KDIGO Controversies Conference New Data & Developments since publication of latest guidelines: Iron Supplementation

Rajiv Agarwal, MD
Professor of Medicine
Division of Nephrology
Indiana University School of Medicine &
Staff Physician, Richard L Roudebush VA Medical Center,
Indianapolis, IN

Acknowledgement

- Dr Anatole Besarab, Henry Ford Hospital, Detroit kindly shared several slides discussed in this presentation.

Presentation Objectives

- Review new developments in iron supplementation since last guidelines
  - Development of new iron formulations
  - Diagnostic tests for iron deficiency
  - Risks of IV iron
  - Benefits of IV iron, independent of anemia correction

Presentation Objectives

- Review new developments in iron supplementation since last guidelines
  - Development of new iron formulations
  - Diagnostic tests for iron deficiency
  - Risks of IV iron
  - Benefits of IV iron, independent of anemia correction

Existing IV Iron Preparations

Product	Indication	Warnings	Total Dose Infusion	Relative Cost
Ferric gluconate (Ferrlecit)	HD pts receiving ESA	General	No	$$$
Iron sucrose (Venofer)	HD, PD, CKD pts	General	No	$$$
LMW iron dextran (INFeD)	Iron-deficiency anemia	Black box	Yes	$$
HMW iron dextran (DexFerrum)	Iron-deficiency anemia	Black box	Yes	$

Investigational Iron Preparations: Ferumoxytol

- Characteristics
  - Semi-synthetic polysaccharide-coated iron oxide
  - Average particle size: 30 nm
  - Molecular weight: 750,000 daltons
  - Minimal analytically free iron (<.1%)

Investigational Iron Preparations: Ferumoxytol

PK Results of Randomized, Double-Blind, Ascending-Dose Study of 41 Normal Volunteers

	1 mg Fe/kg (n=8)	2 mg Fe/kg (n=8)	4 mg Fe/kg (n=17)
Half-life, h*	9.3 ± 1.1	10.2 ± 1.5	14.7 ± 2.2
C_{max}, μg Fe/mL*	26.3 ± 7.0	62.0 ± 11.6	130 ± 32.5
AUC, μg Fe•h/mL*	396 ± 122	997 ± 320	2912 ± 683
V_d, mL/kg	36.3 ± 10.0	31.1 ± 7.4	30.4 ± 7.3
CL, mL/hr•kg*	2.82 ± 1.21	2.17 ± .63	1.44 ± .33

- Significant increases in TSAT, serum iron, and serum ferritin with rapid IV injection at rate of 60 mg iron/min
- Drug well tolerated

*P<0.01, one-way analysis of variance.

Landry et al. *Am J Nephrol*. 2005;25:400-410.

Investigational Iron Preparations: Ferumoxytol

PK Results of Open-Label, Ascending-Dose Study of 20 HD Patients

Half-life	Dose-dependent and similar to that in healthy patients
AUC C_{max}	Dose-dependent

- Patients received single bolus dose of 125 mg or 250 mg shortly after the start of dialysis
- Increases were observed in serum iron, TSAT, serum ferritin, and reticulocyte count at 48 hours posttreatment
- Ferumoxytol was not removed with HD

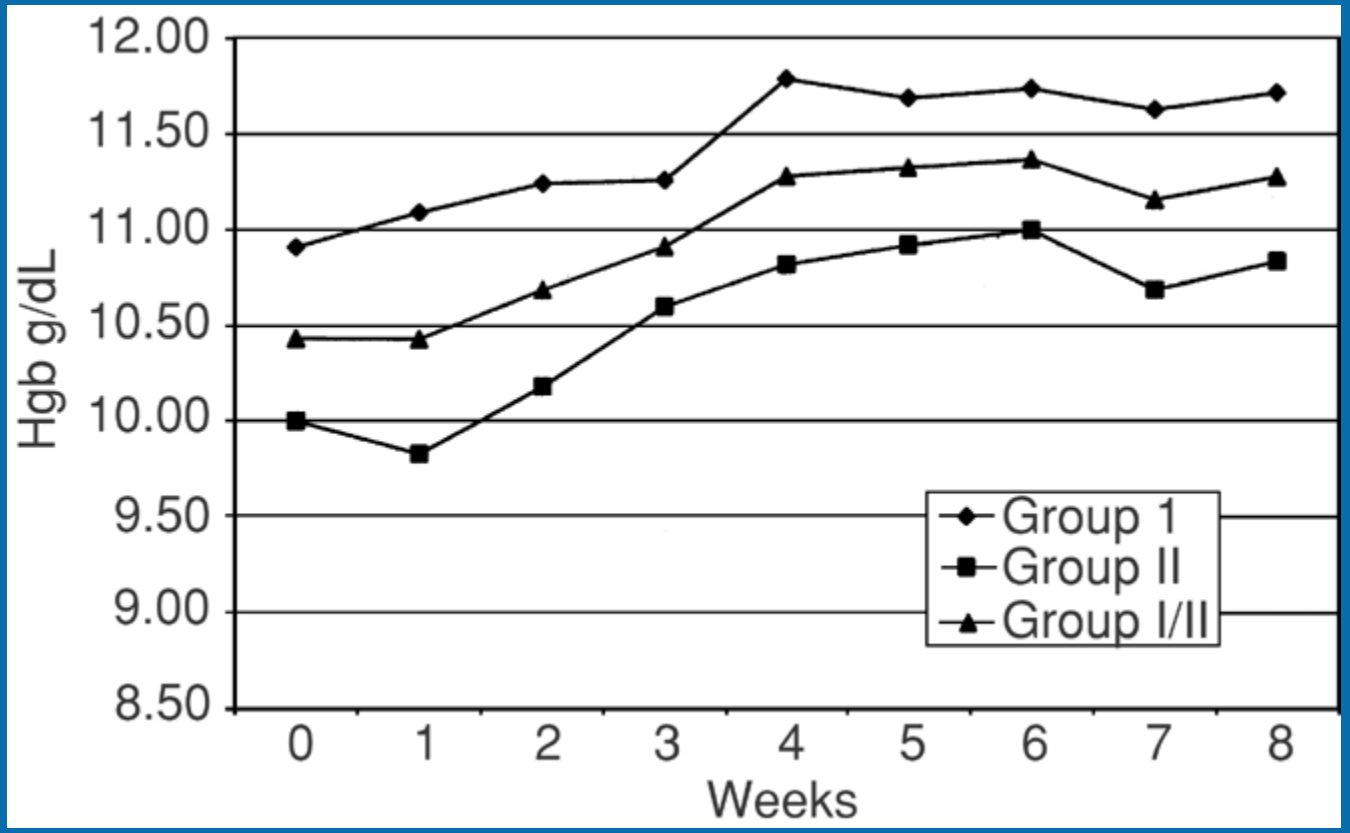
Landry et al. *Am J Nephrol*. 2005;25:400-410.

Ferumoxytol in non-HD patients

- Phase 2, open-label trial
- 21 PD or CKD patients; 13 on ESA, 8 no ESA
- ESA dose could be changed
- Randomized to:
  - 4 doses of 225 mg in 2 weeks
  - 2 doses of 510 mg in 1-2 weeks
- Rapid push 30 mg iron/sec
- Seven possibly related AEs in 5 patients
  - Constipation, chills, tingling, GI viral syndrome, delayed pruritic erythematous rash, pain at injection site

Spinowitz et al. *Kidney Int*. 2005;68:1801-1807.

Time Course of Hgb Response



4 x 225 mg

both

2 x 510 mg

Spinowitz et al. *Kidney Int*. 2005;68:1801-1807.

Investigational Iron Preparations: Ferumoxytol

	Baseline	1 Week	4 Weeks	6 Weeks	8 Weeks
Serum Ferritin, ng/mL	232 ± 216*	711 ± 430*	748 ± 495*	584 ± 310*	548 ± 291*
TSAT, %	21 ± 10	37 ± 22.1	27 ± 11.3	31 ± 9.6	27 ± 8.7
Hb, g/dL	10.4 ± 1.3	10.4 ± 1.1	11.3 ± 1.2	11.4 ± 1.2	11.3 ± 1.2

*$P<0.05$ compared to baseline.

Spinowitz et al. *Kidney Int*. 2005;68:1801-1807.

Investigational Iron Preparations: Ferumoxytol

Results of 4th and Final Phase 3 Study: Open-Label, Multicenter, Randomized Trial in HD-CKD

	Two 510-mg Ferumoxytol Doses in 1 Week	200 mg Oral Iron Daily for 3 Weeks	*P* Value
Change in Hb from baseline to day 35, g/dL	1.02 ± 1.13	.46 ± 1.06	0.0002
Patients with ≥1.0 g/dL increase in Hb from baseline to day 35, %	49.1	25	0.0002
Mean increase in serum ferritin from baseline at day 21, ng/mL	356.7 ± 247.1	-37.6 ± 107.0	<0.0001

- 230 HD-CKD patients receiving stable ESA doses randomized 1:1 to ferumoxytol or oral iron
- Significantly greater mean increase in Hb compared with oral iron (primary end point)
- No anaphylactoid events

Advanced Magnetics, Inc [press release]; July 23, 2007.

Investigational Iron Preparations: Ferumoxytol

- Clinical program
  - 4th and final phase 3 study has been completed
  - NDA planned for 4th quarter of 2007

1. Landry et al. *Am J Nephrol*. 2005;25:400-410.
2. Advanced Magnetics, Inc [press release]; July 23, 2007.

Investigational Iron Preparations: Ferumoxytol

- Potential advantages
  - Rapid bolus possible
  - Larger doses possible
  - Fewer injections to restore iron stores
  - Test dose?
  - Black box?

Investigational Iron Preparations: VIT-45

- Characteristics
  - Ferric carboxymaltose injection (American Regent Laboratories, Inc)
  - In development worldwide for variety of anemia-related indications, including CKD, whether HD or not

Investigational Iron Therapies: VIT-45

- Clinical program
  - NDA submitted 2007, currently under review
  - Market launch expected 2008 or 2009
  - 2 phase 3 trials under way (vs oral iron in predialysis CKD and long-term safety study in same population)

Investigational Iron Preparations: VIT-45

- Potential advantages
  - Can be administered in single and repeated high doses within short time period (in clinical trials, dosing of 200- to 1000-mg IV push over 15 minutes)
  - Not removed by high-flux or high-efficiency dialysis membranes in clinically significant amounts over 4-hour dialysis session[1]

1. Manley et al. *Int J Artif Organs*. 2006;29:1062-1066.

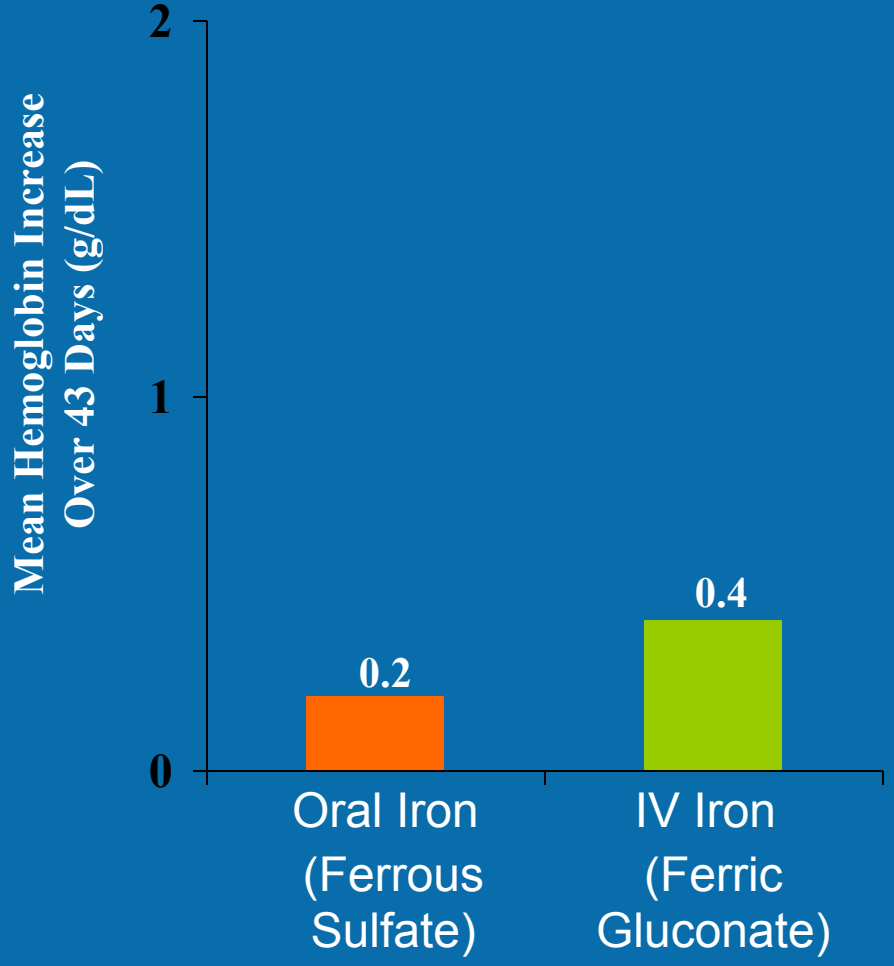
Other New Agents

Product	Characteristics
Ferric pyrophosphate Rockwell Medical Technologies, Inc	• Dialysate concentrate product containing ferric pyrophosphate (FePPi), water-soluble form of iron, for anemia in HD patients • In phase 2 clinical development • Company believes administration method may be safer and more effective in maintaining iron balance and reduce administration costs
Iron oligosaccharide Abbott Laboratories, Inc (US) and Pharmacosmos A/S (Denmark)	• IV iron oligosaccharide (FeOS) • Currently in clinical trials with Pharmacosmos • Potentially lower incidence of hypotensive events at higher doses

Data after K/DOQI…

Is IV iron really needed in non-dialysis CKD?

Oral Iron vs IV Iron in Stage 3 or 4 CKD Patients (cont)

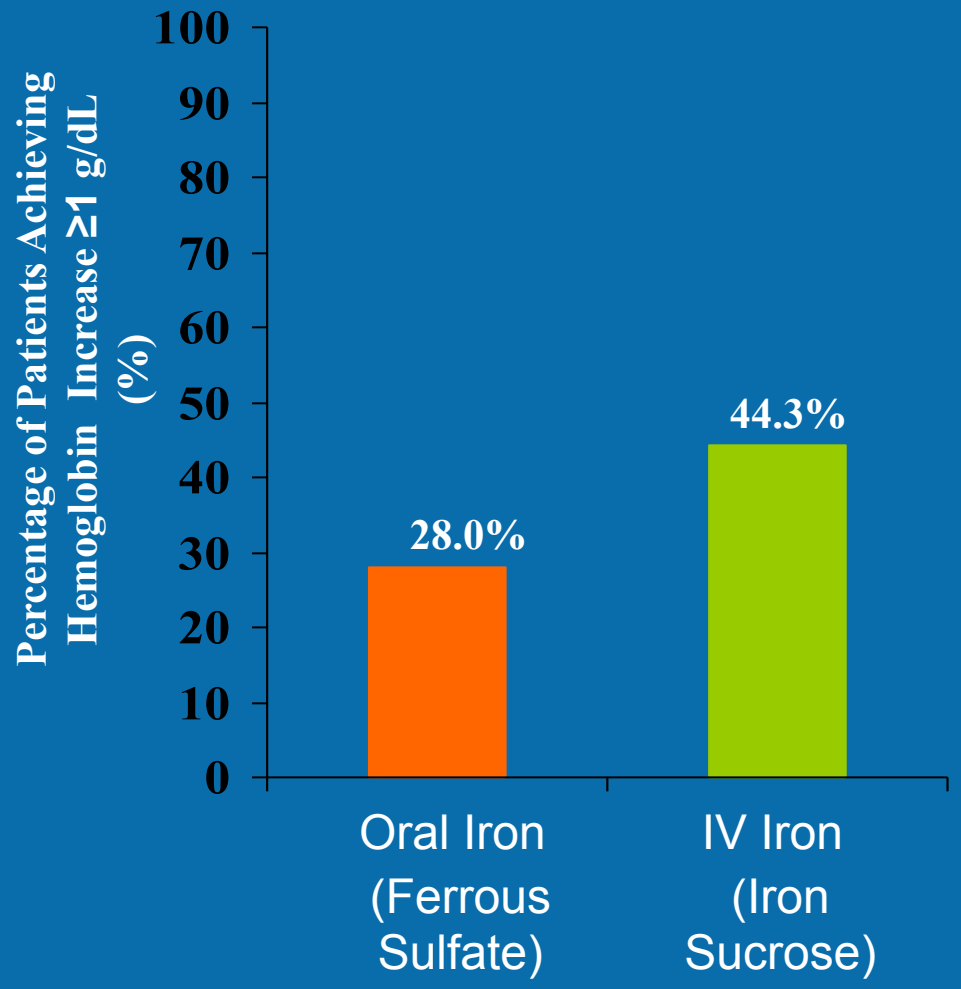


- In a study of oral iron vs iron gluconate in patients not treated with ESA (N=75), the change from baseline in Hb between the oral and IV iron groups was similar

Agarwal R, et al. *Am J Nephrol*. 2006;26:445-454.

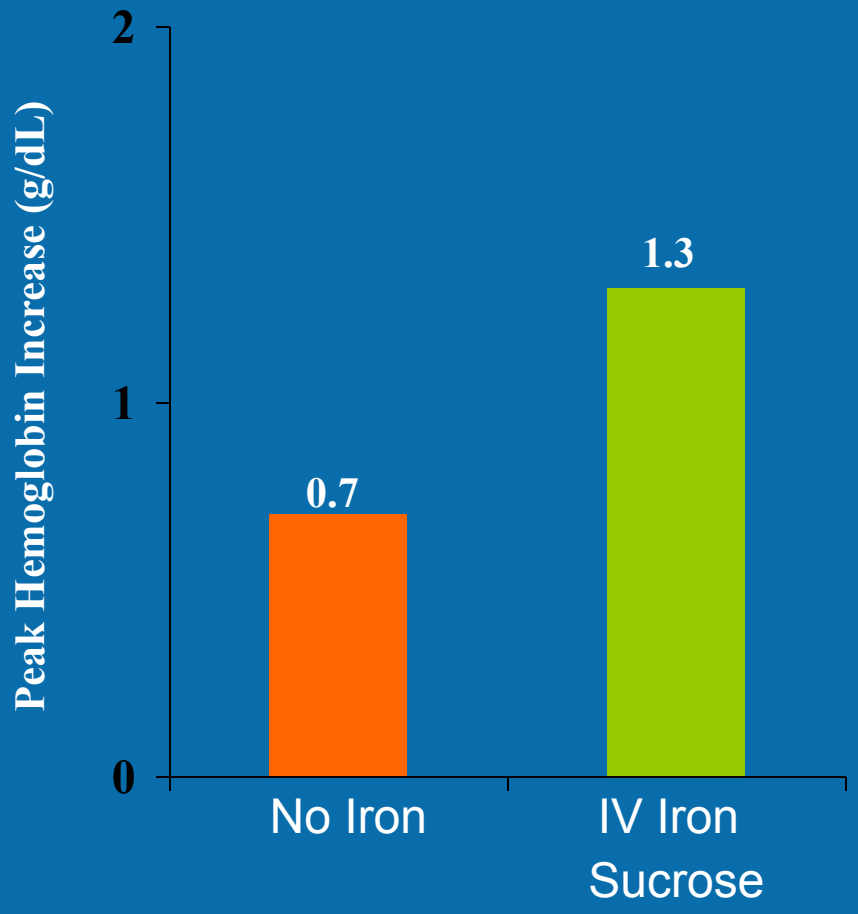
Oral Iron vs IV Iron in Stage 3 or 4 CKD Patients (cont)

- However, intravenous iron was more effective than oral iron in another report of predialysis patients
- In this study, ESA were allowed.



Van Wyck DB, et al *Kidney Int*. 2005;68:2846-2856.

IV Iron in Patients on Peritoneal Dialysis



- In 126 peritoneal dialysis patients, IV iron sucrose (as an adjunct to ESA) increased Hb effectively
- Oral iron was not tested in this study

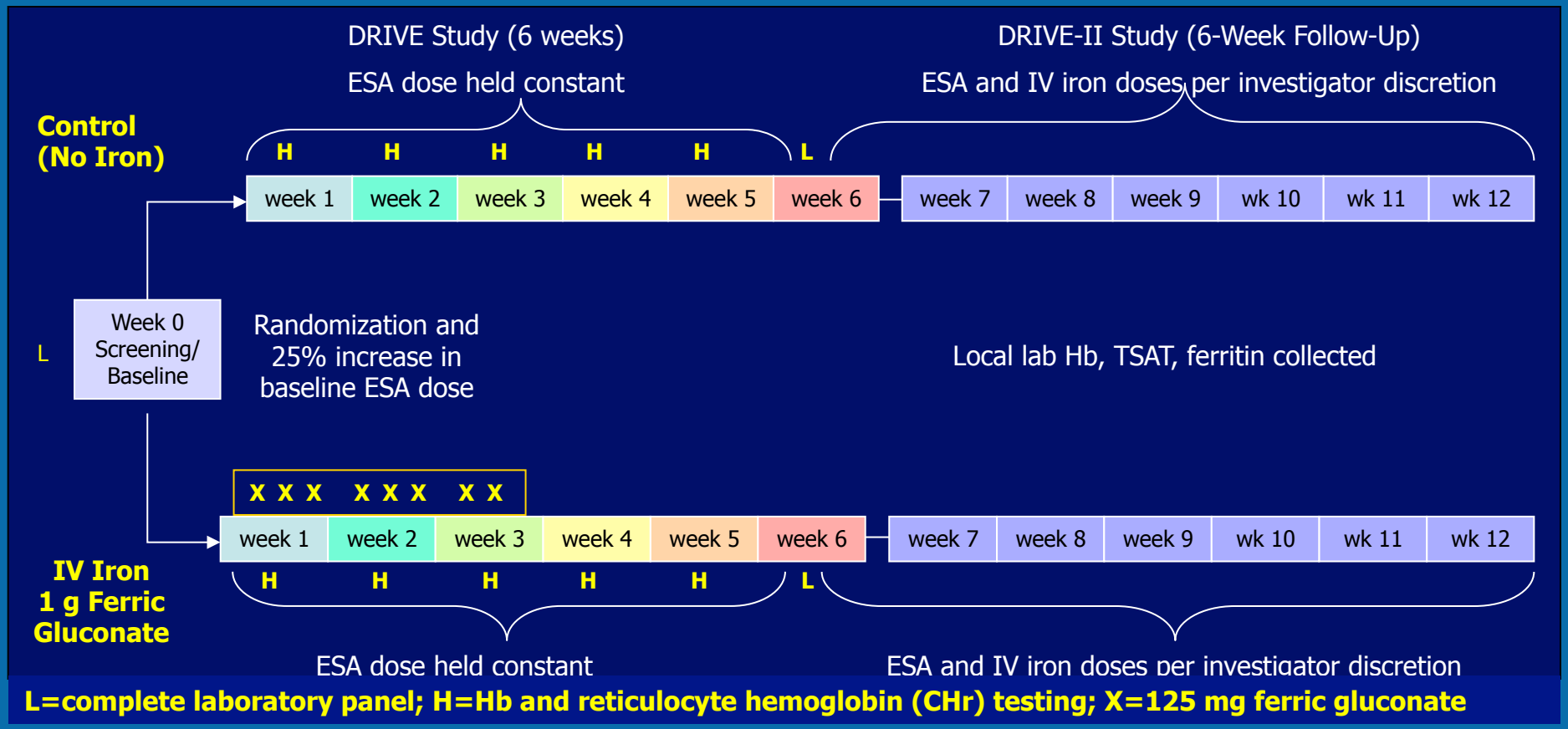
Singh H, et al. *Clin J Am Soc Nephrol*. 2006;1:475-482.

Presentation Objectives

- Review new developments in iron supplementation since last guidelines
  - Development of new iron formulations
  - Diagnostic tests for iron deficiency
  - Risks of IV iron
  - Benefits of IV iron, independent of anemia correction

DRIVE and DRIVE-II Studies:

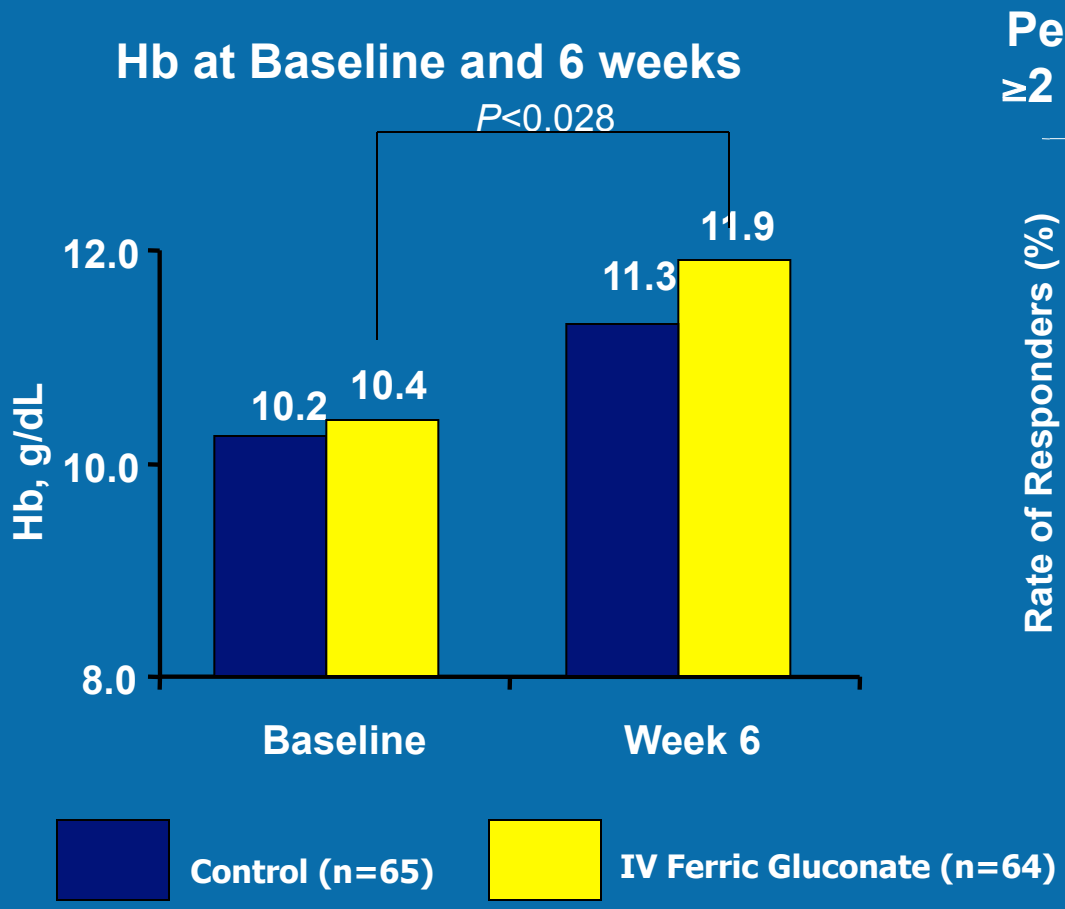
(HD Patients With High Ferritin/Low TSAT)

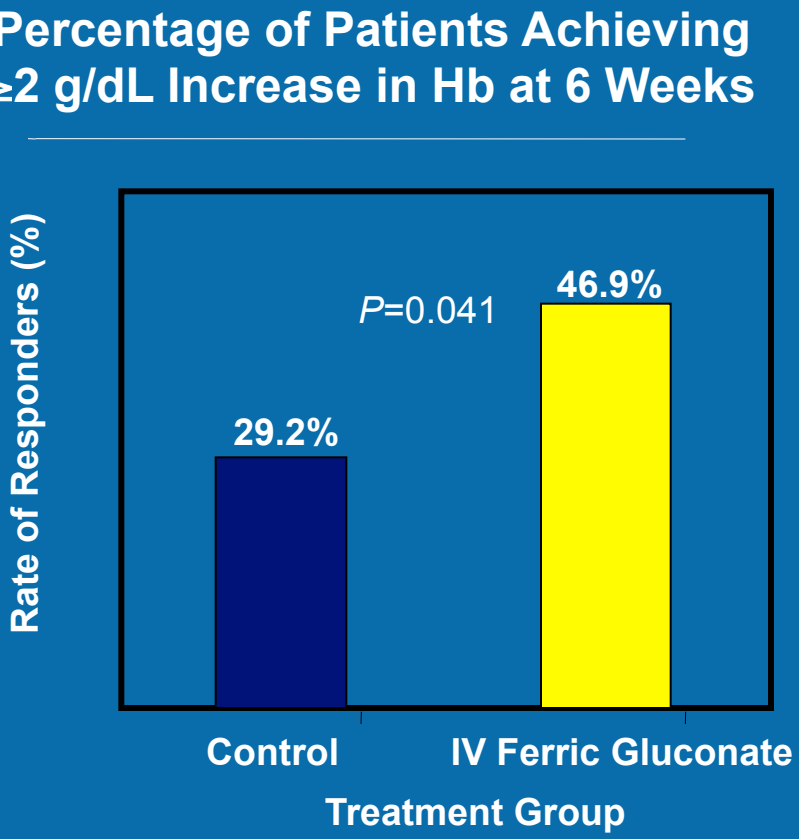


ESA=erythropoietin-stimulating agent; IV=intravenous; Hb=hemoglobin; TSAT=transferrin saturation

Coyne D, et al. *J Amer Soc Nephrol*. 2007;18:975-984.
Adapted from Kapoian T, et al. Presented at the American Society of Nephrology 2006 Annual Meeting, November 15-19, 2006. Poster.

IV Iron Increases Hb Response and Percentage of Patients Responding to an ESA Increase

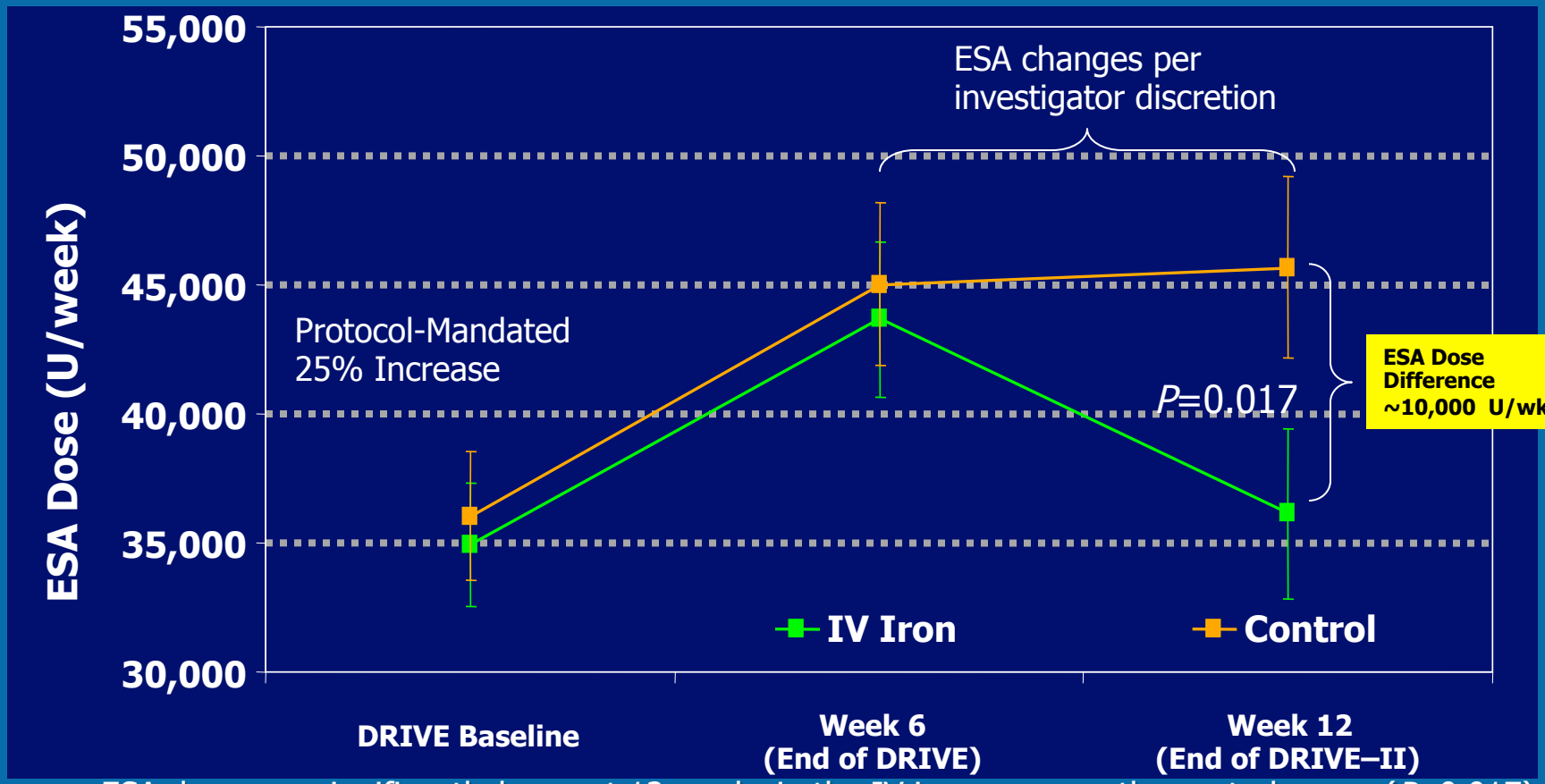




IV=intravenous; Hb=hemoglobin; ESA=erythropoietin-stimulating agent

Adapted from Coyne D, et al. *J Amer Soc Nephrol*. 2007;18:975-984.

ESA Use Decreased Significantly Following Administration of IV Iron



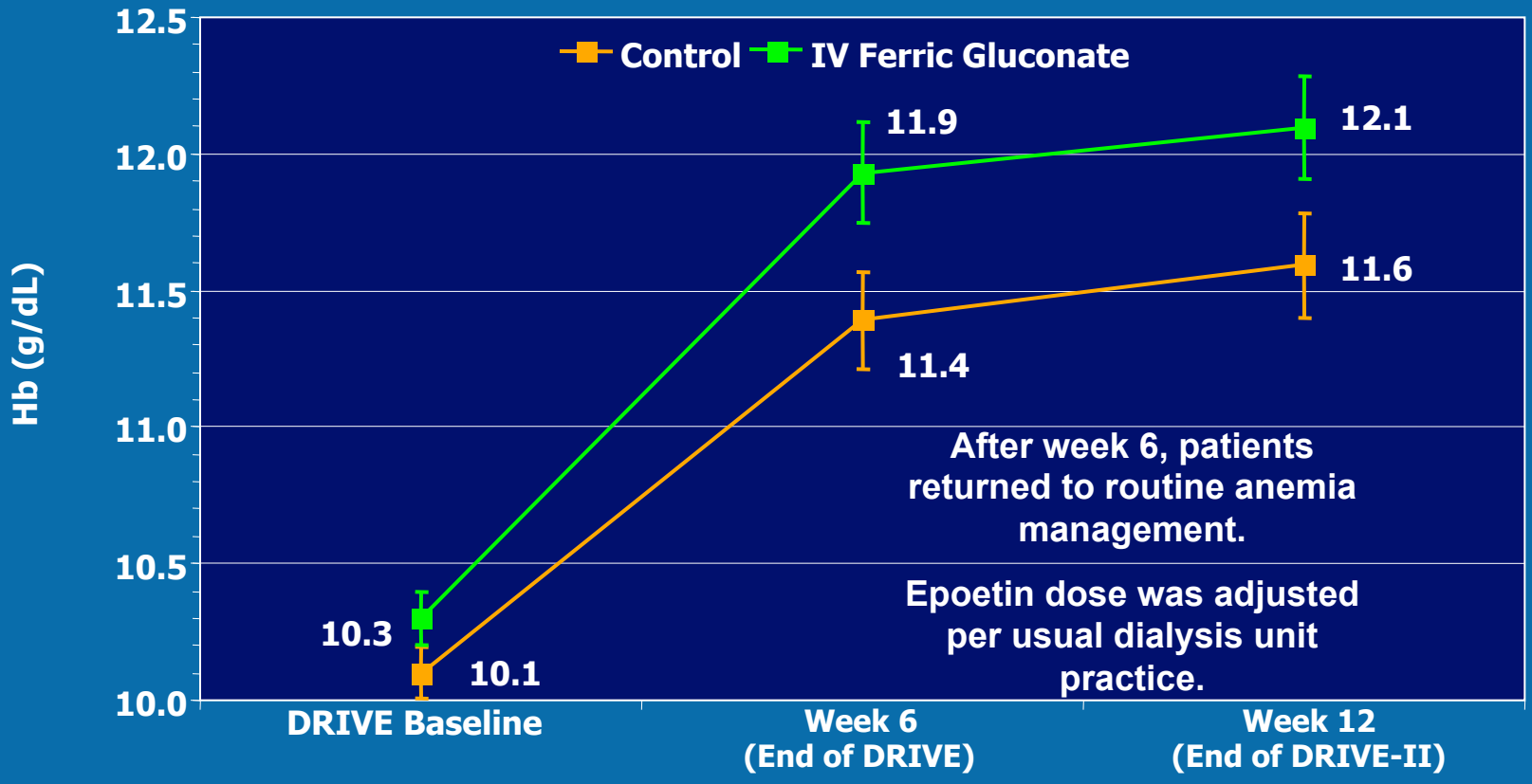
- ESA dose was significantly lower at 12 weeks in the IV iron group vs the control group (*P*=0.017)
- Control group: ESA doses remained significantly elevated (*P*=0.0004)
- IV Iron group: ESA doses returned to baseline level (*P*=0.6039)

ESA=erythropoietin-stimulating agent; IV=intravenous

Adapted from Coyne D, et al. *J Amer Soc Nephrol*. 2007;18:975-984.

Adapted from Kapoian T, et al. Presented at the American Society of Nephrology 2006 Annual Meeting, November 15-19, 2006. Poster.

Increase in Hb With IV Iron Persists at 12 Weeks, Despite Lower ESA Dose



Hb=hemoglobin; IV=intravenous; ESA=erythropoietin-stimulating agent

Adapted from Coyne D, et al. *J Amer Soc Nephrol*. 2007;18:975-984.
Adapted from Kapoian T, et al. Presented at the American Society of Nephrology 2006 Annual Meeting, November 15-19, 2006. Poster.

DRIVE Study Conclusions

- In anemic dialysis patients with high ferritin and TSAT ≤25%, IV iron and an increase in ESA dose
  - Greater Hgb response & in observational follow up to
  - Lowered ESA requirements

TSAT=transferrin saturation; IV=intravenous; ESA=erythropoietin-stimulating agent; Hb=hemoglobin

Adapted from Coyne D, et al. *J Amer Soc Nephrol*. 2007;18:975-984.
Adapted from Kapoian T, et al. Presented at the American Society of Nephrology 2006 Annual Meeting, November 15-19, 2006. Poster.

Presentation Objectives

- Review new developments in iron supplementation since last guidelines
  - Development of new iron formulations
  - Diagnostic tests for iron deficiency
  - Risks of IV iron
  - Benefits of IV iron, independent of anemia correction

Intravenous iron causes oxidative stress in hemodialysis patients

Study	n	Design	Intervention	Results
Lim PS 1999	50	Interventional, observational	IV infusion of 100 mg ferric saccharate	Patients with serum ferritin >601 ng/mL had greater increase in plasma lipid peroxides and greatest fall in superoxide dismutase with exposure to IV iron.
Roob JM 2000	22	Cross-over randomized trial	All received 100 mg IV iron sucrose either with or without 1000 IU of Vitamin E.	Lipid peroxidation was seen with IV iron. Vit E reduced but did not abolish the generation of oxidative stress.
Salahudeen AK 2001	22	Interventional, observational	Infusion of 700 mg IV iron dextran on a non-dialysis day	Free F2-isoprostanes did not increase but esterified F2-isoprostanes were increased.
Drueke, T 2002	60	Cross sectional study	None	Iron therapy was associated with advance oxidation protein products, and carotid intima-media thickness
Anraku, M 2004	22	Randomized controlled trial, parallel group	IV saccharated ferric oxide 40 mg every dialysis for 4 weeks.	Increased plasma protein carbonyl content by oxidation of albumin with IV iron.

Intravenous iron causes renal injury in CKD patients

Author	n	Trial Design	Intervention	Result
Agarwal R 2004	20	RCT, parallel group	RCT, infusion of 100 mg iron sucrose on two occasions one week apart with or without n-acetyl cysteine.	Increase in malondialdehyde within 15-30 minutes and proteinuria with IV iron sucrose. Iron infusion led to increase in monocyte chemoattractant protein-1 accumulation and oxidation of urinary albumin.
Leehey, DJ 2005	8	Four-way, cross-over RCT	IV iron infusion either 125 mg or 250 mg of ferric gluconate with or without n-acetyl cysteine every week.	Ferric gluconate caused oxidative stress but no renal injury.
Agarwal R 2007	12	Cross-over RCT	IV iron sucrose 100 mg or same dose of IV ferric gluconate administered 1 week apart in random order	IV iron sucrose caused greater proteinuria and albuminuria compared to ferric gluconate. Enzymuria occurred with either drug in similar amount.

Controversies…

- Long term significance
  - Accelerated renal injury?
  - Accelerated cardiovascular disease?

Presentation Objectives

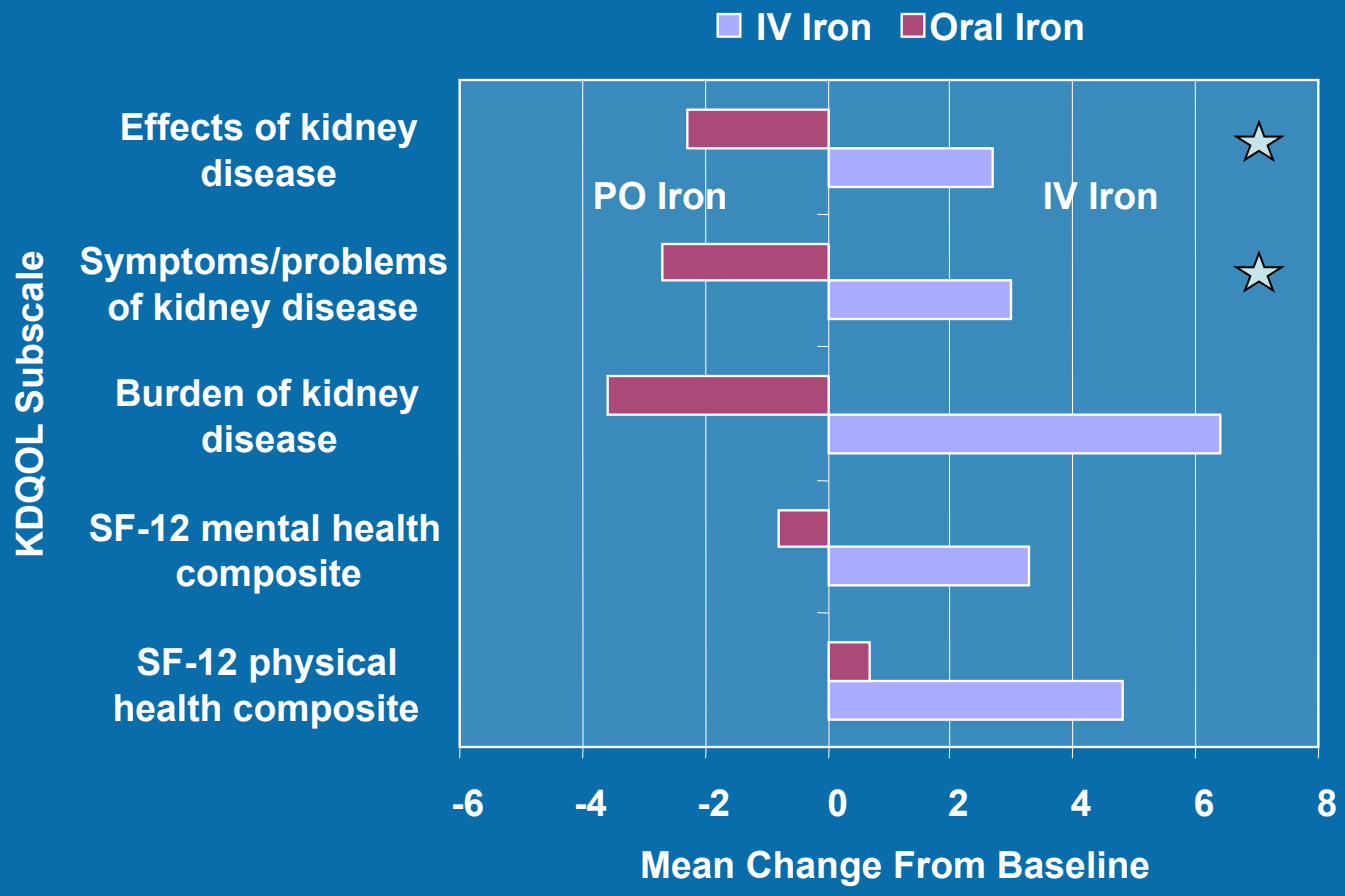
- Review new developments in iron supplementation since last guidelines
  - Development of new iron formulations
  - Diagnostic tests for iron deficiency
  - Risks of IV iron
  - Benefits of IV iron, independent of anemia correction

Hemoglobin Independent Benefits of Iron

- Iron deficiency impairs
  - Physical Performance
  - Thermoregulation
  - Cognition
  - Immune function
- Iron deficiency also is associated with
  - Restless legs syndrome (RLS)
  - Reduced Aluminum absorption (animal data)

Agarwal R, Am J Nephrol 27: 565-571, 2007

QOL Change From Baseline to Day 43 or Early Termination



Agarwal R, Am J Nephrol 26: 445-454, 2006

Hemoglobin Independent Benefits of Iron in non-dialysis CKD

Subscale	IV iron n=36	Within gp change	PO iron n=39	Within gp change	P value: IV vs PO
Physical Composite	35.9	4.8	36.4	0.7	0.08
Mental Composite	49.8	3.3	49.8	-0.8	0.11
Kidney Dis Burden	72.7	6.4	71.5	-3.6	0.056
Symptoms/Problem List	78.1	3.0	75.6	-2.7	0.025
Effects of Kidney Disease	86.2	2.7	80.5	-2.3	0.048

Agarwal R, Am J Nephrol 26: 445-454, 2006