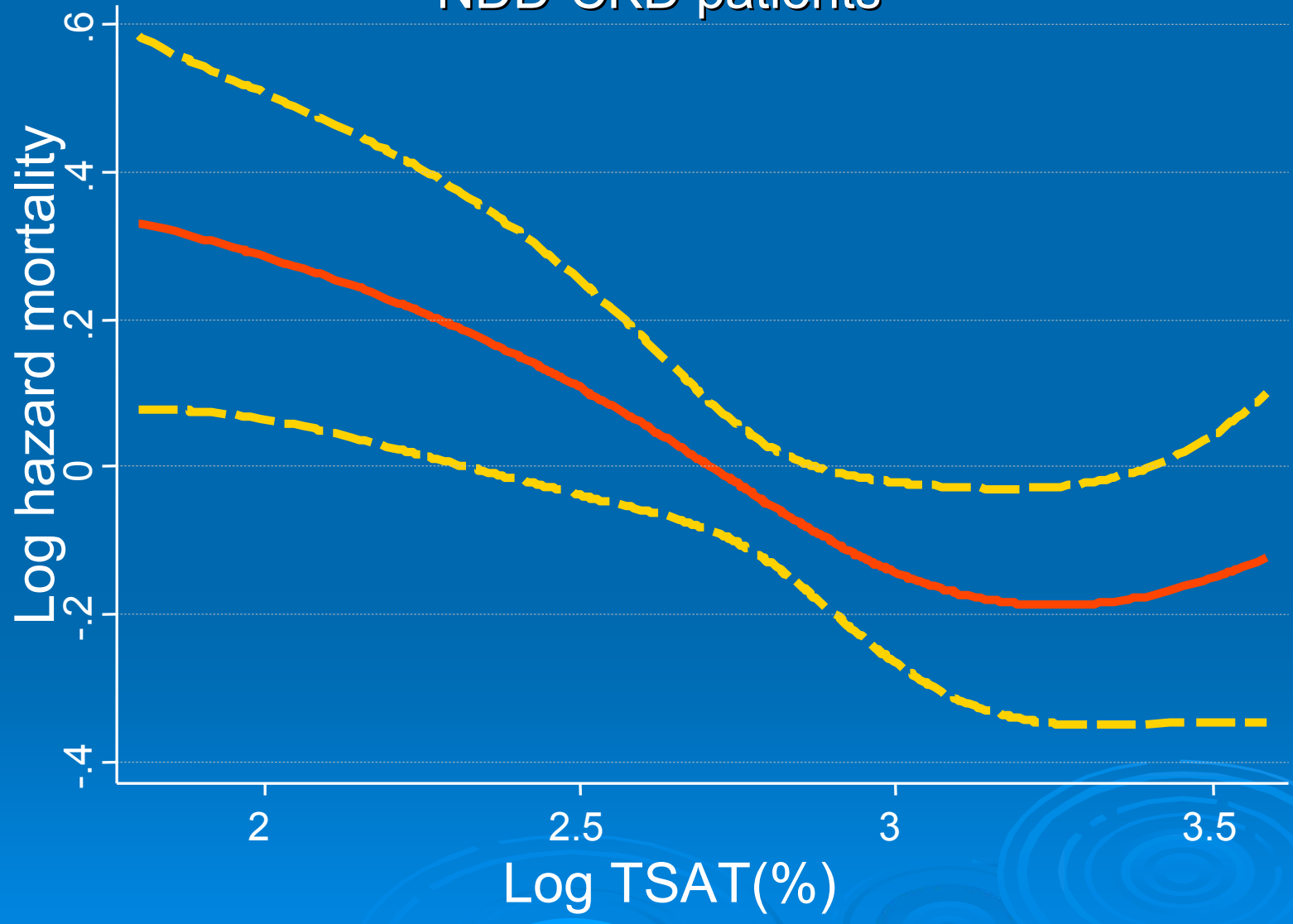
Iron and mortality in ESRD

- Iron concentration of 60-120 mcg/ml associated with best outcomes.
- TSAT of 30-50% associated with the best outcomes.
- Ferritin <1200 ng/ml associated with best outcomes.

Iron levels and outcomes in NDD-CKD

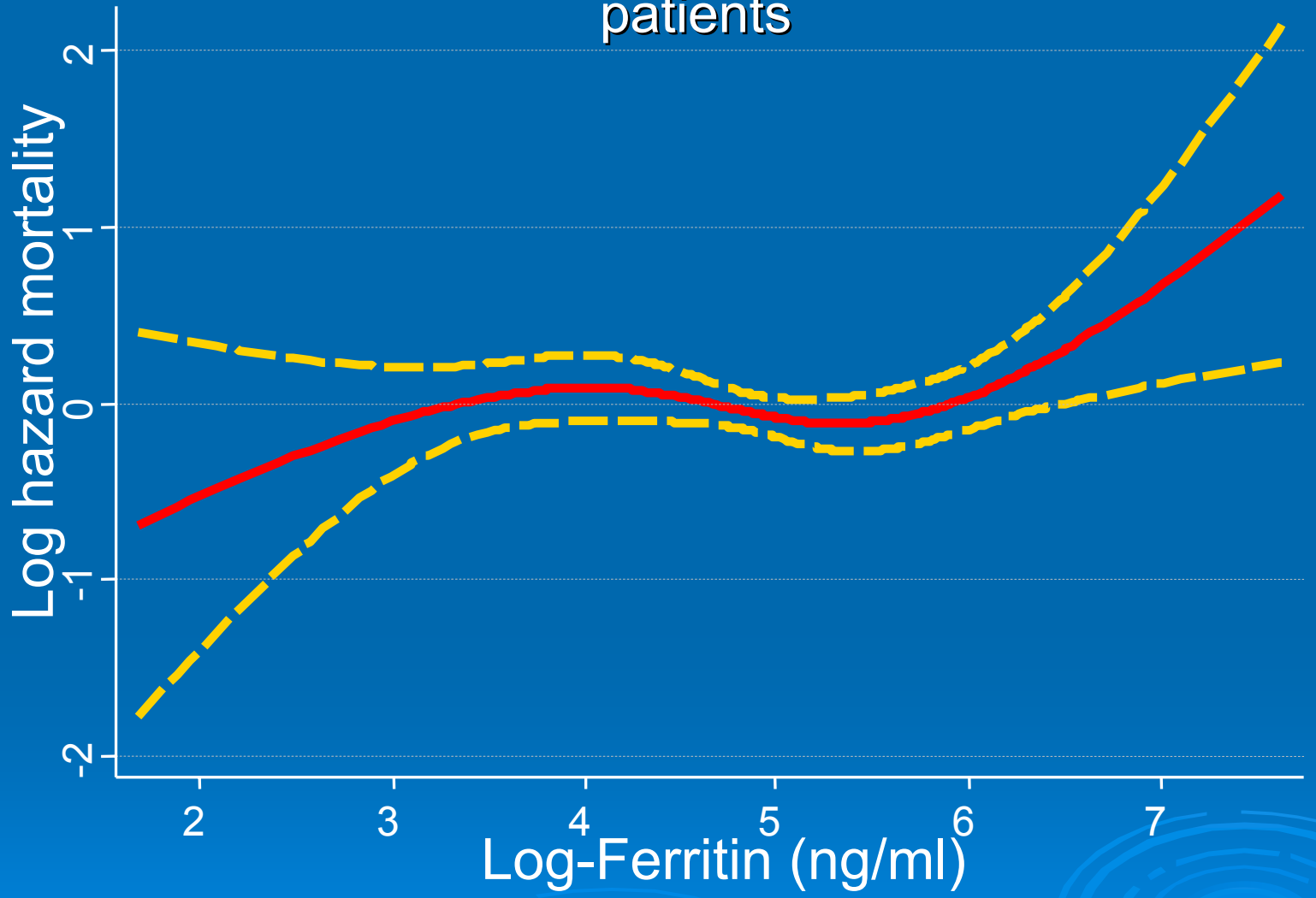
- Anemia less severe.
- Use of ESA less prevalent.
- Use of IV iron less prevalent.
- Progression of CKD separate outcome (competes with mortality).

Transferrin Saturation (TSAT) and mortality in 453 NDD-CKD patients

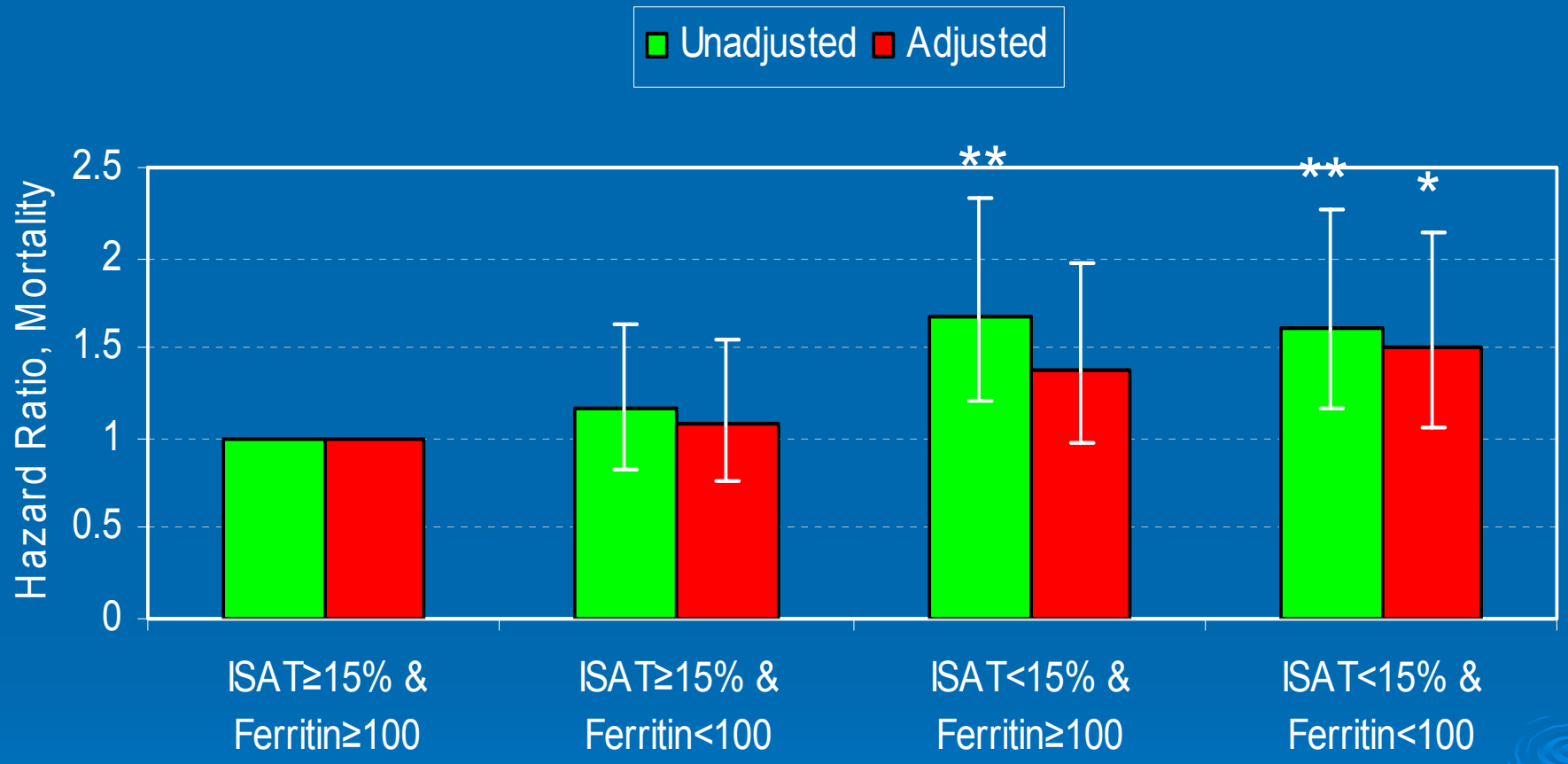


Kovesdy et al, Clin J Am Soc Nephrol 2009; 4:435-41

Serum ferritin and mortality in 453 NDD-CKD patients



Kovesdy et al, Clin J Am Soc Nephrol 2009; 4:435-41



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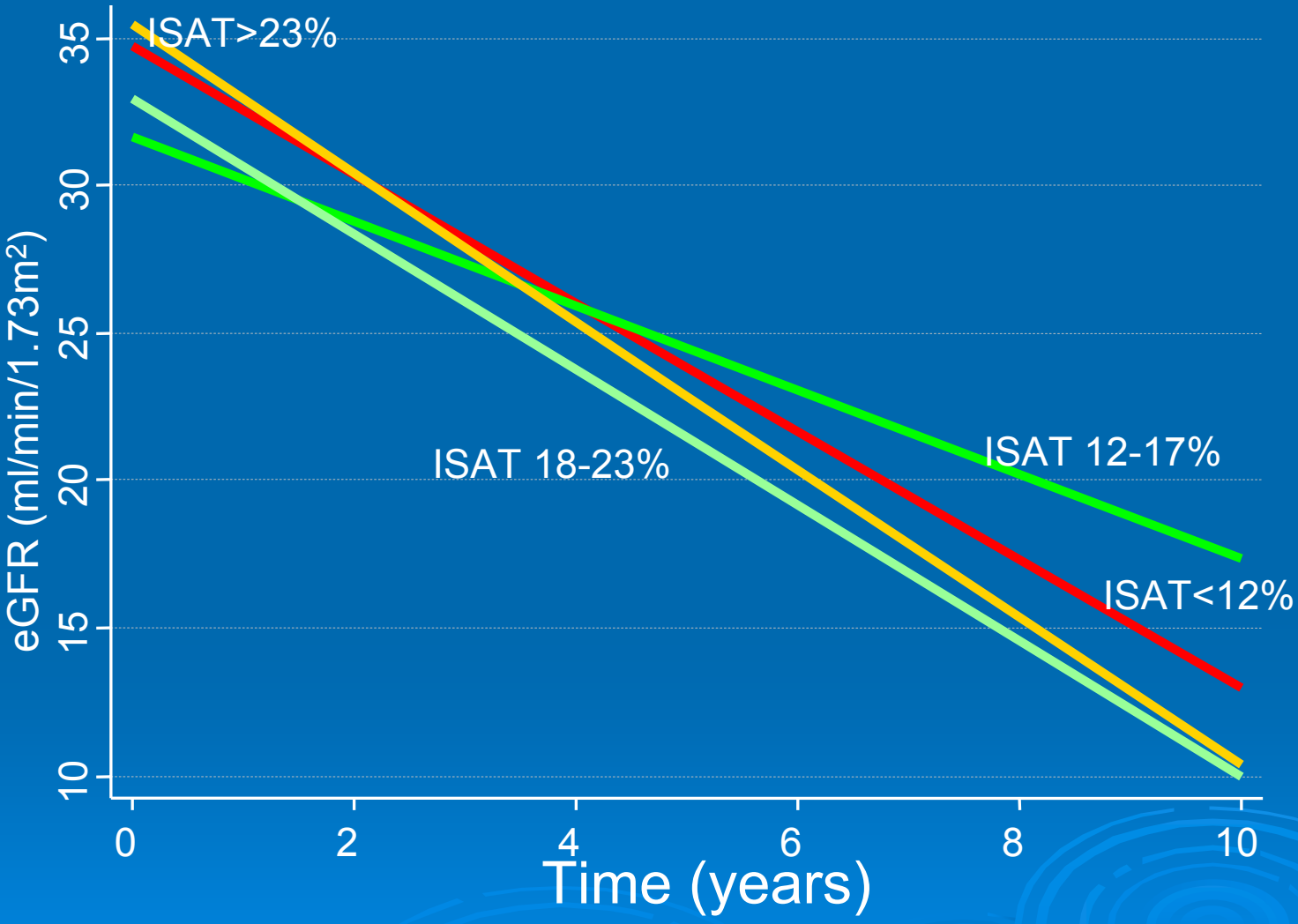


Kovesdy et al, Clin J Am Soc Nephrol 2009; 4:435-41

Iron levels and outcomes in NDD-CKD

- TSAT >25% associated with lower mortality.
- Ferritin >400 ng/ml associated with trend towards higher mortality.
- TSAT>23% associated with faster progression of CKD in patients with lower albumin levels.

Iron replacement and mortality

- It is unclear why low levels of iron markers are associated with higher mortality.
  - Causal?
  - Residual confounding?
- Very high levels of iron markers are also associated with mortality.
- Clinical trials of iron replacement will provide guidance on the benefit vs. harm of iron replacement.
  - Caveat: there are no such RCTs!

IV Iron and Mortality

- Feldman et al I:
  - increased mortality (RR: 1.11) with receipt of >10 vials of iron dextran over 6 months (*P*=0.05)[1]
- Feldman et al II:
  - designed to expand on previous findings by[2]
    - Determining the contribution of comorbidity variables to mortality
    - Assessing the effects of iron dosing over time

1. Feldman et al. J Am Soc Nephrol. 2002;13:734-744.
2. Feldman et al. J Am Soc Nephrol. 2004;15:1623-1632.

Study Design

- Baseline model: examined association between total iron dose during 6-month baseline period and mortality during follow-up
- Time-dependent model: examined probability of survival as a function of cumulative iron dosing in rolling 6-month intervals during follow-up
  - Incorporated detailed comorbidity analyses
  - “Unlagged” (iron in prior 0-6 months) and “lagged” (iron in prior 6-12 and 12-18 months) models used to determine whether mortality changed with increasing time following iron administration

Feldman et al. J Am Soc Nephrol. 2004;15:1623-1632.

Iron Exposure Periods/ Assessment of Variables

- 2 baseline periods: 1/96-6/96 and 7/96-12/96; both followed through 9/98
- Potential confounders
  - Demographics (race, gender, age)
  - Comorbidities (duration of ESRD, hospitalization, antibiotic use)
  - EPO dose
  - Lab data (serum ferritin, TSAT, Hgb, AST/SGOT, PTH, albumin)

Jan 1996 — Jul 1996 — Sep 1998

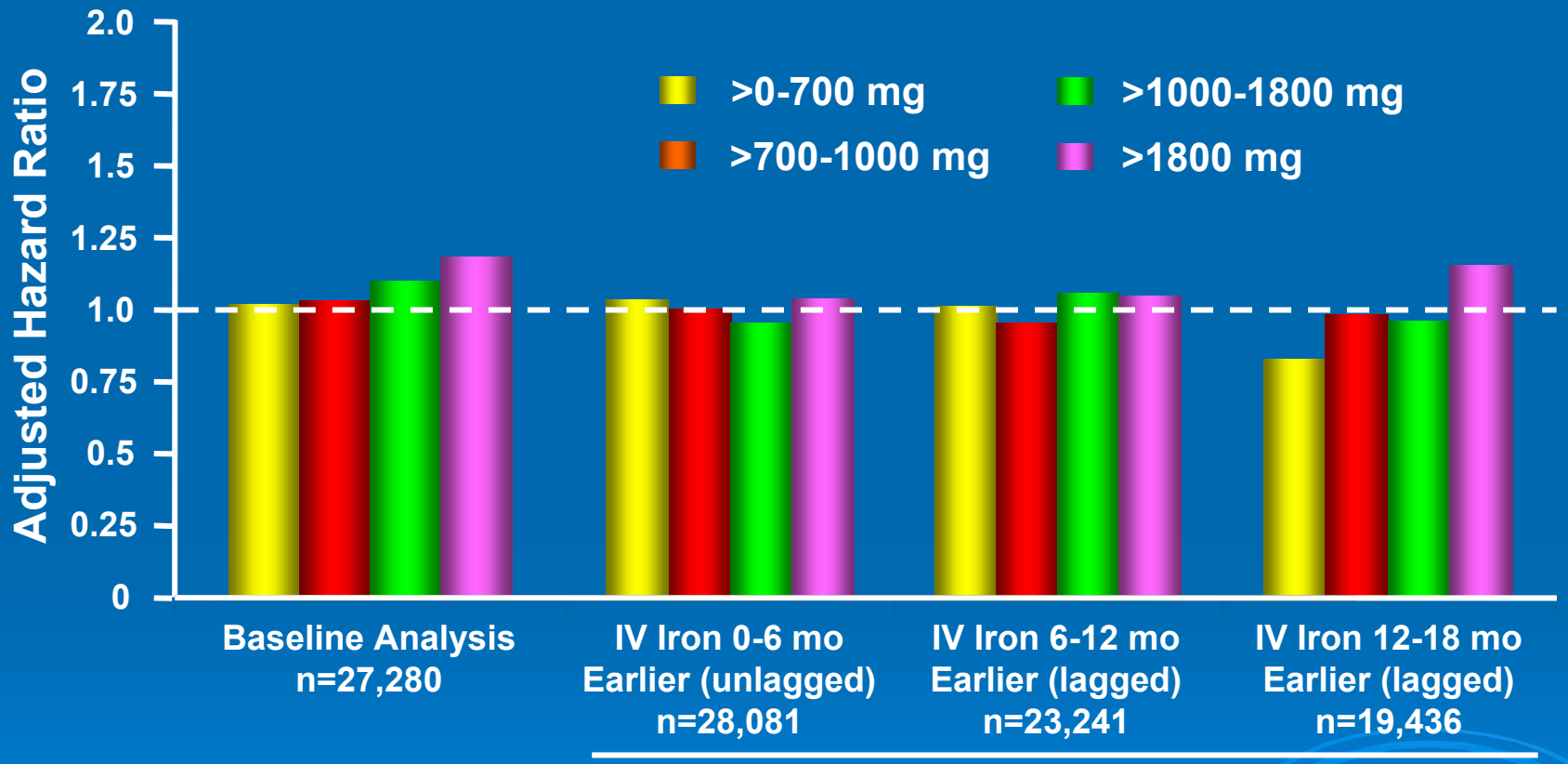
6-mo iron exposure period*

1-mo risk period

*This diagram is a simplified representation of the rolling 6-month iron exposure periods. Overall, there were 21 such periods between 7/96 and 9/98.

Feldman et al. *J Am Soc Nephrol.* 2004;15:1623-1632.

Adjusted Hazard Ratios for Mortality by Iron Dosing



Time-Dependent Models

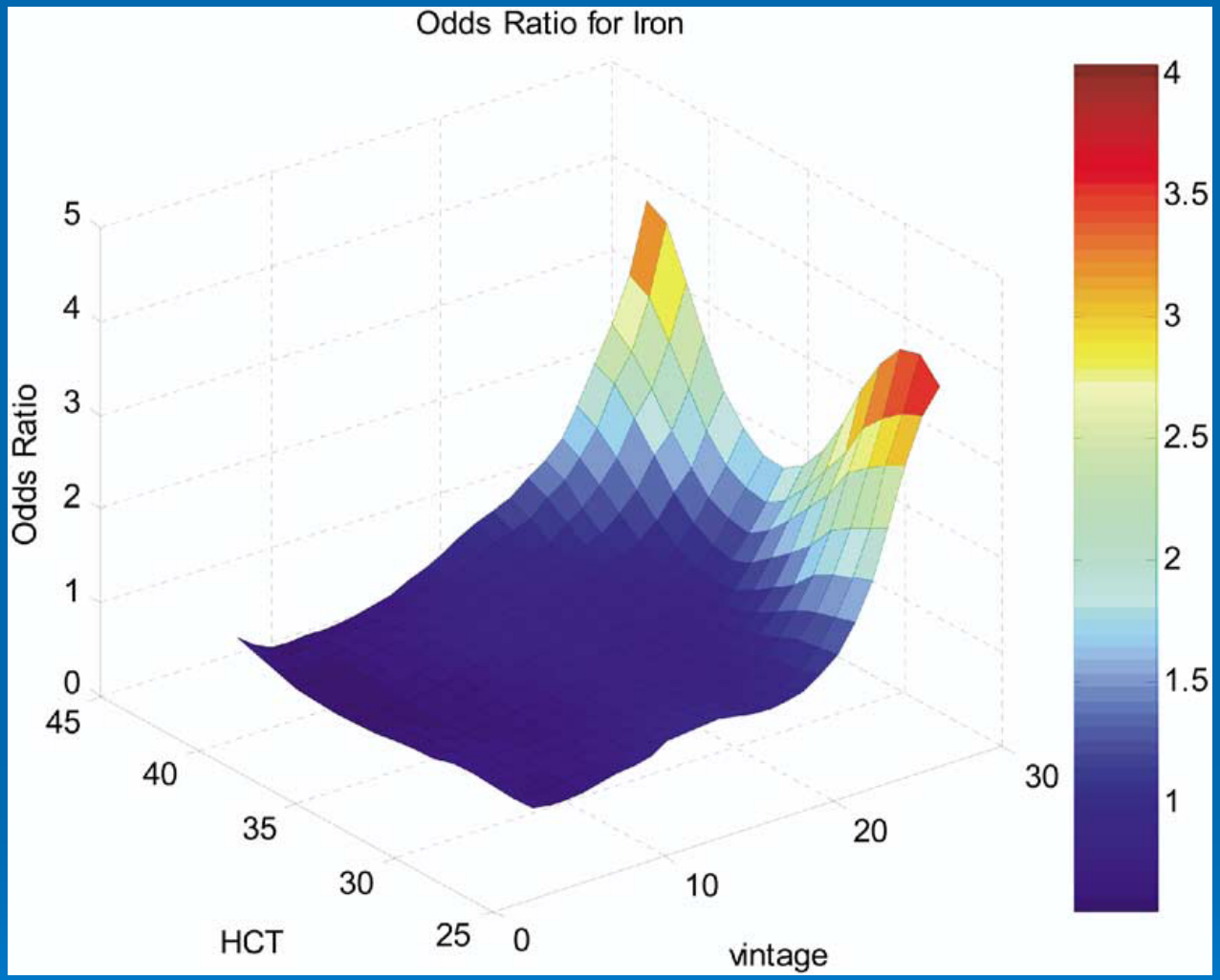
Dotted line at hazard ratio 1.0 indicates reference value (no iron).

Feldman et al. J Am Soc Nephrol. 2004;15:1623-1632.

Does IV Iron Contribute to Mortality? Summary

- Caveats
  - Iron dextran was the only product administered.
  - Study was conducted before widespread use of maintenance IV iron (bolus vs. small dose maintenance).

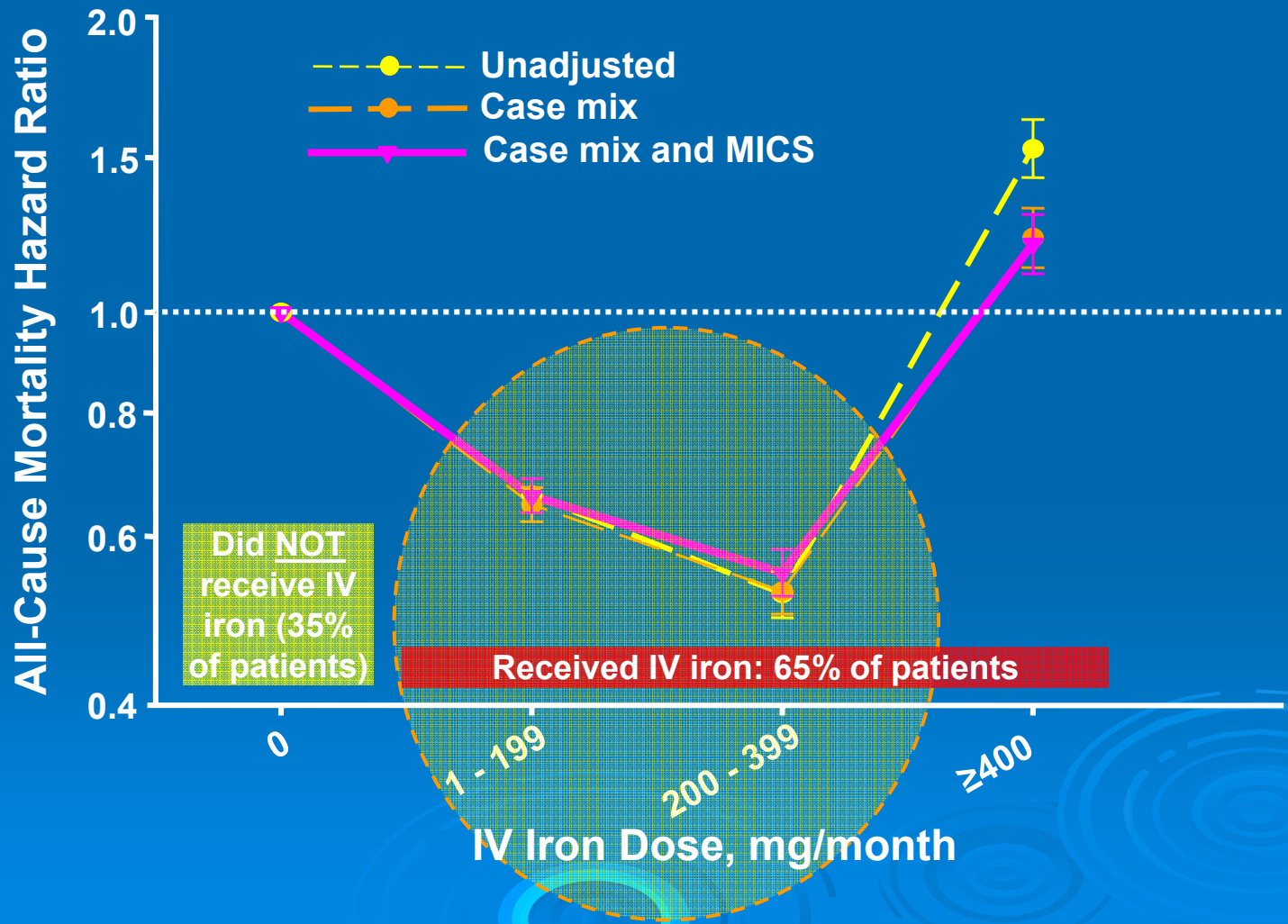
Feldman et al. J Am Soc Nephrol. 2004;15:1623-1632.



Time-varying logistic models to analyze the association between IV iron and survival in US HD patients (1/1/99-12/31/00) and followed up for up to 3 yrs (n=59,480)

Kaysen et al, Am J Kidney Dis 2006; 47:166

Risk of Death by IV Iron Dose (58,058 HD patients, 2001-2003)



Kalantar-Zadeh et al. J Am Soc Nephrol. 2005

Conclusions

- Both lower and higher levels of serum iron markers are associated with increased mortality in ESRD and NDD-CKD.
  - The imperfect nature of the markers make interpretation especially difficult.
- Observational studies of iron replacement suggest a benefit associated with modest doses of IV iron replacement.
  - Higher doses and longer exposure may be associated with increase in adverse outcomes.
- No RCTs on the horizon to provide a definitive answer to the debate…