Iron & Infections: Preferred Dosing Regimens for IV Iron

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Disclosure of Interests

- Salary supported from federal grants (NIDDK, NHLBI, NIAMS, AHRQ) and clinical activities
- Advisory Boards (past 12 months: Amgen, Keryx, GlaxoSmithKline, Rockwell Pharma)
- Data Safety Monitoring Boards (Medtronic, Medgenics)
- Consultancy (ACUMEN)
- Co-Editor, AJKD
- Associate Editor, JAMA
- Member, Public Policy Board, ASN

Premise #1 - Benefits

Iron supplementation is an essential tool for the effective and efficient treatment of anemia in patients with CKD

- May raise hemoglobin concentrations without any need for ESA in some patients
- Reduces ESA requirements in patients who need ESA treatment

Premise #2 - Utility

The intravenous route is the preferred, if not only effective, iron supplementation modality for (almost) all patients with CKD-5D

- (at least with currently available treatment options)

Premise #3 - Risks

Intravenous iron supplementation is un-physiological and may acutely or chronically overwhelm biological systems in place to handle the "hot potato."

- Infectious consequences
- Cardiovascular consequences
- Other (hepatic, bone, neurological, etc.)

Premise #4 - Solution

The risk-benefit relationship may vary among different dosing strategies for intravenous iron supplementation

- A dosing regimen exists that maximizes benefits while minimizing risks
- What constitutes this optimal regimen may differ among types of patients

Control Knobs

Can manipulate:

- Relative input of ESA, iron, transfusion into the “production function” of anemia care
- Zooming in on iron:
  - Indication/Target (laboratory constellation)
  - Dose
  - Frequency
  - Duration
  - Formulation

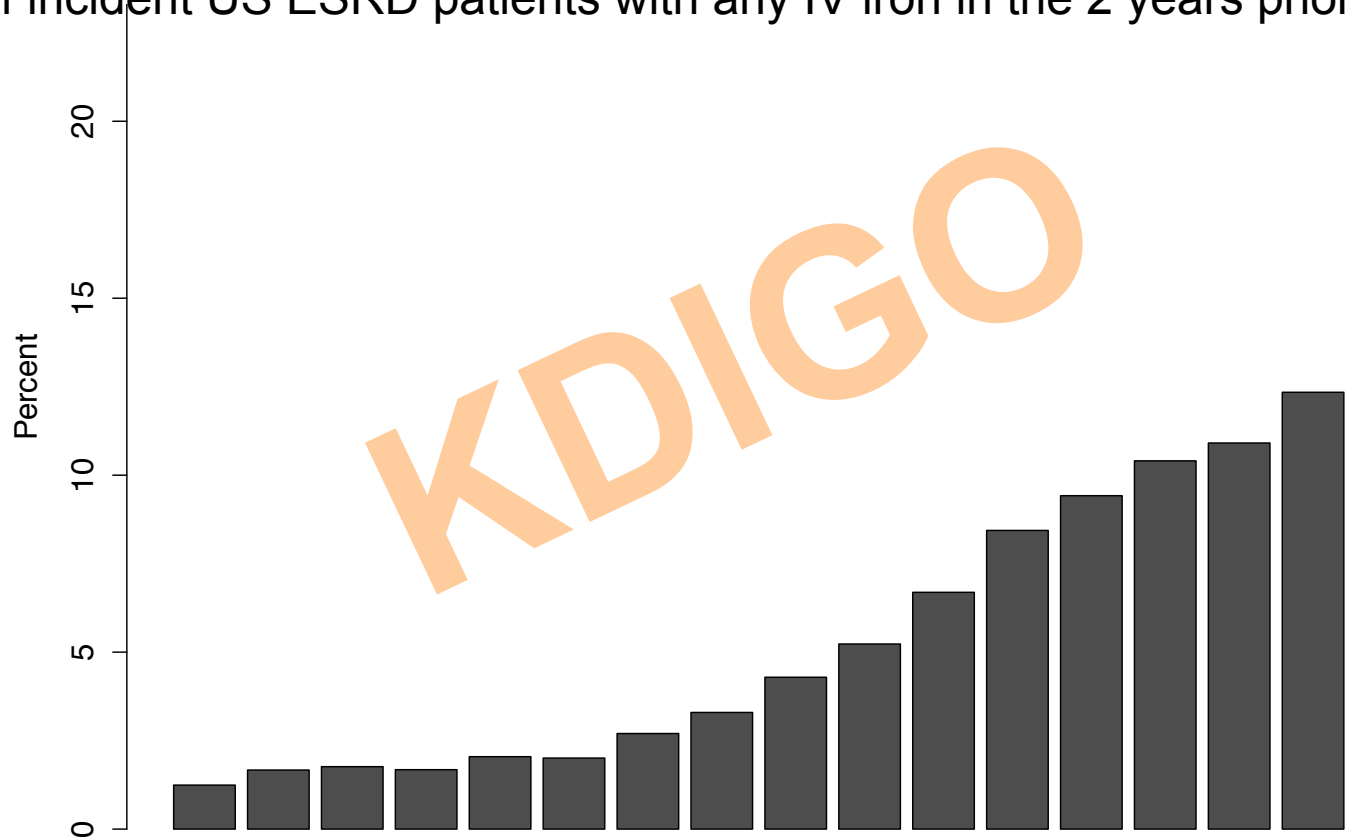
Control Knobs

Initial iron repletion:

"[…] It is common practice to provide an initial course of IV iron amounting to approximately 1000 mg; this may be repeated if an initial dose fails to increase Hb level and/or allow a decrease in ESA dose and if the TSAT remains ≤30% and serum ferritin remains ≤500 ng/ml (≤500 mcg/l). […]" (KDIGO Anemia 2012)

Control Knobs

% of incident US ESRD patients with any IV iron in the 2 years prior to ESRD



Winkelmayer W C, et al. JAMA Internal Medicine 2014; doi:10.1001/jamainternmed.2014.87

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Alternatives for subsequent dosing:

- Bolus ("periodic iron depletion" -KDIGO Anemia 2012)
- Maintenance (continuous)

- Formulation/substance

The Evidence

Meta-analysis of 72 studies (19 renal)

comparing IV iron *vs.* no iron or IV iron *vs.* oral iron

- Increase in standardized hemoglobin with IV iron *vs.* no iron or *vs.* oral iron (+6.5 g/dL; [5.1-7.9])
- Decreased risk of transfusion with IV iron *vs.* no iron or *vs.* oral iron (RR: 0.74; 0.62-0.88)
- Increased risk of infectious outcomes (RR: 1.34 [1.10-1.64])

(Litton E, et al.: *BMJ* 2013;347:f4822)

The Evidence

In the kidney space, limited and mixed –

"[…] the optimal iron dosing strategy to minimize infection risk has yet to be determined […]"

(Ishida JH & Johansen KL: *Semin Dial* 2014; 27;26-36)

– 24 studies

- 2 trials (Coyne D, et al. 2007; Besarab A, et al. 2000)
- 22 observational studies, mostly any *vs.* no iron or high *vs.* low iron; mostly small N; mixed results.

The Evidence

Ideal (observational) study needed to fill this evidence gap on infectious outcomes:

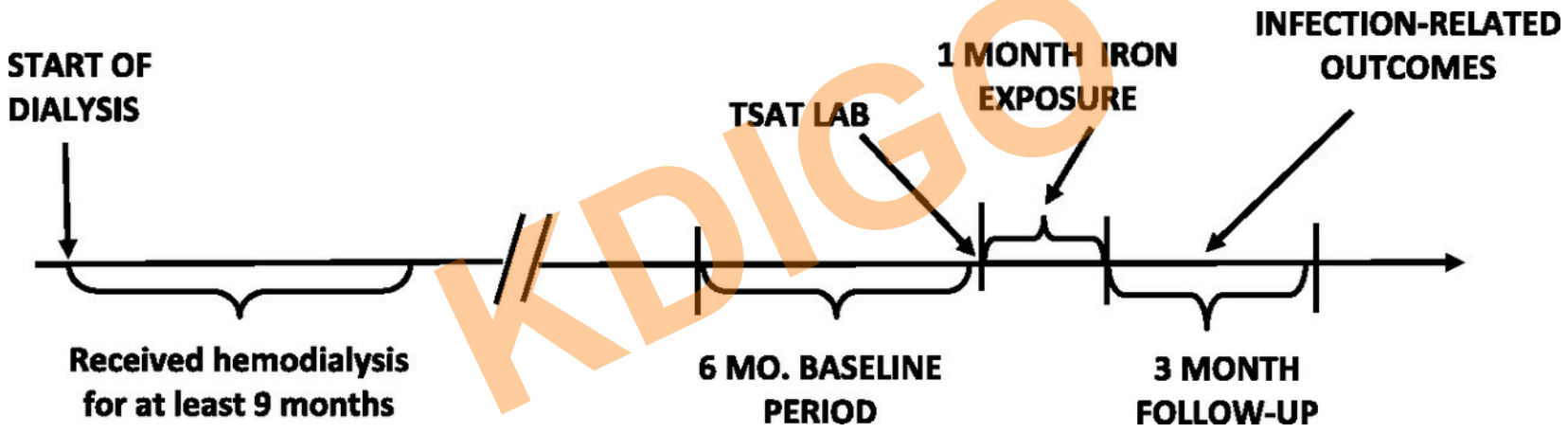
- Large, representative database
- Highly granular data on sociodemographics, laboratories, medical conditions, health care utilization
- Strict temporal separation of baseline, clinical motivation, treatment, and outcome ascertainment windows
- Sophisticated analytics

A Study

- Merged USRDS and DaVita EHR (2004-8)
- Studied 117,050 patients
- Analyses anchored on TSAT measurement (776,203 episodes analyzed)
- Studied:
  - Bolus vs. maintenance
  - High vs. low dose

Brookhart M A et al. JASN 2013;24:1151-1158

A Study



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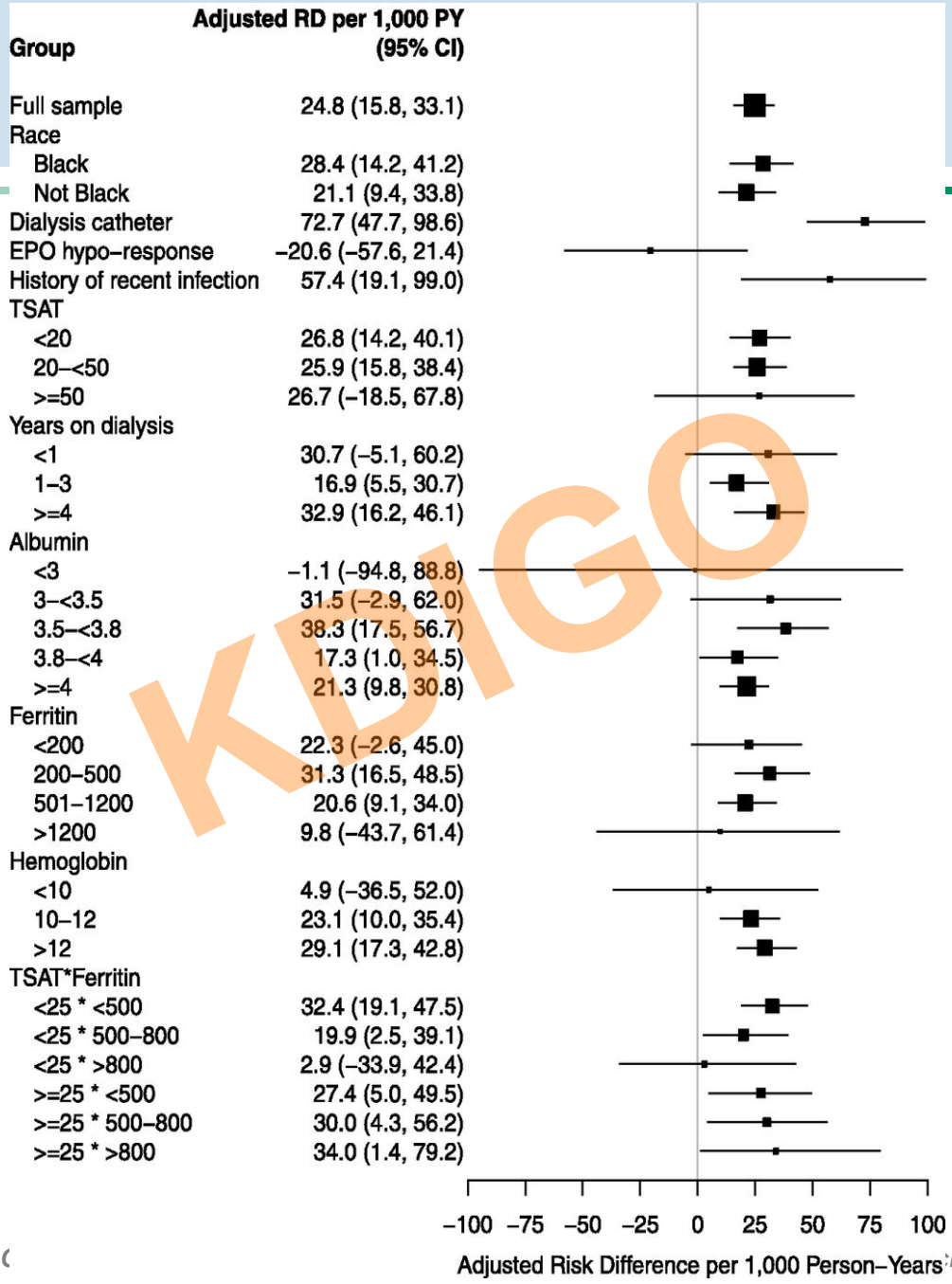
A Study

Bolus *vs.* maintenance iron (reference)

	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization or Death
Unadjusted HR	1.51 (1.47 to 1.56)	1.63 (1.48 to 1.78)	1.52 (1.48 to 1.56)
Adjusted HR	1.08 (1.05 to 1.11)	1.11 (1.00 to 1.23)	1.08 (1.05 to 1.11)
Adjusted RD/1000 person-yr	24.8 (15.8 to 33.1)	2.0 (−0.36 to 4.1)	26.1 (17.6 to 35.0)

Brookhart M A et al. JASN 2013;24:1151-1158



A Study

High (>200 mg/mo.) *vs.* low dose iron (reference)

	Hospitalized for Infection	Infection-Related Death	Infection-Related Hospitalization or Death
Unadjusted HR	1.37 (1.33 to 1.40)	1.43 (1.32 to 1.55)	1.37 (1.34 to 1.40)
Adjusted HR	1.05 (1.02 to 1.07)	1.08 (0.99 to 1.19)	1.05 (1.02 to 1.08)
Adjusted RD/1000 person-yr	12.1 (5.7 to 18.8)	1.2 (−0.74 to 2.8)	13.0 (6.2 to 19.5)

Brookhart M A et al. JASN 2013;24:1151-1158

A Study

- No associations between maintenance dosing or low dose and no iron groups
- Also note, no associations with cardiovascular outcomes (next slide)

Another Study

Bolus *vs.* maintenance iron (reference) – cardiovascular outcomes (same cohort as before)

	Myocardial Infarction (n=6,078)	**Stroke** (n=8,618)	**CV Death** (n=12,584)	**Composite** (n=25,350)
Unadjusted HR	1.14 (1.06,1.23)	1.27 (1.19,1.35)	1.37 (1.30,1.44)	1.30 (1.25,1.34)
Adjusted HR	0.98 (0.90,1.06)	1.05 (0.98,1.12)	1.02 (0.96,1.07)	1.03 (0.99,1.07)
Adjusted RD/ 1000 person-yr	-0.82 (-3.9, 2.2)	2.5 (-1.6, 6.2)	0.90 (-3.2, 4.7)	3.7 (-2.4, 9.9)

Kshirsagar A V et al. PLoS ONE 8(11): e78930

Conclusion

- Absent RCTs, high-quality comparative effectiveness research can provide useful evidence informing practice
- Evidence suggests increased infection risk in patients receiving bolus dosing, or high dose iron supplementation, compared with maintenance dosing, or low dose iron supplementation
- The infectious risk appears to be augmented in patients dialyzing *via* a central venous catheter

Conclusion

- Additional questions remain unanswered:
  - Long-term effects of iron dosing strategies
  - Other clinical outcomes
  - Validity of the class assumption
  - Safety of IV iron in CKD-NOD