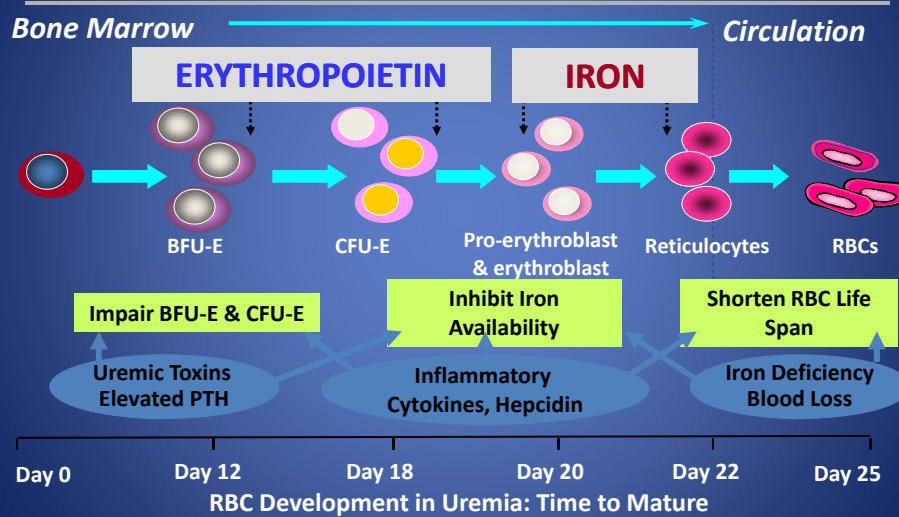


Achieving/Targeting Optimal Hemoglobin and Outcomes in CKD: Less ESA, More Iron

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ASN 2010

Iron Is Required for Erythropoiesis



Kalantar-Zadeh et al. *Adv Chron Kidney Dis.* 2009;16:143-151.

Objective:
Use of Less ESA, More Iron Is...

- Effective
- Safe
- Less costly

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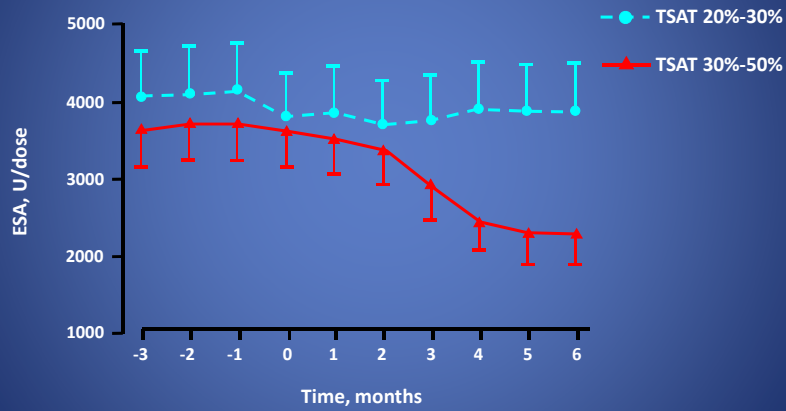
Data Supporting Response to IV Iron in Patients with Serum Ferritin Levels Higher than 500 ng/mL

- Current practice (mean serum ferritin in U.S. HD patients was 586 ± 366 ng/mL in 2007)
- Besarab (RCT)
- DRIVE Study (RCT)
- Kalantar-Zadeh (Observational)

“Low” vs. “High” TSAT Study

- Besarab et al (JASN 11:530-538, 2000)
- Prospective study, randomized patients to maintain TSAT 20-30% (control, n=19) vs. 30-50% (study, n=23)
- At month 6, avg. control TSAT=27.6%, ferritin=297.5; avg. study TSAT=32.6%, ferritin=730.5. Avg. Hgb same
- 40% reduction in EPO dose in study group with net cost savings (incl. cost of add'l iron)

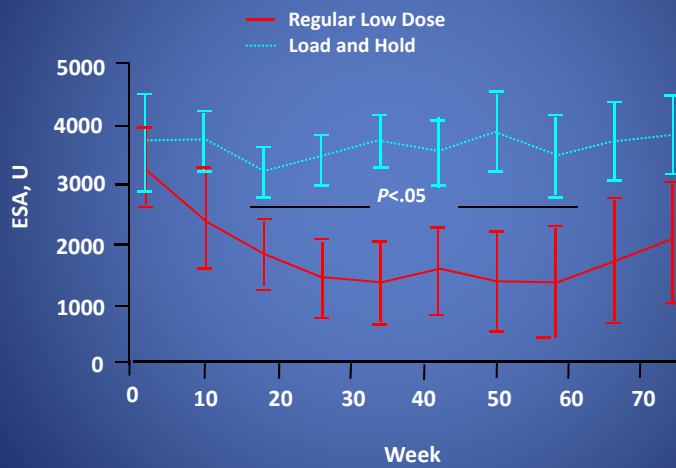
Maintenance of TSAT Between 30%-50% Reduces ESA Doses



Besarab et al. *J Am Soc Nephrol.* 2000;11:530-538.

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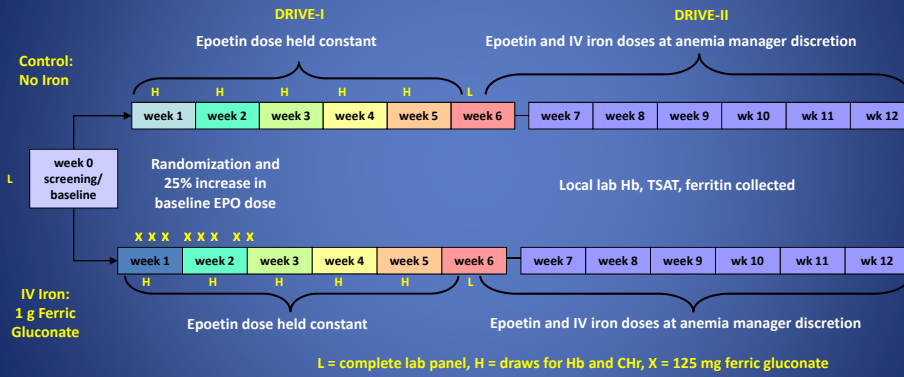
Regular Low-Dose IV Iron Reduces ESA Doses vs Load and Hold Strategy



Besarab et al. *Am J Kidney Dis.* 1999;34:21-28.

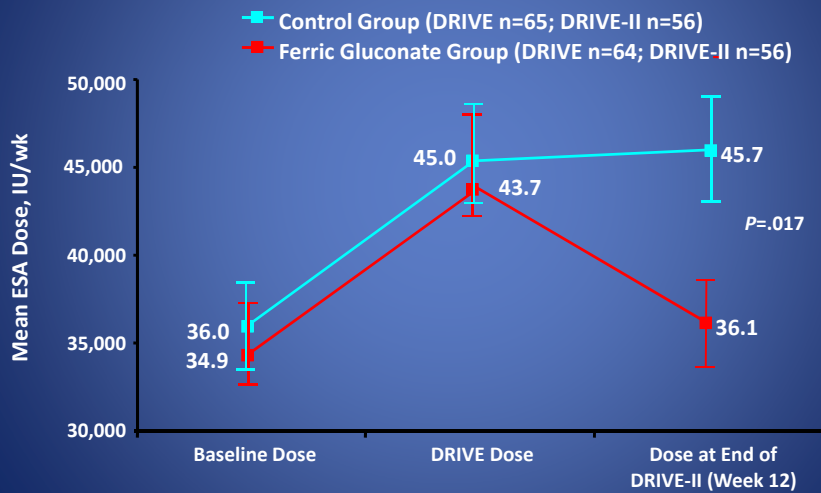
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ESA Dose Reduction and Cost Savings Observed in DRIVE Studies: Design



Kapoian et al. *J Am Soc Nephrol.* 2008;19:372-379.

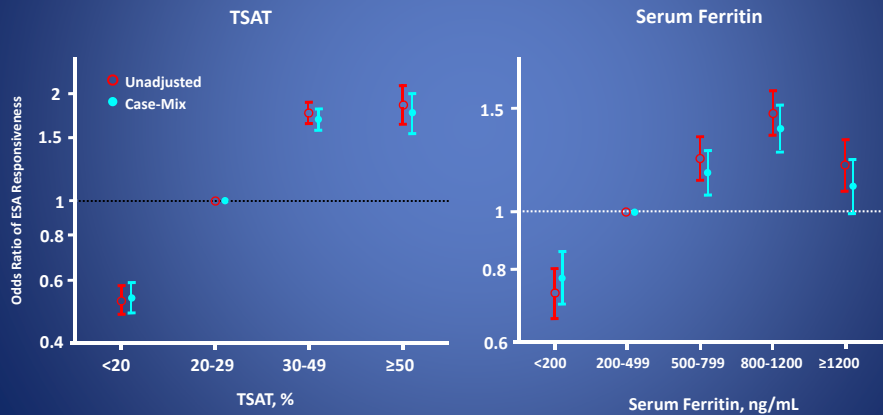
DRIVE-II: ESA Doses Significantly Reduced in Ferric Gluconate Group by Week 12



Kapoian et al. *J Am Soc Nephrol.* 2008;19:372-379.

Higher TSAT and Serum Ferritin Are Associated With Greater ESA Responsiveness

Odds ratio of ESA responsiveness for iron markers before and after adjustment for case-mix variables in 38,393 long-term HD patients



Kalantar-Zadeh et al. *Am J Kidney Dis* 2009;53:823-34.

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Serum Ferritin Levels in Hemochromatosis

- Serum ferritin levels accurately reflect iron burden
- Iron overload with organ damage occurs in patients >40 years with >20 g of parenchymal iron storage
- Hemochromatosis patients with severe fibrosis or cirrhosis have mean serum ferritin levels of 4411 ± 1158 ng/mL and TSAT of $91.2\% \pm 1.7\%$
- No evidence of cirrhosis in hemochromatosis patients with serum ferritin <1000 ng/mL

Morrison et al. *Ann Intern Med.* 2003;138:627-633.
Guyader et al. *Gastroenterology.* 1998;115:929-936.
Bacon et al. *Ann Intern Med.* 1999;130:953-962.
Powell et al. *Ann Intern Med.* 1998;129:925-931.
Tavill. *Hepatology.* 2001;33:1321-1328.
Adams et al. *Hepatology.* 1997;25:162-166.
Crawford et al. *Gastroenterology.* 1998;114:1003-1008.

Potential for Iron Deposition in ESRD

- Hemochromatosis patients with organ damage have dramatically higher serum ferritin and TSAT levels than the general HD population
- The estimated 20 g of excess iron needed to cause organ damage in hemochromatosis patients is an amount few HD patients receive in a lifetime, even before accounting for ongoing blood losses
- There have been no reports in HD patients of cirrhosis, pancreatic fibrosis, or cardiac failure due to transfusional iron overload
- One study detected hepatic iron overload in HD patients with serum ferritin below high-end range

Eschbach et al. *Kidney Int Suppl.* 1999;69:S35-S43.
Schafer et al. *N Engl J Med.* 1981;304:319-324.
Besarab et al. *J Am Soc Nephrol.* 1999;10:2029-2043.
Canavese et al. *Kidney Int.* 2004;65:1091-1098.

Infection and Inflammation

- In the post-ESA era, no relationship has been found between infection and serum ferritin level
 - A prospective, multicenter study found no association between serum ferritin or cumulative iron dose and risk of bacteremia in HD patients¹
- Longitudinally designed studies have not demonstrated an association between IV iron use and increased morbidity and mortality related to cardiovascular disease or infection²
- Caution should be exercised in patients with an active infection

1. Hoen et al. *J Am Soc Nephrol.* 1998;9:869-876.
2. Feldman et al. *J Am Soc Nephrol.* 2004;15:1623-1632.

Association Between Serum Ferritin and Survival in HD Patients

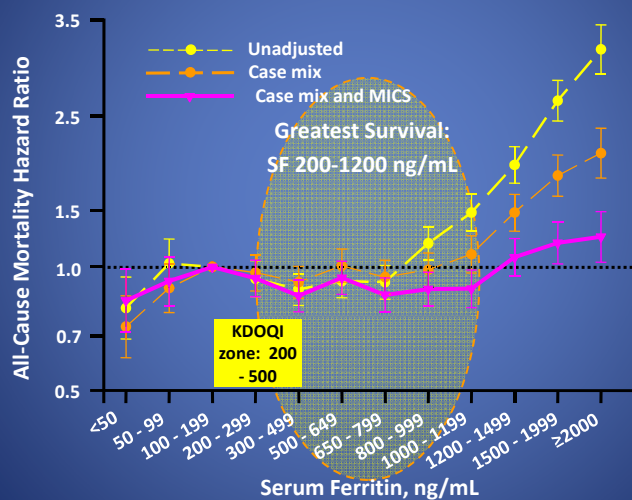
- Analyzed prospectively collected data of the 2-year (July 2001-June 2003) historical cohort of 58,058 maintenance HD patients from virtually all DaVita dialysis clinics in the United States
- Performed time-dependent and multivariate adjustment for case mix, administered IV iron and ESA doses, and available surrogates of malnutrition-inflammation-cachexia syndrome (MICS)

Kalantar-Zadeh et al. *J Am Soc Nephrol.* 2005;16:3070-3080.

Multivariate Cox Regression: Hazard Ratio of Death

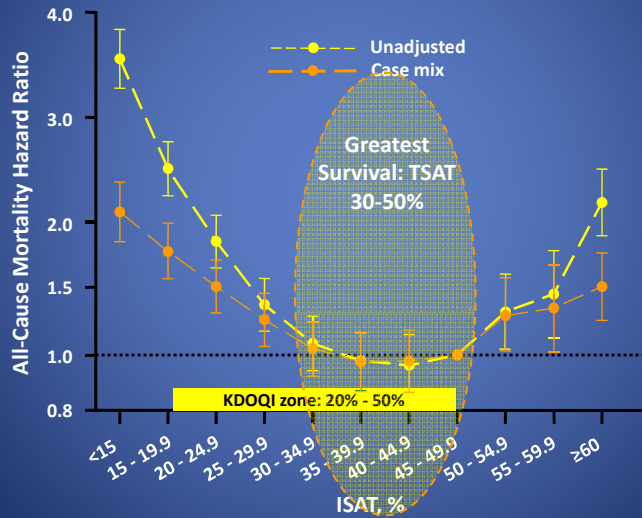
- Unadjusted model included only categories of iron markers (predictors), entry quarter (covariate), and mortality (outcome)
- Case-mix adjusted models included
 - Age, gender, race and ethnicity, DM, dialysis vintage, entry quarter, primary insurance, marriage status, standardized mortality ratio, dialysis dose (Kt/V), and residual renal function (Kru), blood Hb, ESA dose, IV iron
- Case-mix and MICS adjusted models included all above plus 10 indicators of nutritional state and inflammation
 - BMI, nPNA (protein intake), serum albumin, TIBC, creatinine, bicarbonate, phosphorus, calcium, WBC, lymphocyte %

Risk of Death by Serum Ferritin Level (Time-dependent Cox Model)



Kalantar-Zadeh et al. *J Am Soc Nephrol.* 2005;16:3070-3080.

Risk of Death by Iron Saturation Ratio (Time-dependent Cox Model)



Kalantar-Zadeh et al. *J Am Soc Nephrol.* 2005;16:3070-3080.

All-Cause Mortality

All patients

Race

Caucasian
Black
Asian
Hispanic

Diabetes mellitus

Diabetic
Non-diabetic

Gender

Female
Male

Age

<65 years
≥65 years

Vintage

<6 months
6-24 mo
2-5 years
>5 years

Serum iron

≤3.8 g/dL
>3.8 g/dL

Proteinuria

≤1.0 g/dL
>1.0 g/dL

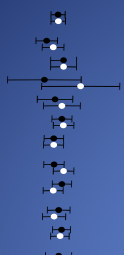
Hb

<10 g/dL
10-11 g/dL
11-12 g/dL
12-13 g/dL
≥13 g/dL

Ferritin (F) & ISAT

F<500 ng/mL & ISAT<25%
F<500 ng/mL & ISAT≥25%
F≥500 ng/mL & ISAT<25%
F≥500 ng/mL & ISAT≥25%

improves survival | worsens survival

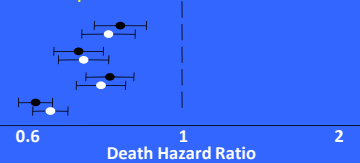


- Examined All Cause and CV mortality in 58,000 US dialysis patients

- All circles and lines to the left of the dotted vertical line favor IV iron

Iron improves survival | Iron worsens survival

Ferritin (F) and ISAT
F<500 ng/mL and ISAT<25%
F<500 ng/mL and ISAT≥25%
F≥500 ng/mL and ISAT<25%
F≥500 ng/mL and ISAT≥25%



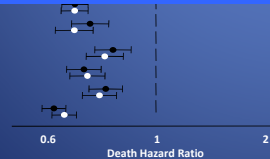
0.6 | 1 | 2
Death Hazard Ratio

and subgroups

and on

adjusted Cox models

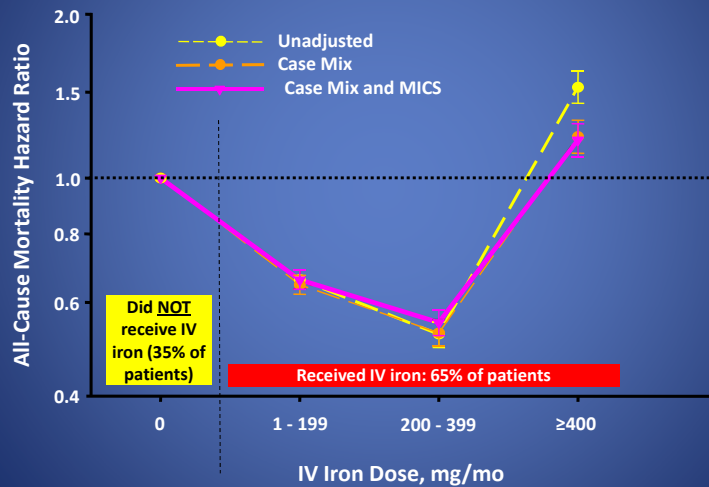
- White circles are based on multivariate adjusted models



0.6 | 1 | 2
Death Hazard Ratio

Kalantar-Zadeh et al. *J Am Soc Nephrol.* 2005;16:3070-3080.

Risk of All-Cause Death by IV Iron Dose



Kalantar-Zadeh et al. *J Am Soc Nephrol.* 2005;16:3070-3080.

Results

- Lowest all-cause and cardiovascular death risks were associated with serum ferritin 200-1200 ng/mL
- Administered IV iron up to 400 mg/mo was associated with improved survival; doses >400 mg/mo correlated with increased death risk

Kalantar-Zadeh et al. *J Am Soc Nephrol.* 2005;16:3070-3080.

Proposed CPM from CMS

CPM 3- Avoidance of iron therapy in iron overload

Measure description

- Percentage of all adult (≥ 18 years old) dialysis patients with a **serum ferritin ≥ 1200 ng/mL** or a TSAT $\geq 50\%$ on at least one simultaneous measurement during the three-month study period who did not receive IV iron in the following three months.

Numerator

- Number of patients in the denominator who did not receive IV iron within three months following the first occurrence of **serum ferritin ≥ 1200 ng/mL** or TSAT $\geq 50\%$ during the study period.

Denominator

- All adult (≥ 18 years) hemodialysis and peritoneal dialysis patients in the facility for the entire three-month reporting period who had serum ferritin ≥ 1200 ng/mL or TSAT $\geq 50\%$ on at least one simultaneous measurement reported during the three-month study period. Simultaneous measurements are those reported with the same collection date.

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ESA Cost Savings in DRIVE and DRIVE-II

- Total cost per patient in the ferric gluconate group was \$3524 per g/dL Hb increase
- Total cost per patient in the control group was \$5065 per g/dL Hb increase
- Net savings for the ferric gluconate group was \$1390 per g/dL Hb increase over 12-week period

Pizzi et al. *Kidney Int.* 2008;74:1588-1595.

Japanese Bundling: Background

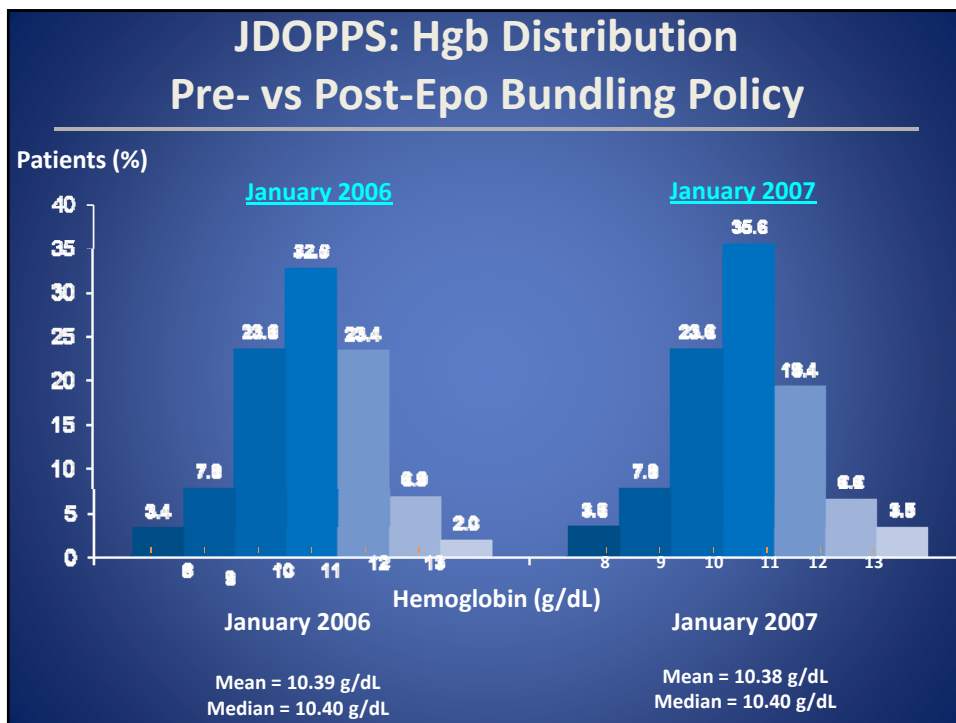
- In Japan prior to April 1, 2006, EPO reimbursement policy was based on a fixed payment per each dose administered
- Thereafter, EPO was not separately billable per dose, but bundled within overall reimbursement for dialysis clinical practice

Hasegawa et al. (*Kidney Int*, in press)

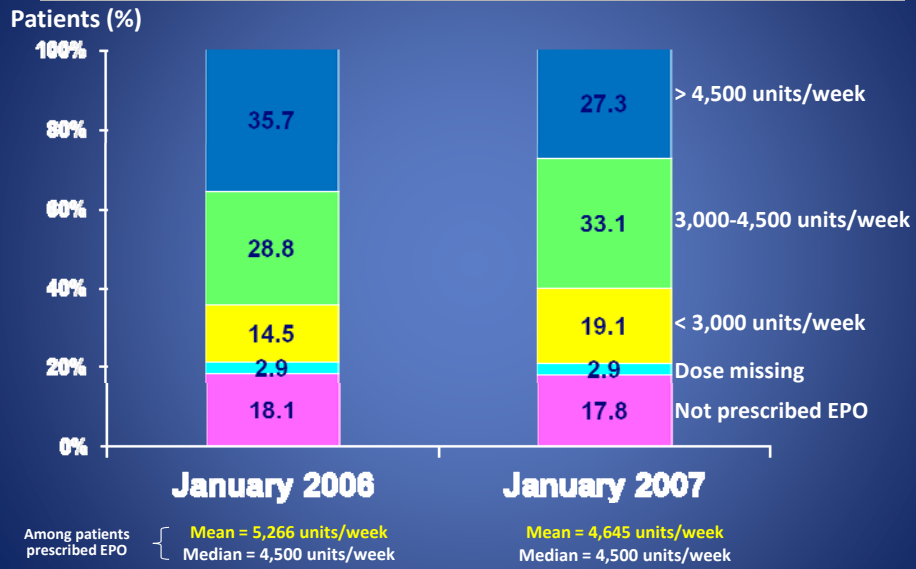
DOPPS Analysis

- Examined:
 - Pre- vs Post-bundling policy levels of
 - Mean hemoglobin values
 - Mean EPO use and EPO dose
 - Mean IV iron use and dose
- Data were from prevalent cross sections of patients before and after the reimbursement policy change date (April 2006) from 53 HD units participating in JDOPPS 3 (2005-08)

Hasegawa et al. (*Kidney Int*, in press)

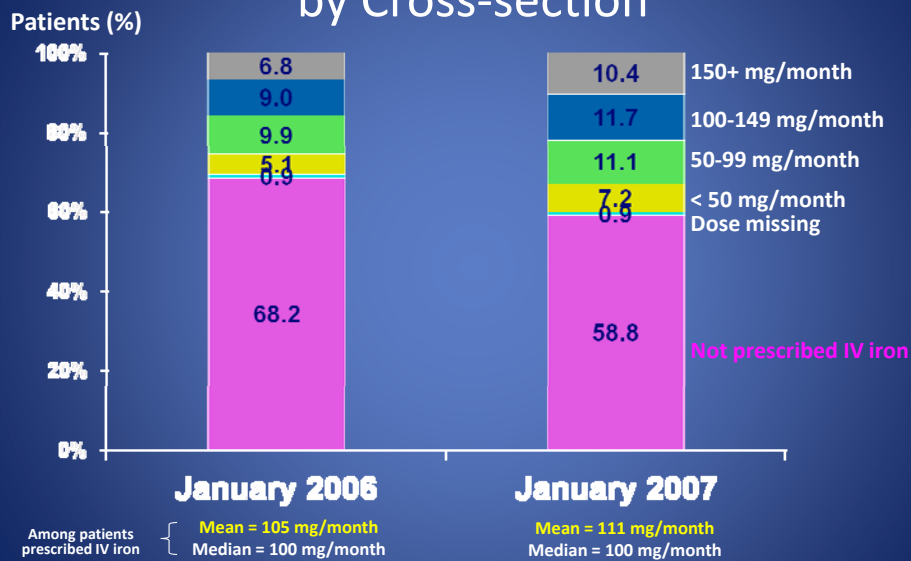


Distributions of EPO Doses by Cross-section



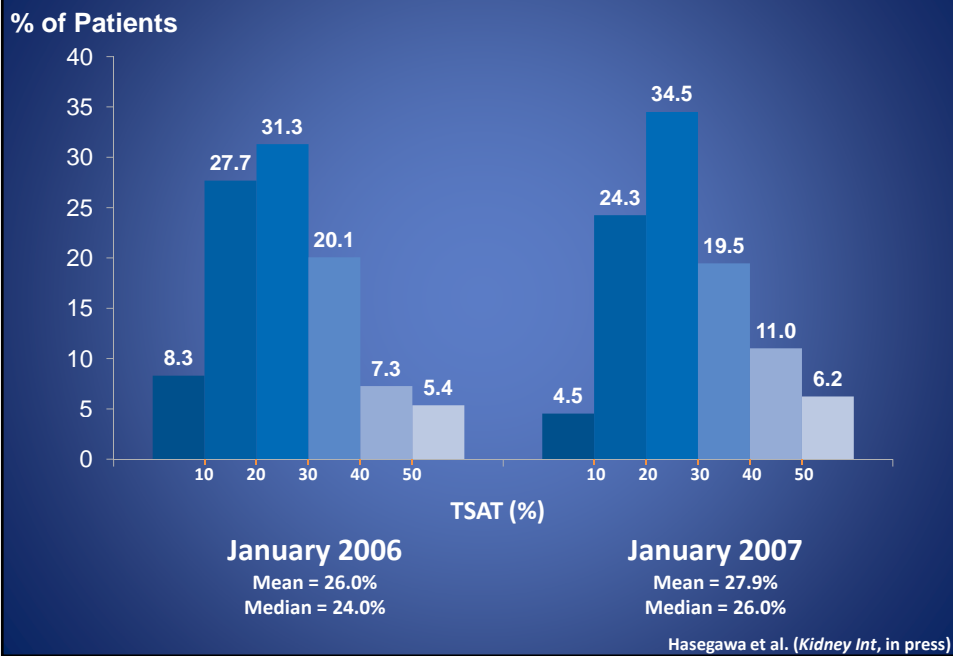
Hasegawa et al. (*Kidney Int*, in press)

Distributions of IV Iron Doses by Cross-section

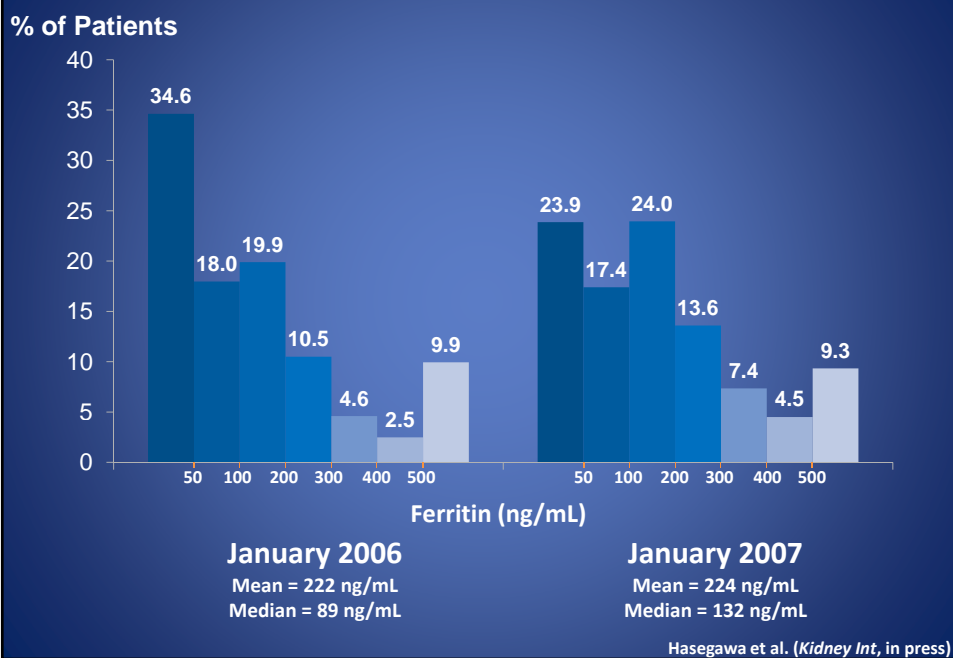


Hasegawa et al. (*Kidney Int*, in press)

Distributions of TSAT by Cross-section



Distributions of Ferritin by Cross-section

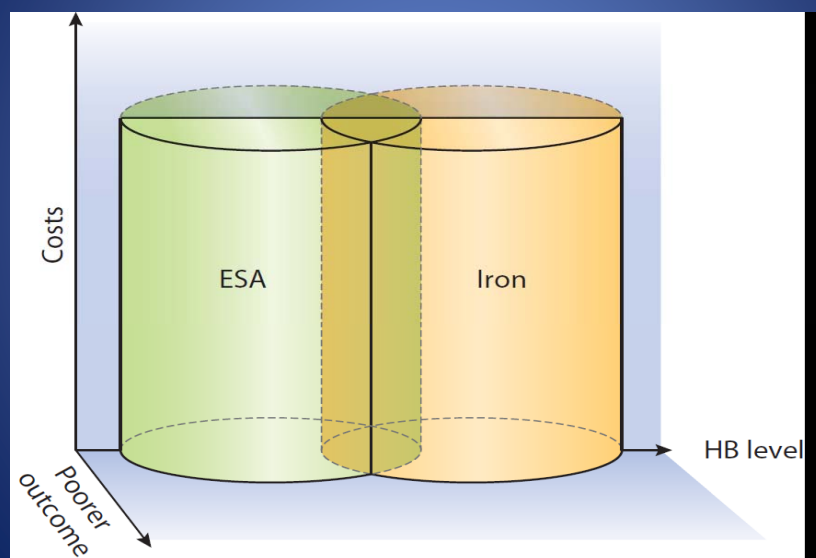


Conclusions of Study

- Across the two cross sections:
 - Hgb distributions were ~ unchanged
(mean Hgb = 10.4 g/dL still seen in 2009/2010 JDOPPS 4 data)
 - Mean dose of rHuEPO decreased ~ 12%
(% EPO use ~ unchanged)
 - IV iron use increased from 32% to 41%
 - Patterns differed slightly by HD facility type
- The observed trends from pre- to post-policy change do not appear to be explained by a prior trend in anemia management

Hasegawa et al. (*Kidney Int*, in press)

Conceptual Model of Anemia Management in ESRD



Summary and Conclusions

- IV iron has an ESA-sparing effect which is dose-related
- IV iron is not associated with adverse outcomes in population studies using doses <400 mg/month and in patients with ferritin <1200 ng/mL
- The ESA-sparing effect of IV iron will be attractive in a bundled payment environment for ESRD