King's College Hospital NHS
NHS Foundation Trust

KING'S College LONDON

Safety of IV iron: facts and folklore

Iain C. Macdougall

Consultant Nephrologist & Professor of Clinical Nephrology

Renal Unit,
King's College Hospital,
London, UK

History of IV iron

Iron in doses of 16 to 32 mgm. a day, given parenterally, is very close to the maximum amoun… severe … injectio… neutrali… the pat… someti… vomiting… there w… flushing… Vomitin… rapid a… were es… the rap… disagreeable symptoms had nearly disappeared. It was thought that such large doses of iron were distinctly dangerous. The injection of 8 mgm. of iron a day was attended by more moderate symptoms of the above nature.

…mes …ir …ards, …ently …tively, …xiety. …se was …ions …yet

QUANTITATIVE ASPECTS OF IRON DEFICIENCY IN HYPOCHROMIC ANEMIA

(THE PARENTERAL ADMINISTRATION OF IRON) [1]

BY CLARK W. HEATH, MAURICE B. STRAUSS, AND WILLIAM B. CASTLE

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital; the Department of Medicine and the Department of Tropical Medicine, Harvard Medical School, Boston)

(Received for publication August 1, 1932)

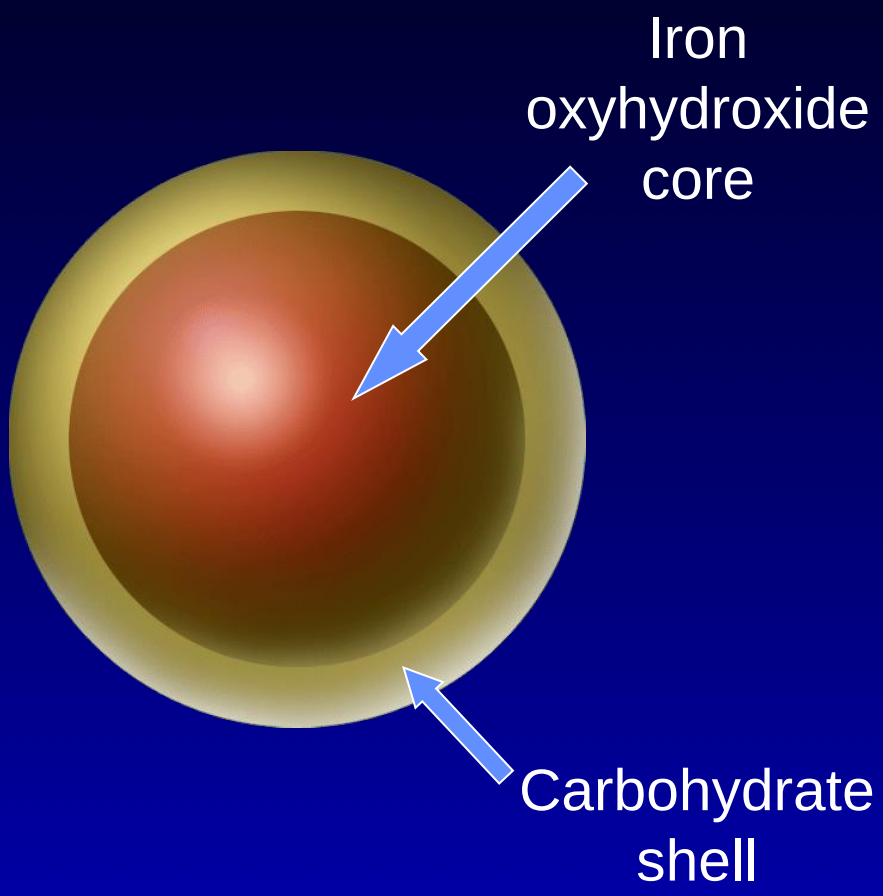
J Clin Invest 11:1293-1312, 1932.

Source: Heath CW et al. *J Clin Invest* 11:1293-1312, 1932

History of IV iron

- 1946 – *Goetsch et al*
  IV infusions of ferric hydroxide
  toxic reactions "severe"
  "should only be used for therapeutic purposes under most unusual circumstances"
- *1947 – Nissim et al*
  IV iron saccharide safer
- 1954 – *Baird & Padmore*
  Iron dextran introduced as IM therapy
  → IV (Imferon; *Fisons Pharmaceuticals*)
- 1990s – rapid increase in use of IV iron coinciding with introduction of EPO
- 1992 – Imferon withdrawn from market

IV iron preparations



Iron dextran

Iron sucrose

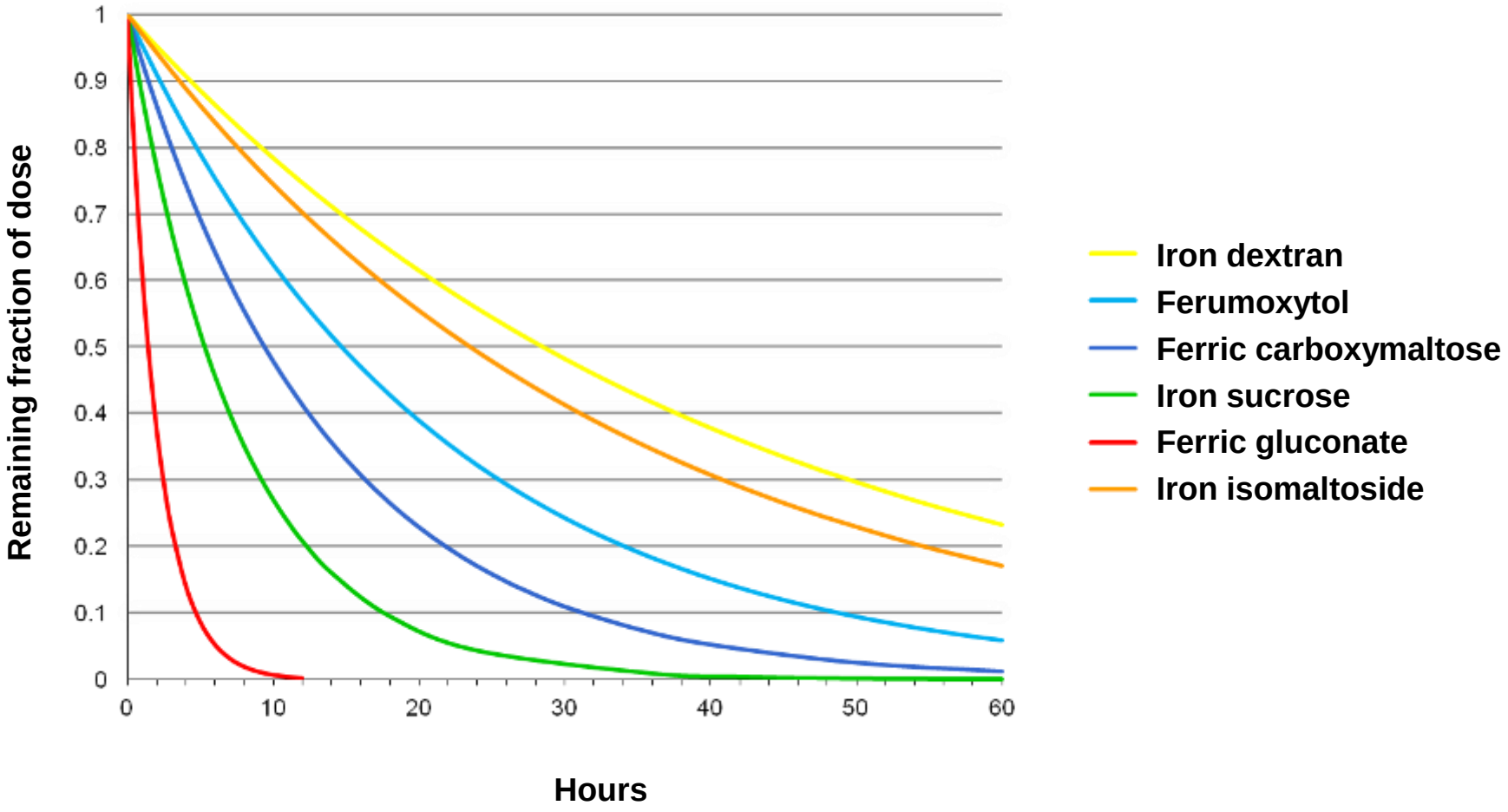
Ferric gluconate

Ferric carboxymaltose

Iron isomaltoside-1000

Ferumoxytol

Elimination kinetics of different IV irons



Adapted from Geisser P *et al. Pharmaceutics* 2011;3:12-33

IV iron preparations available in Europe

- **Iron sucrose** *(Venofer®)*
- **Iron dextran** *(Cosmofer®)*
- **Ferric carboxymaltose** *(Ferinject®)*
- **Iron iso-maltoside 1000** *(Monofer®)*

Safety concerns with IV iron

- Iron overload
- Increased risk of infection
- Increased oxidative stress
- Increased mortality risk
- Hypersensitivity reactions

KDIGO 2014 Controversies Conference

San Francisco, 27–30 March, 2014

IRON MANAGEMENT IN CKD

Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

Iain C. Macdougall[1], Andreas J. Bircher[2], Kai-Uwe Eckardt[3], Gregorio T. Obrador[4], Carol A. Pollock[5,6], Peter Stenvinkel[7], Dorine W. Swinkels[8], Christoph Wanner[9], Günter Weiss[10], and Glenn M. Chertow[11]; for Conference Participants[12]

[1]Department of Renal Medicine, King's College Hospital, London, UK; [2]Allergy Unit, Dermatology Clinic, University Hospital Basel, Basel, Switzerland; [3]Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [4]Universidad Panamericana School of Medicine, Mexico City, Mexico; [5]University of Sydney, Sydney, Australia; [6]Royal North Shore Hospital, Sydney, Australia; [7]Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska University Hospital, Stockholm, Sweden; [8]Department of Laboratory Medicine, Translational Metabolic Laboratory, Radboud University Medical Center, Nijmegen, the Netherlands; [9]Renal Division, University Hospital of Würzburg, Würzburg, Germany; [10]Department of Internal Medicine VI, Infectious Disease, Immunology, Rheumatology, Pneumology, Medical University of Innsbruck, Innsbruck, Austria; and [11]Division of Nephrology, Stanford University School of Medicine, Palo Alto, California, USA

Macdougall et al. *Kidney Int* 2016; 89 : 28-39.

Iron Management in CKD Conference

Steering Committee

Glenn Chertow, USA – Conference Co-Chair
Iain Macdougall, UK – Conference Co-Chair

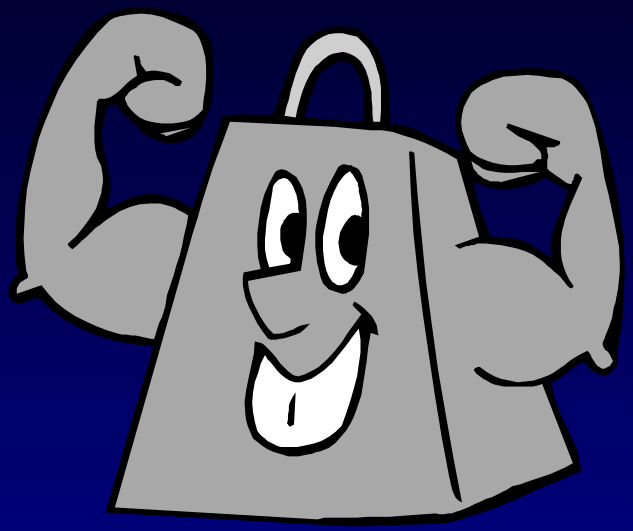
Iron Overload Co-Chairs
Kai-Uwe Eckardt, *Germany* & Dorine Swinkels, *Netherlands*

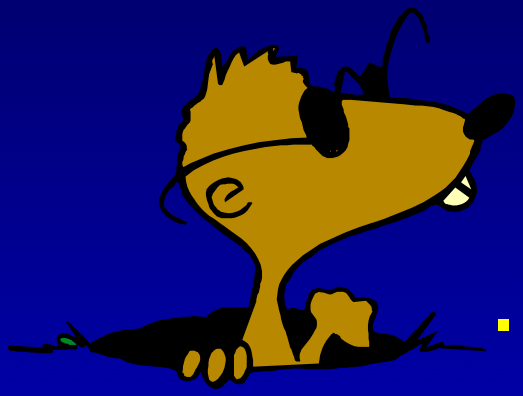
Inflammation & Oxidative Stress Co-Chairs
Peter Stenvinkel, *Sweden* & Christoph Wanner, *Germany*

Iron & Infection Co-Chairs
Gregorio Obrador, *Mexico* & Günter Weiss, *Austria*

Hypersensitivity Reactions to IV Iron Co-Chairs
Andreas Bircher, *Switzerland* & Carol Pollock, *Australia*

How much iron is too much?





...and where does it go?

Thalassaemia

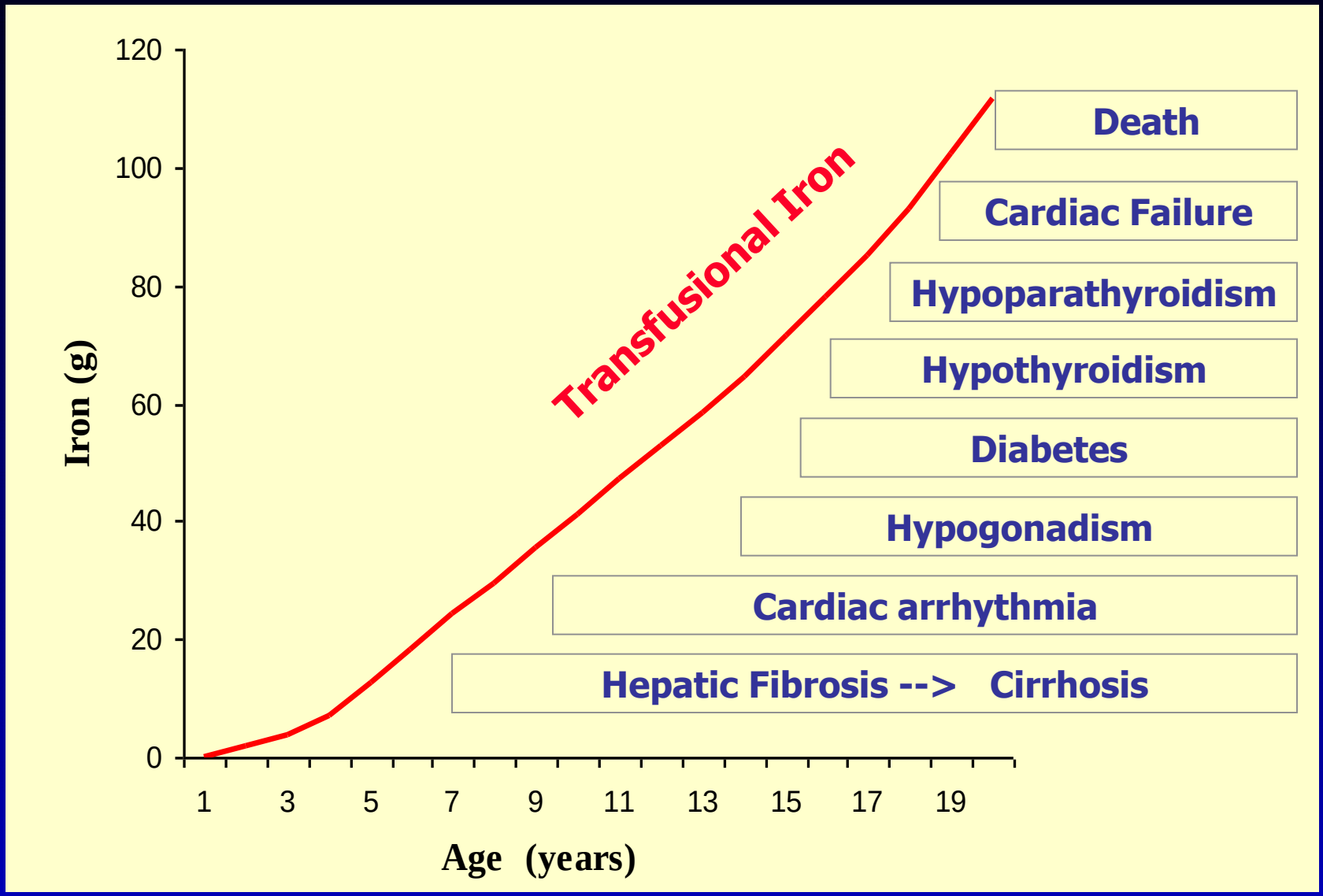
Transfusion requirements:

2-4 units / month
24-48 units / year
~ 100 units / 2-4 years

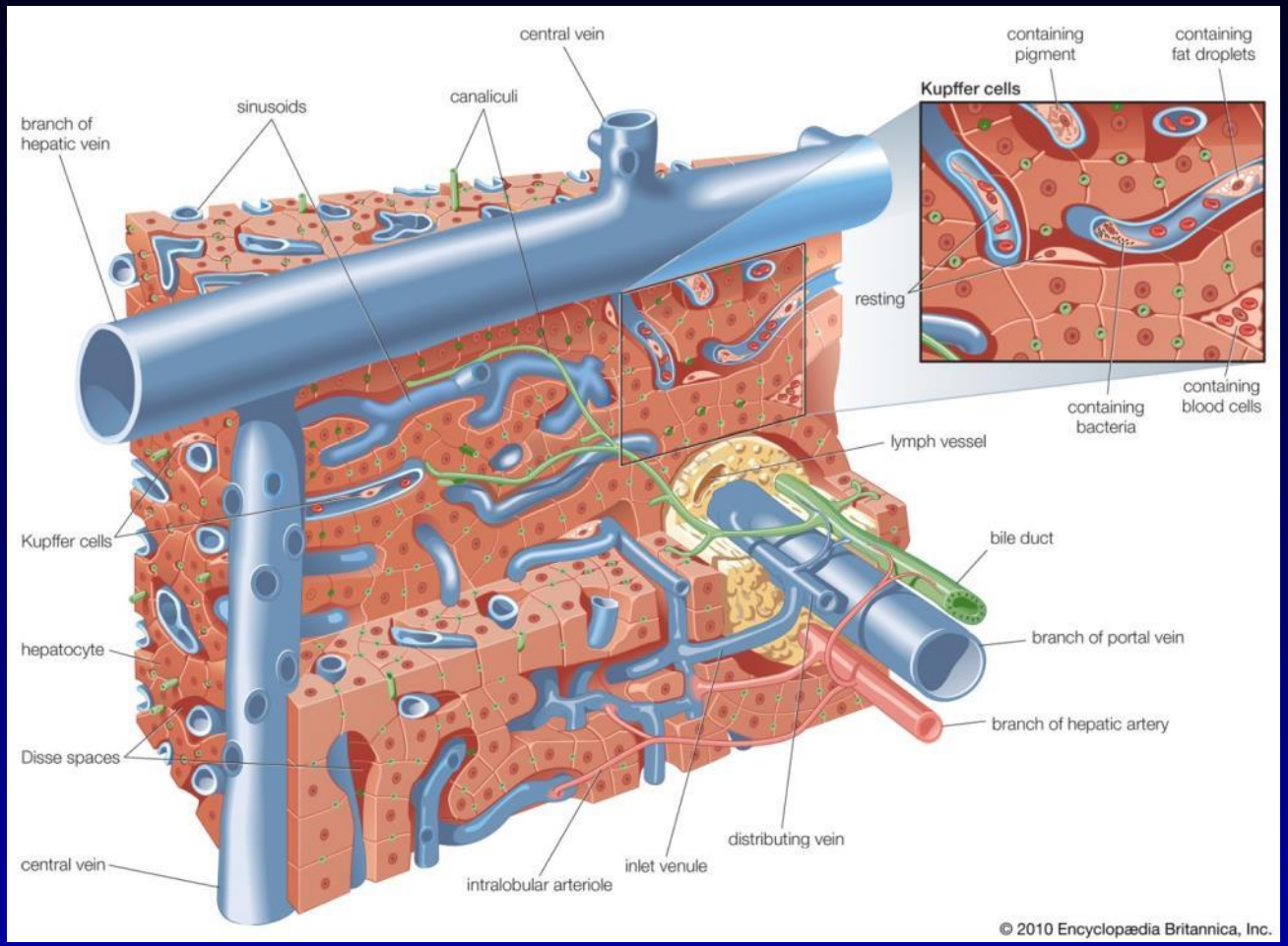
100 units: ≥ 20 g iron

Normal body iron: 3-4 g

Transfusional iron overload in thalassaemia



Iron deposition in the liver

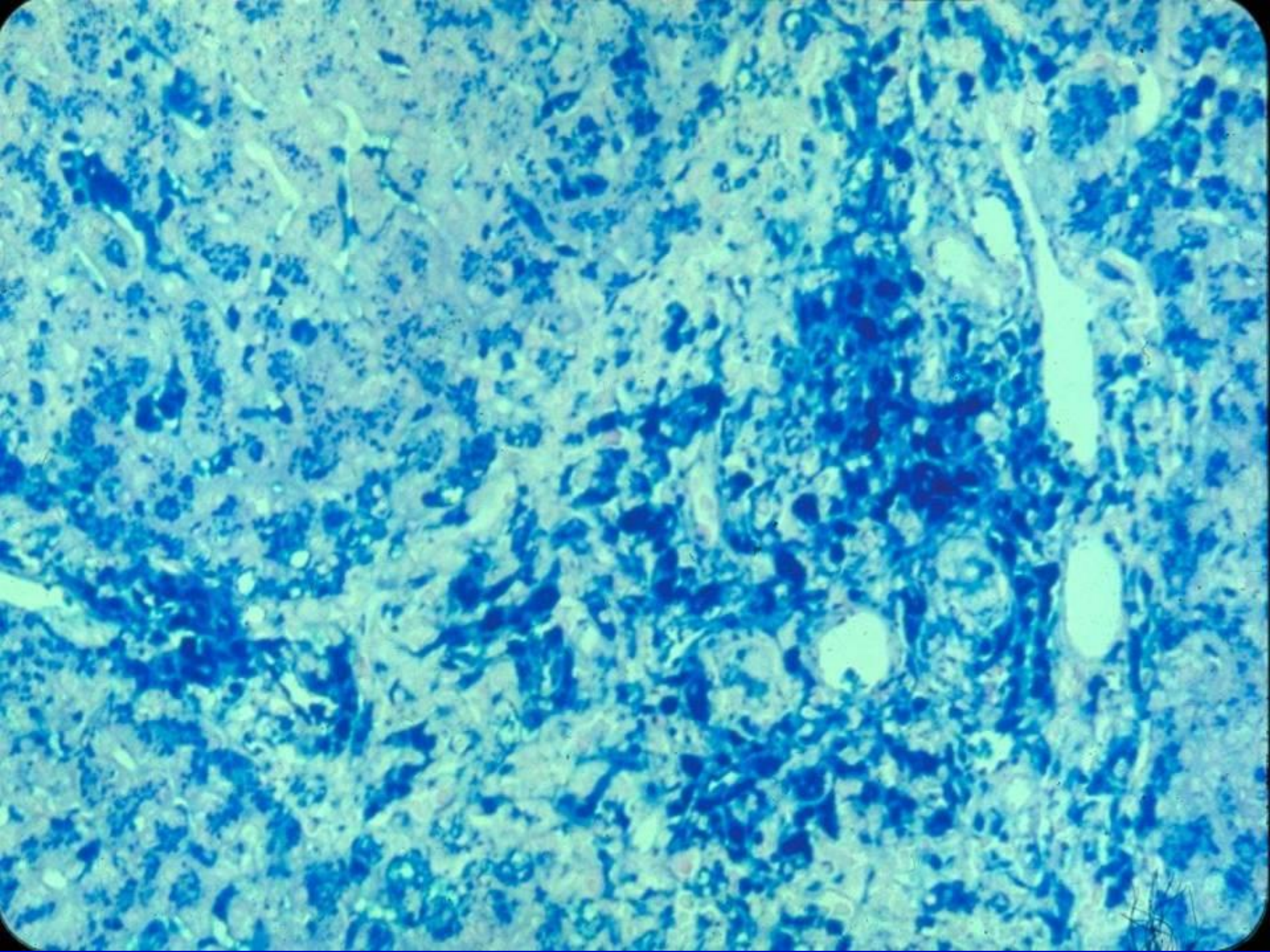


<u>Intravenous iron</u> is deposited and stored in Kupffer cells of the reticuloendothelial system (RES) which is the iron storage system of the liver

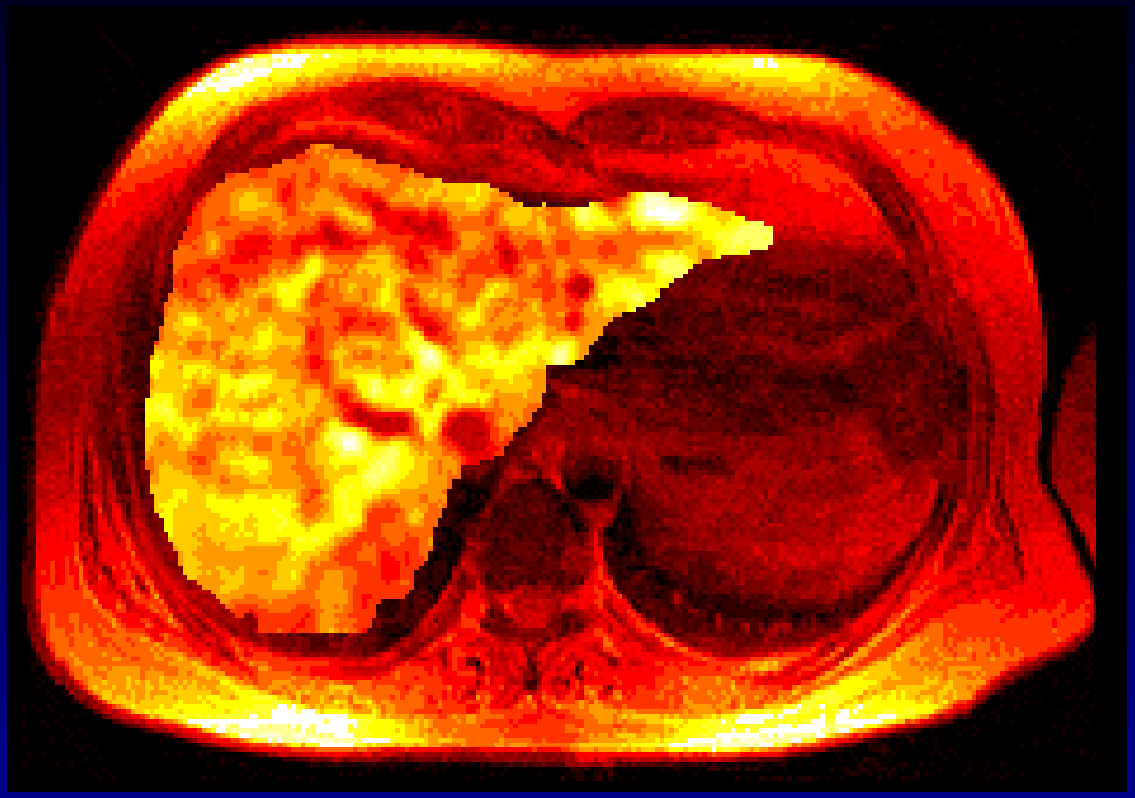
Iron can also be deposited in hepatocytes of the liver parenchyma

Liver: structure of human liver. Art. Encyclopædia Britannica Online. Web. 07 Dec. 2015. http://www.britannica.com/science/liver/images-videos/Microscopic-structure-of-the-liver-Liver-cells-or-hepatocytes-have/60419>


S. 9 / 62



Monitoring iron overload by MRI



R2 image of an iron-overloaded human liver superimposed on a T-2 weighted image.
Bright areas represent high iron concentration; dark areas represent low iron concentration.

Clark PR *et al*. *Magn Reson Med* 2003;49:572–5.

Serum ferritin and iron overload

Table 1. Recommended Interpretation of Serum Ferritin Levels in CKD Patients

Serum Ferritin Range	<200 ng/mL*	≥200 but <500 ng/mL	≥500 but <1,200 ng/mL	≥1,200 ng/mL
Common conditions in CKD patients	Absolute iron deficiency (most common); ferritin deficiency syndrome*	Likely associated with both absolute and functional iron deficiency	Most commonly associated with inflammation, infection, liver disease, or malignancy	Iron overload may have overwhelmed the effect of inflammation on serum ferritin
Association with iron stores	↓ferritin←→↓iron	↑ferritin←?→↓↑iron	↑↑ferritin←?→↑↓iron	↑↑↑ferritin←→↑iron
What serum ferritin means	Serum ferritin = iron	Serum ferritin = inflammation + iron + others	Serum ferritin = inflammation + iron + others	Serum ferritin = iron
Recommended course of action	De novo IV iron administration or increasing the IV iron dose is usually indicated irrespective of TSAT	Maintenance oral or IV iron supplementation (eg, 100 to 500 mg/mo) is indicated to target TSAT between 25% and 50%	Check liver enzymes, assess serum CRP and MIS, rule out latent infection or malignancies. If ESA hyporesponsiveness persists, iron administration may be beneficial especially if TSAT<25%	Iron supplementation should generally be avoided, especially if TSAT >50%

NOTE. In NDD-CKD patients or those undergoing PD, the cutoff level of <100 ng/mL has been suggested by KDOQI guidelines.[57]
Abbreviations: CRP, C-reactive protein; MIS, malnutrition inflammation score.
*The ferritin deficiency syndrome can be present if serum ferritin level is <50 ng/mL (see text).

Kalantar-Zadeh K *et al. Adv Chron Kid Dis* 2009;16:143–51.

Iron Management in CKD Conference

Steering Committee

Glenn Chertow, USA – Conference Co-Chair
Iain Macdougall, UK – Conference Co-Chair

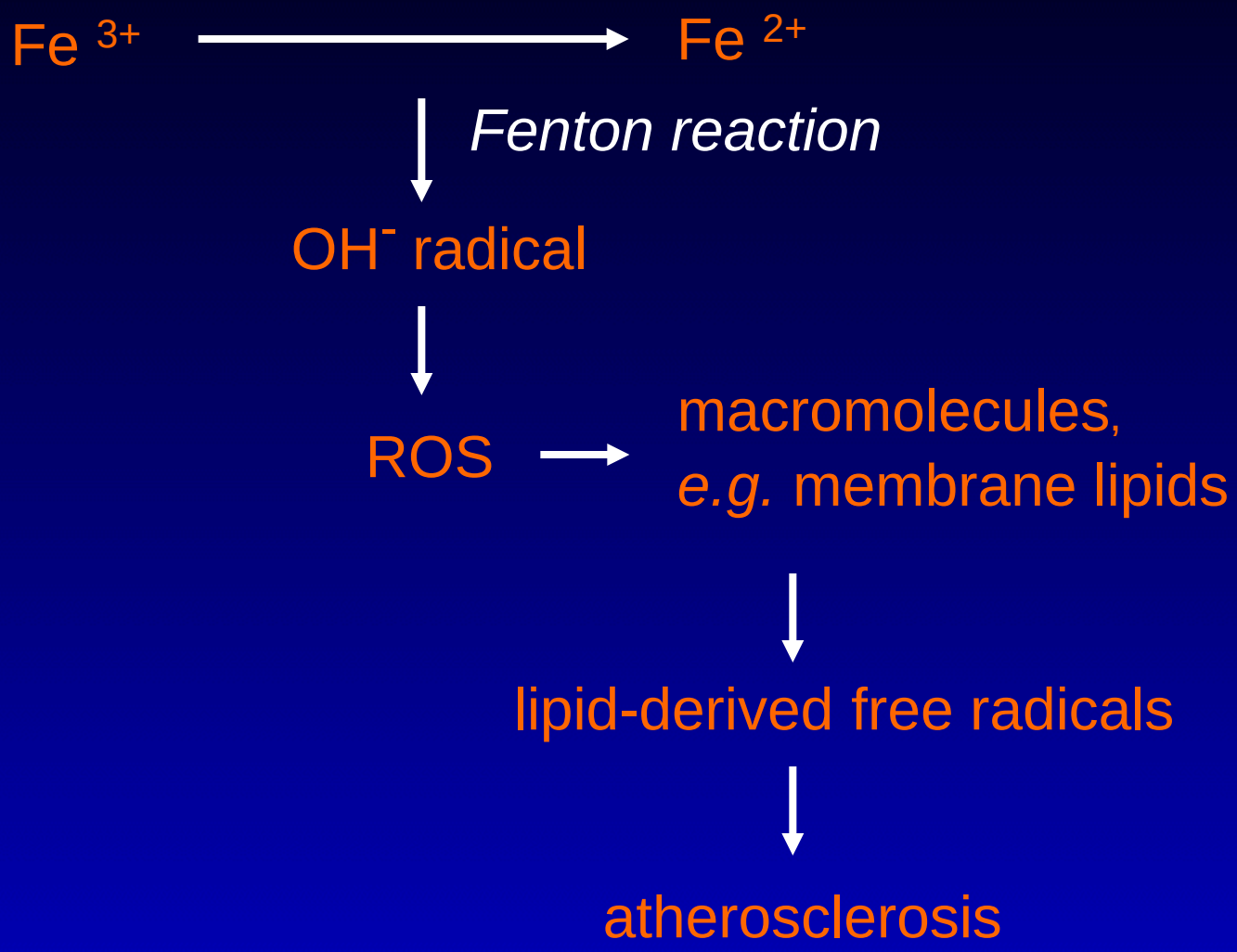
Iron Overload Co-Chairs
Kai-Uwe Eckardt, *Germany* & Dorine Swinkels, *Netherlands*

Inflammation & Oxidative Stress Co-Chairs
Peter Stenvinkel, *Sweden* & Christoph Wanner, *Germany*

Iron & Infection Co-Chairs
Gregorio Obrador, *Mexico* & Günter Weiss, *Austria*

Hypersensitivity Reactions to IV Iron Co-Chairs
Andreas Bircher, *Switzerland* & Carol Pollock, *Australia*

Iron and oxidative stress



Increased oxidative stress

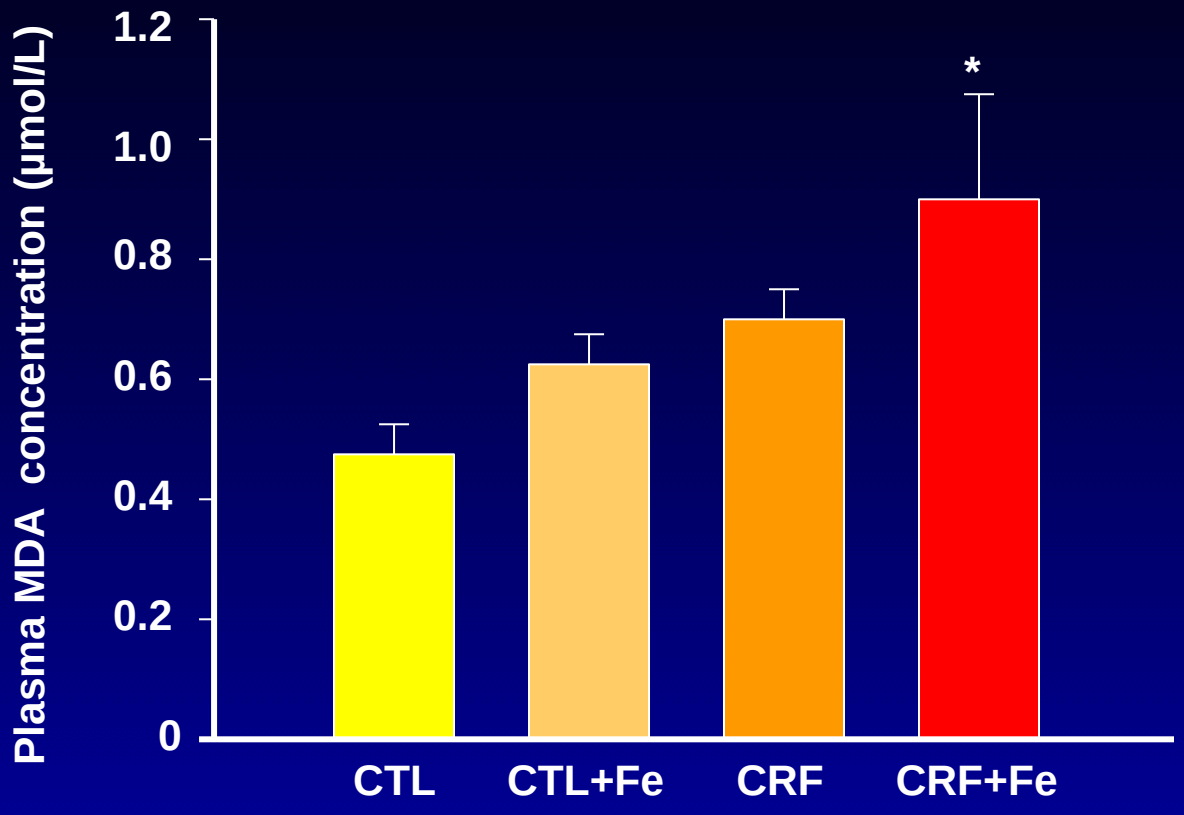
- Because of its ability to generate free radical formation *in vitro*, iron has been implicated as a cause of oxidative stress

- Association between iron and oxidative stress in *in vitro* studies[1,2]

All IV iron preparations show potential to increase oxidative stress, but evidence is transient and lacking in clinical situations[3]

1. Zager RA et al. *Kidney Int* 2004;65:2108–12.2. Zager RA *et al*. *Am J Kidney Dis* 2002;40:90–103.
3. Scheiber-Mojdehkar B *et al*. *J Am Soc Nephrol* 2004;15:1648–55.

Increased ROS-mediated oxidation



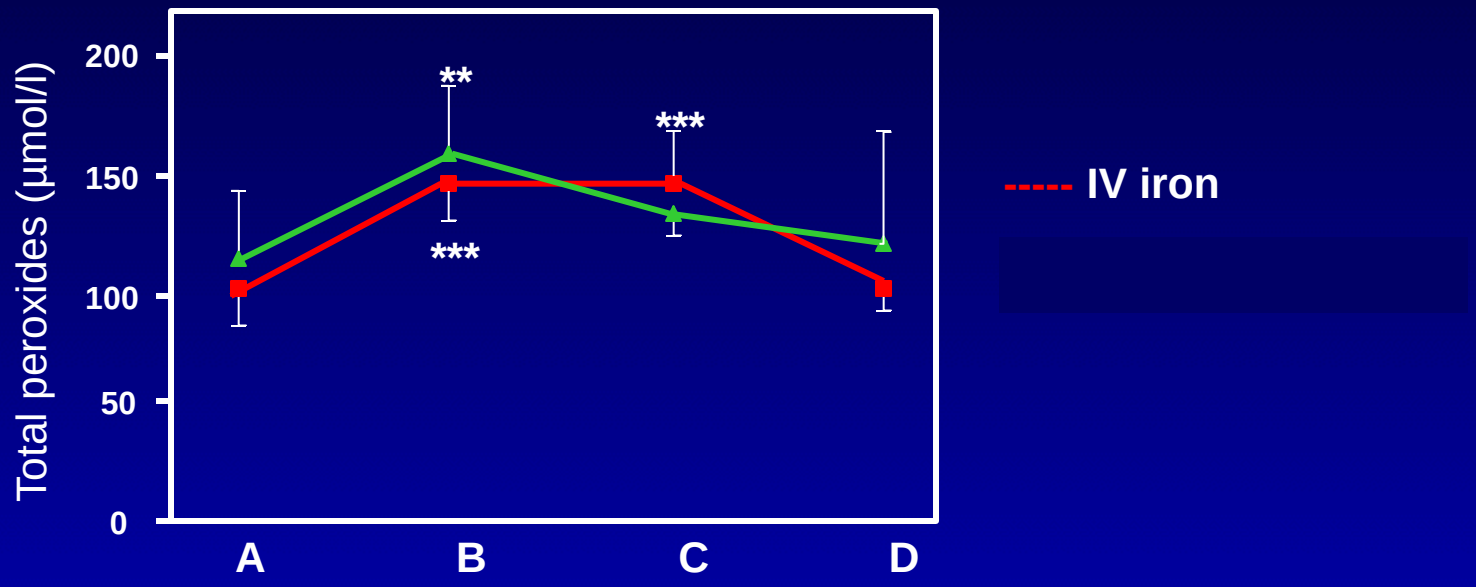
Plasma malondialdehyde (MDA) levels in control rats (CTL), Fe-injected control rats (CTL+Fe), chronic renal failure rats (CRF), and Fe-injected CRF rats (CRF+ Fe). (*N = 6 in each group)* ⁎*P < 0.05 vs. CTL group.*

Lim C *et al. Kidney Int* 2004;65:1802–9.

J Am Soc Nephrol 15: 1648–1655, 2004

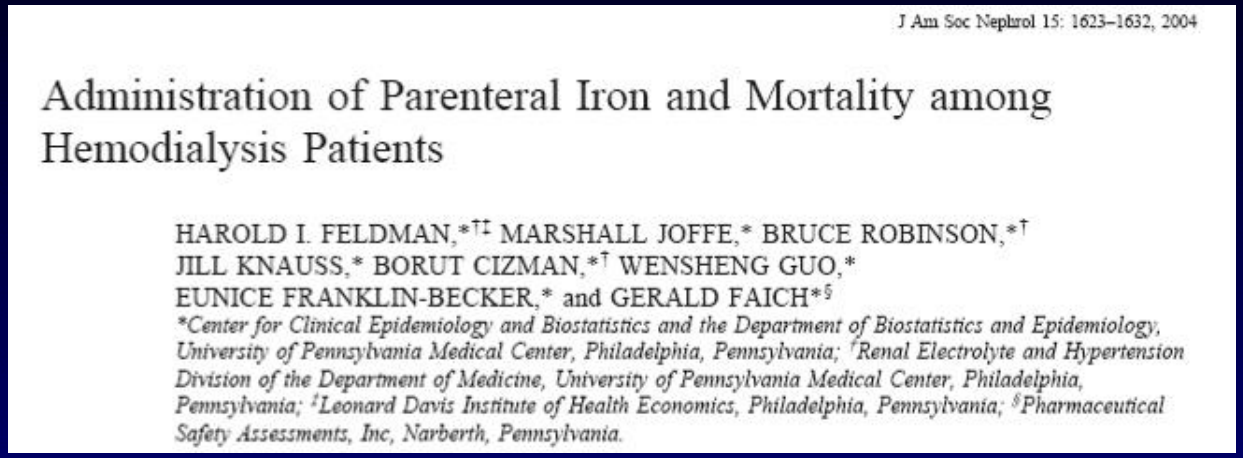
Non–Transferrin-Bound Iron in the Serum of Hemodialysis Patients Who Receive Ferric Saccharate: No Correlation to Peroxide Generation

BARBARA SCHEIBER-MOJDEHKAR,* BARBARA LUTZKY,*
ROLAND SCHAUFLER,† BRIGITTE STURM,* and HANS GOLDENBERG*
*Department of Medical Chemistry, Medical University of Vienna, Austria; and †Department of Nephrology and Dialysis, Wilhelminenspital, Vienna, Austria



Scheiber-Mojdehkar B *et al. J Am Soc Nephrol* 2004;15:1648–55.

IV iron and mortality in HD patients



J Am Soc Nephrol 15: 1623–1632, 2004

Administration of Parenteral Iron and Mortality among Hemodialysis Patients

HAROLD I. FELDMAN,*†‡ MARSHALL JOFFE,* BRUCE ROBINSON,*†
JILL KNAUSS,* BORUT CIZMAN,*† WENSHENG GUO,*
EUNICE FRANKLIN-BECKER,* and GERALD FAICH*§

*Center for Clinical Epidemiology and Biostatistics and the Department of Biostatistics and Epidemiology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; †Renal Electrolyte and Hypertension Division of the Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; ‡Leonard Davis Institute of Health Economics, Philadelphia, Pennsylvania; §Pharmaceutical Safety Assessments, Inc, Narberth, Pennsylvania.

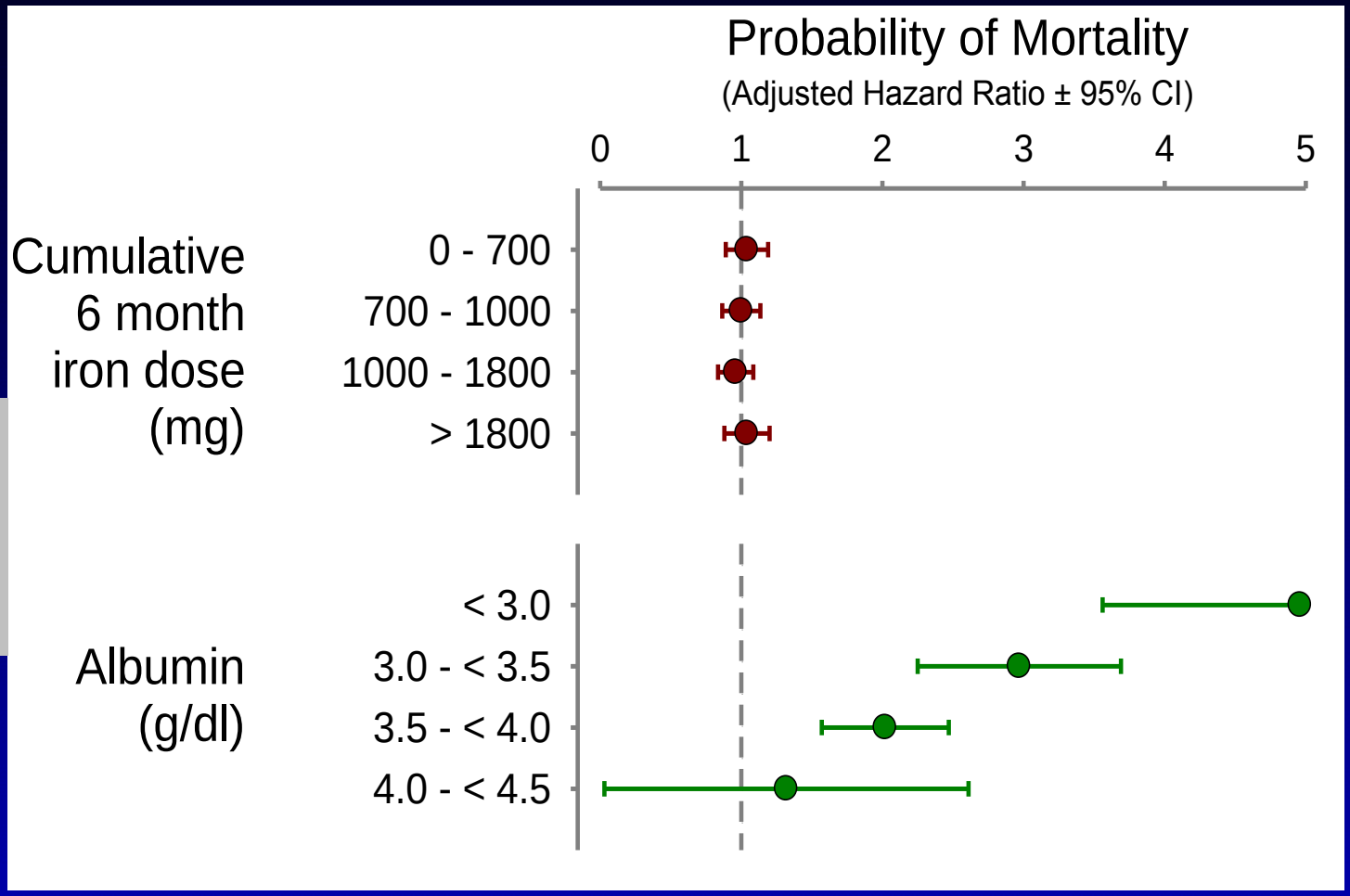
Cohort study

- 32,566 HD patients (Fresenius dialysis centres)
- All-cause mortality
- 2-year follow-up
- Multivariate models to account for timing of IV iron and also co-morbidity

Feldman et al. JASN 2004;15:1623-32.

Iron dose, unlike low albumin, is *not* linked to increased mortality in HD

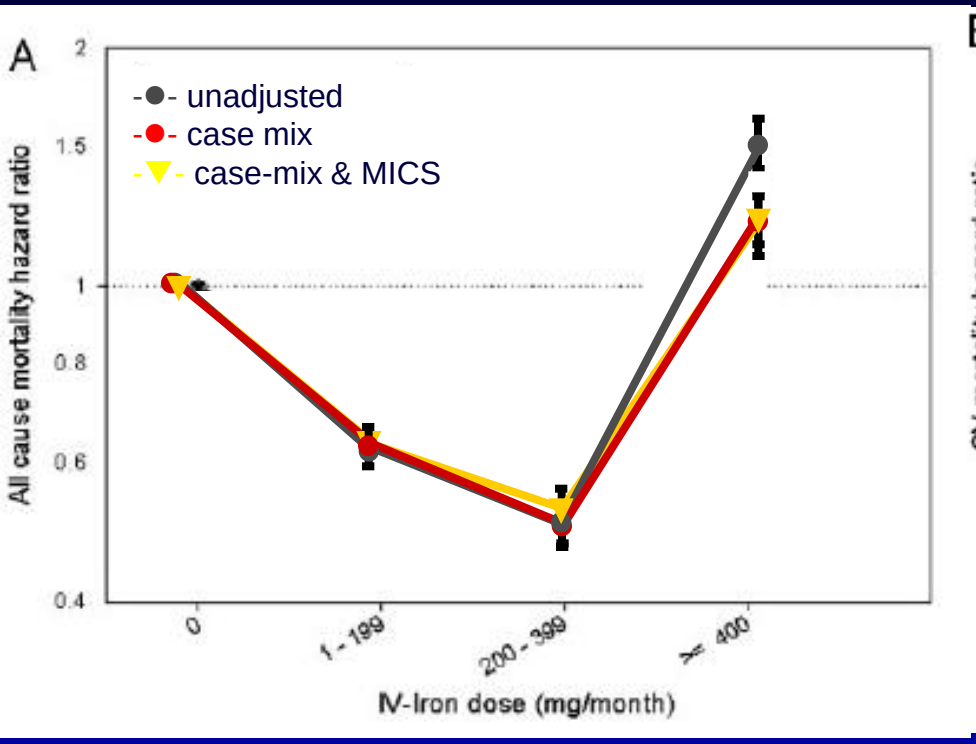
Results for both covariates are from unlagged time-dependent model.



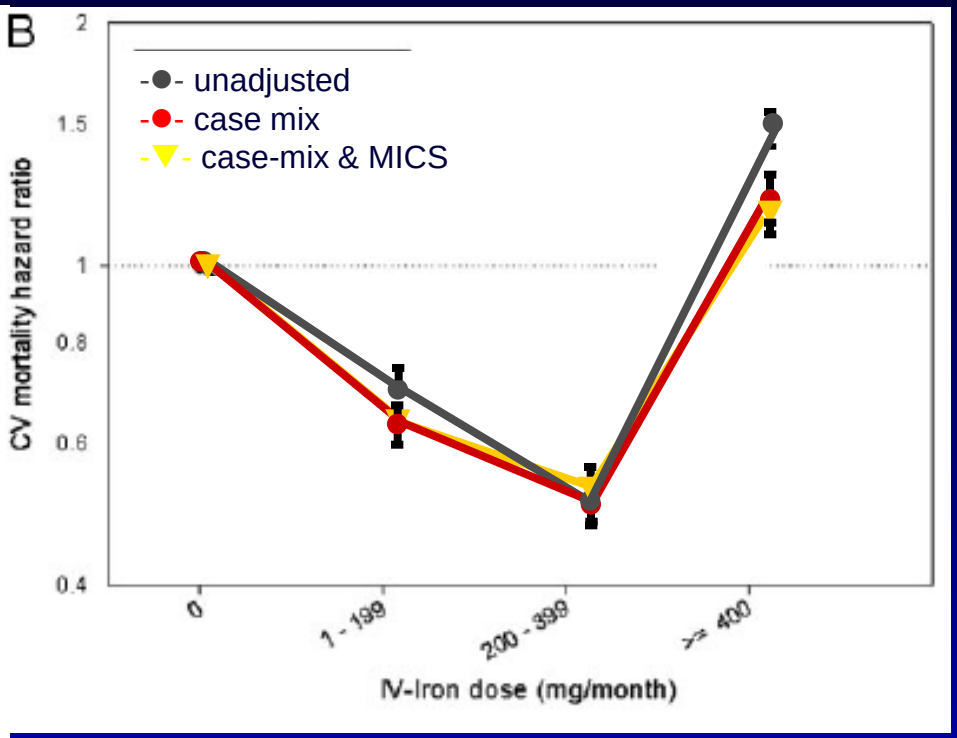
Adapted from: Feldman H *et al. J Am Soc Nephrol* 2004;15:1623–32.

Association between IV iron and all-cause and CV mortality

All-cause mortality



CVS-cause mortality



Kalantar-Zadeh K et al. J Am Soc Nephrol 2005;16:3070-80.

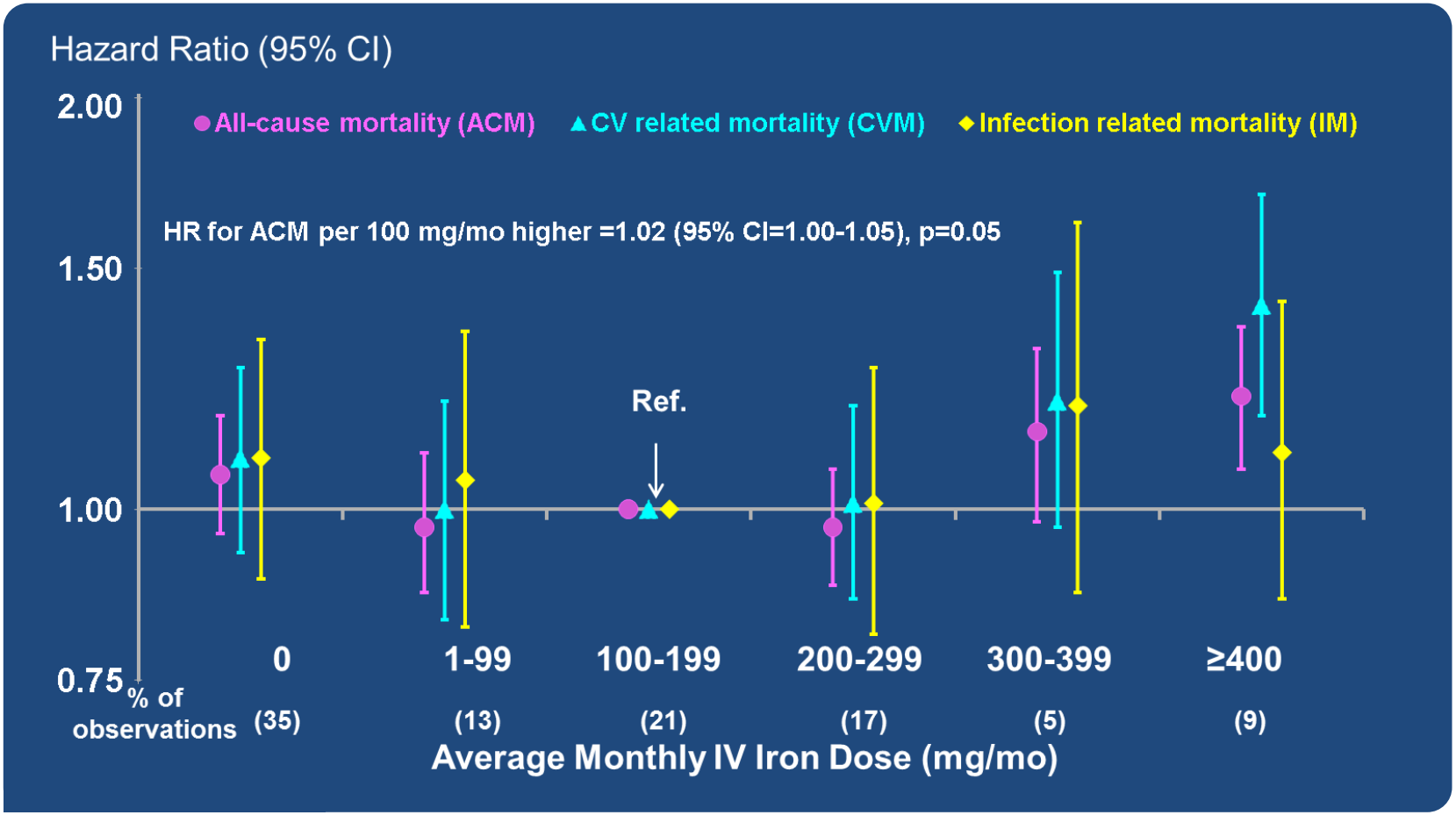
Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality

George R. Bailie[1], Maria Larkina[2], David A. Goodkin[2], Yun Li[2,3], Ronald L. Pisoni[2], Brian Bieber[2], Nancy Mason[4], Lin Tong[2], Francesco Locatelli[5], Mark R. Marshall[6], Masaaki Inaba[7] and Bruce M. Robinson[2,3]

[1]Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, New York, USA; [2]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [3]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA; [4]College of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA; [5]Department of Nephrology and Dialysis and Renal Transplant, Alessandro Manzoni Hospital, Lecco, Italy; [6]Department of Renal Medicine, Middlemore Hospital, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand and [7]Department of Metabolism, Endrocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

Associations between IV iron dose and mortality

DOPPS



CJASN ePress. Published on October 15, 2014 as doi: 10.2215/CJN.03370414

Article

Intravenous Iron Exposure and Mortality in Patients on Hemodialysis

Dana C. Miskulin, Navdeep Tangri, Karen Bandeen-Roche, Jing Zhou, Aidan McDermott, Klemens B. Meyer, Patti L. Ephraim, Wieneke M. Michels, Bernard G. Jaar, Deidra C. Crews, Julia J. Scialla, Stephen M. Sozio, Tariq Shafi, Albert W. Wu, Courtney Cook, and L. Ebony Boulware for The Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network Patient Outcomes in End Stage Renal Disease Study Investigators

Abstract

Background and objectives Clinical trials assessing effects of larger cumulative iron exposure with outcomes are lacking, and observational studies have been limited by assessment of short-term exposure only and/or failure to assess cause-specific mortality. The associations between short- and long-term iron exposure on all-cause and cause-specific mortality were examined.

Design, setting, participants, & measurements The study included 14,078 United States patients on dialysis initiating dialysis between 2003 and 2008. Intravenous iron dose accumulations over 1-, 3-, and 6-month rolling windows were related to all-cause, cardiovascular, and infection-related mortality in Cox proportional hazards models that used marginal structural modeling to control for time-dependent confounding.

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence:
Dr. Dana C. Miskulin, Tufts Medical Center, Box 391, Division of Nephrology, 800 Washington Street,

Table 3. Association of intravenous iron dose with time to all-cause, cardiovascular, and infection-related death

Doses (mg)	*n* (patient-mo)	Percent	All-Cause Mortality		Cardiovascular Mortality		Infection-Related Mortality[a]	
			HR (95% CI)	*P* Value[b]	HR (95% CI)	*P* Value[b]	HR (95% CI)	*P* Value[b]
One-month iron exposure								
None	90,178	34.32	0.98 (0.79 to 1.22)	0.01	1.11 (0.84 to 1.48)	0.66	0.92 (0.54 to 1.57)	0.43
>0–150	53,302	20.16	Reference		Reference		Reference	
>150–350	63,327	23.96	0.78 (0.64 to 0.95)		1.08 (0.80 to 1.44)		0.77 (0.47 to 1.26)	
>350	56,993	21.56	0.79 (0.62 to 0.99)		0.95 (0.70 to 1.29)		1.26 (0.75 to 2.12)	
Three-month iron exposure								
None	45,247	19.17	1.19 (0.90 to 1.57)	0.41	1.06 (0.72 to 1.54)	0.49	0.86 (0.38 to 1.96)	0.24
>0–450	60,407	25.59	Reference		Reference		Reference	
>450–1050	81,396	34.48	0.99 (0.81 to 1.20)		0.87 (0.67 to 1.14)		0.99 (0.56 to 1.74)	
>1050	49,038	20.77	1.09 (0.84 to 1.42)		1.02 (0.74 to 1.41)		1.69 (0.87 to 3.28)	
Six-month iron exposure								
None	18,555	9.19	1.24 (0.92 to 1.69)	0.31	1.46 (0.98 to 2.16)	0.28	0.75 (0.29 to 1.95)	0.48
>0–900	62,845	31.14	Reference		Reference		Reference	
>900–2100	95,058	47.10	0.98 (0.80 to 1.21)		1.15 (0.85 to 1.56)		0.98 (0.53 to 1.81)	
>2100	25,375	12.57	1.12 (0.81 to 1.57)		1.17 (0.76 to 1.79)		1.59 (0.73 to 3.46)	

The weighting on cumulative iron doses received was on the basis of iron history, age, sex, race, ethnicity, baseline comorbidity at 90 days, baseline body mass index, cause of ESRD, year of starting dialysis, baseline iron doses, hemoglobinopathies, saturation of transferrin (TSat)/ferritin categories, hemoglobin categories, weekly erythropoietin (EPO) doses categories, change in EPO, interaction of TSat/ferritin categories and hemoglobin categories, albumin, creatinine, predialysis systolic BP, body weight, change in weight, vascular access type, noninfection-related hospitalization, and infection. Demographics and baseline comorbidity were included in the outcome models. HR, hazard ratio; 95% CI, 95% confidence interval.

[a]Models were adjusted for all covariates included in all-cause and cardiovascular morality models, except recent infection.

[b]Global tests of iron exposure.

Miskulin et al, 2014.

Iron Management in CKD Conference

Steering Committee

Glenn Chertow, USA – Conference Co-Chair
Iain Macdougall, UK – Conference Co-Chair

Iron Overload Co-Chairs
Kai-Uwe Eckardt, *Germany* & Dorine Swinkels, *Netherlands*

Inflammation & Oxidative Stress Co-Chairs
Peter Stenvinkel, *Sweden* & Christoph Wanner, *Germany*

Iron & Infection Co-Chairs
Gregorio Obrador, *Mexico* & Günter Weiss, *Austria*

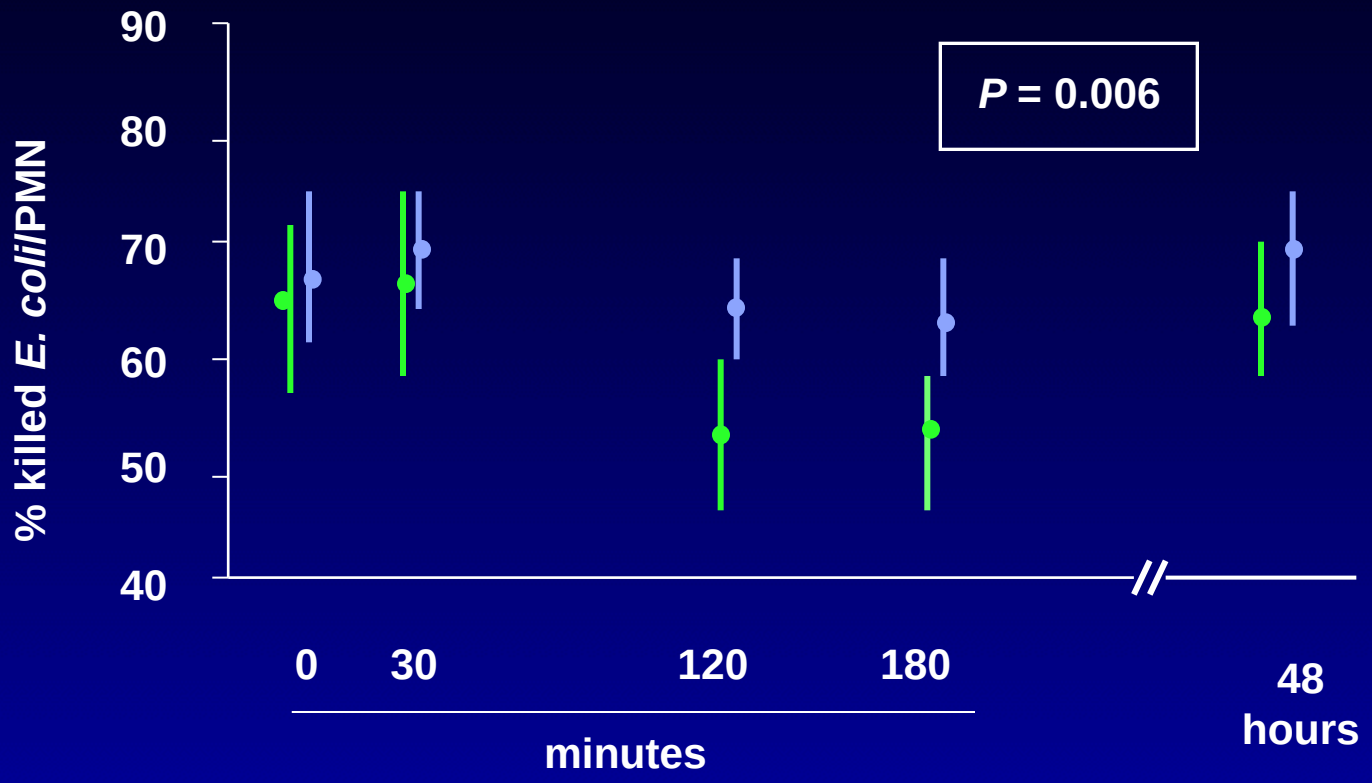
Hypersensitivity Reactions to IV Iron Co-Chairs
Andreas Bircher, *Switzerland* & Carol Pollock, *Australia*

Iron and infection

Iron overload: ↑ bacterial growth / virulence
↓ PMN phagocytosis / bacterial killing

Animals: parenteral iron administered to rats or mice with active infection → harmful

High dose IV iron depresses neutrophil killing capacity



300 mg of iron sucrose (•) or placebo (o)

PMN, polymorphonuclear leukocytes

Deicher R *et al*. *Kidney Int* 2003;64:728–36.

Iron and infection

Clinical Nephrology, Vol. 57 – No. 6/2002 (457-461)

Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients

B. Hoen[1], A. Paul-Dauphin[2] and M. Kessler[3]

- Data from prospective study of 985 HD patients
- Risk factors for bacteraemia analysed
- In multivariate analysis, neither IV iron administration in the whole population nor the weekly amount of iron were significant factors for bacteraemia

Hoen B et al. Clin Nephrol 2002;6:457–61.

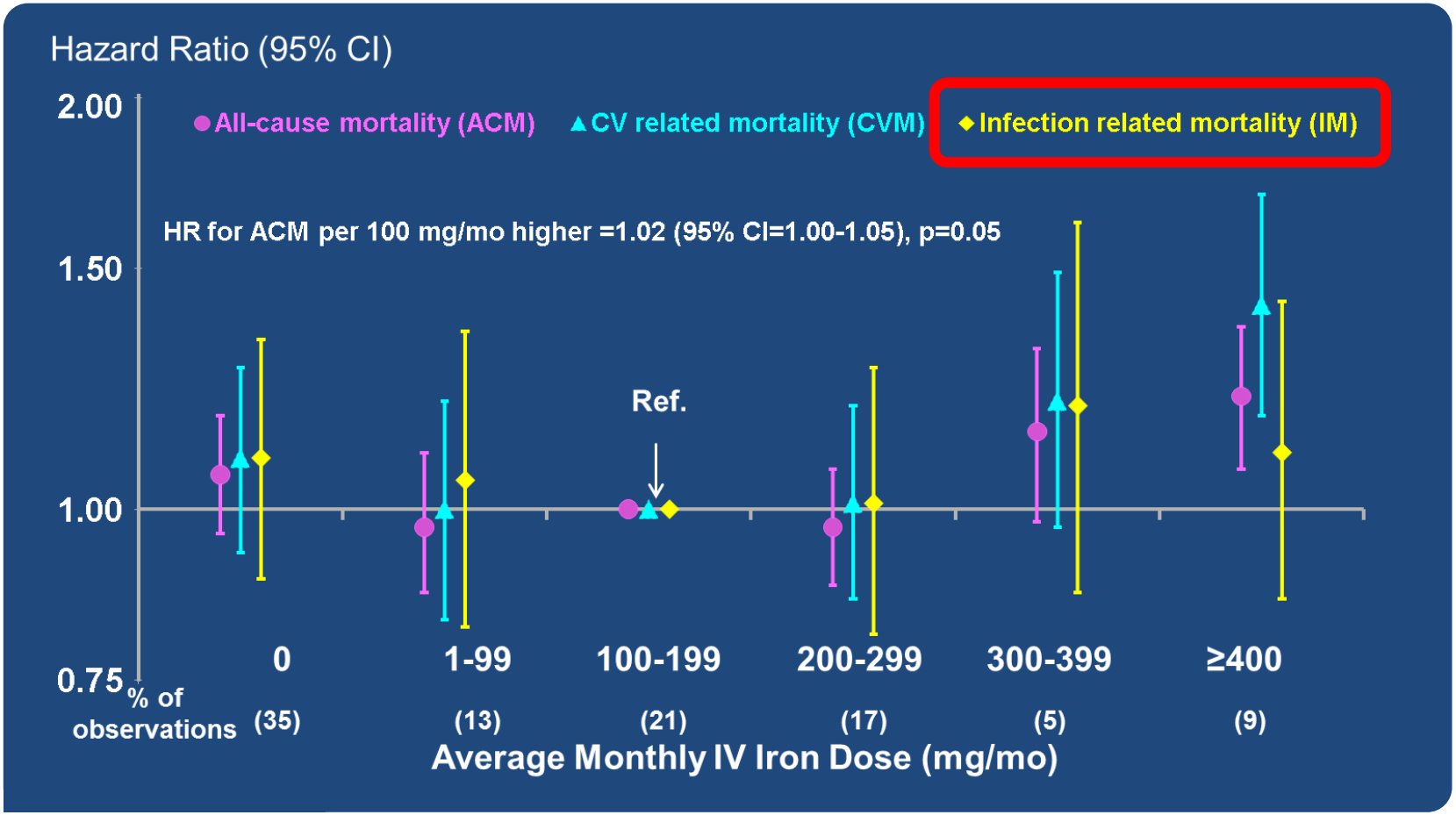
Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality

George R. Bailie[1], Maria Larkina[2], David A. Goodkin[2], Yun Li[2,3], Ronald L. Pisoni[2], Brian Bieber[2], Nancy Mason[4], Lin Tong[2], Francesco Locatelli[5], Mark R. Marshall[6], Masaaki Inaba[7] and Bruce M. Robinson[2,3]

[1]Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, New York, USA; [2]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [3]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA; [4]College of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA; [5]Department of Nephrology and Dialysis and Renal Transplant, Alessandro Manzoni Hospital, Lecco, Italy; [6]Department of Renal Medicine, Middlemore Hospital, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand and [7]Department of Metabolism, Endrocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

Associations between IV iron dose and mortality

DOPPS



CJASN ePress. Published on October 15, 2014 as doi: 10.2215/CJN.03370414

Article

Intravenous Iron Exposure and Mortality in Patients on Hemodialysis

Dana C. Miskulin, Navdeep Tangri, Karen Bandeen-Roche, Jing Zhou, Aidan McDermott, Klemens B. Meyer, Patti L. Ephraim, Wieneke M. Michels, Bernard G. Jaar, Deidra C. Crews, Julia J. Scialla, Stephen M. Sozio, Tariq Shafi, Albert W. Wu, Courtney Cook, and L. Ebony Boulware for The Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network Patient Outcomes in End Stage Renal Disease Study Investigators

Abstract

Background and objectives Clinical trials assessing effects of larger cumulative iron exposure with outcomes are lacking, and observational studies have been limited by assessment of short-term exposure only and/or failure to assess cause-specific mortality. The associations between short- and long-term iron exposure on all-cause and cause-specific mortality were examined.

Design, setting, participants, & measurements The study included 14,078 United States patients on dialysis initiating dialysis between 2003 and 2008. Intravenous iron dose accumulations over 1-, 3-, and 6-month rolling windows were related to all-cause, cardiovascular, and infection-related mortality in Cox proportional hazards models that used marginal structural modeling to control for time-dependent confounding.

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence:
Dr. Dana C. Miskulin, Tufts Medical Center, Box 391, Division of Nephrology, 800 Washington Street,

Table 3. Association of intravenous iron dose with time to all-cause, cardiovascular, and infection-related death

Doses (mg)	*n* (patient-mo)	Percent	All-Cause Mortality		Cardiovascular Mortality		Infection-Related Mortality	
			HR (95% CI)	*P* Value[b]	HR (95% CI)	*P* Value[b]	HR (95% CI)	*P* Value[b]
One-month iron exposure								
None	90,178	34.32	0.98 (0.79 to 1.22)	0.01	1.11 (0.84 to 1.48)	0.66	0.92 (0.54 to 1.57)	0.43
>0–150	53,302	20.16	Reference		Reference		Reference	
>150–350	63,327	23.96	0.78 (0.64 to 0.95)		1.08 (0.80 to 1.44)		0.77 (0.47 to 1.26)	
>350	56,993	21.56	0.79 (0.62 to 0.99)		0.95 (0.70 to 1.29)		1.26 (0.75 to 2.12)	
Three-month iron exposure								
None	45,247	19.17	1.19 (0.90 to 1.57)	0.41	1.06 (0.72 to 1.54)	0.49	0.86 (0.38 to 1.96)	0.24
>0–450	60,407	25.59	Reference		Reference		Reference	
>450–1050	81,396	34.48	0.99 (0.81 to 1.20)		0.87 (0.67 to 1.14)		0.99 (0.56 to 1.74)	
>1050	49,038	20.77	1.09 (0.84 to 1.42)		1.02 (0.74 to 1.41)		1.69 (0.87 to 3.28)	
Six-month iron exposure								
None	18,555	9.19	1.24 (0.92 to 1.69)	0.31	1.46 (0.98 to 2.16)	0.28	0.75 (0.29 to 1.95)	0.48
>0–900	62,845	31.14	Reference		Reference		Reference	
>900–2100	95,058	47.10	0.98 (0.80 to 1.21)		1.15 (0.85 to 1.56)		0.98 (0.53 to 1.81)	
>2100	25,375	12.57	1.12 (0.81 to 1.57)		1.17 (0.76 to 1.79)		1.59 (0.73 to 3.46)	

The weighting on cumulative iron doses received was on the basis of iron history, age, sex, race, ethnicity, baseline comorbidity at 90 days, baseline body mass index, cause of ESRD, year of starting dialysis, baseline iron doses, hemoglobinopathies, saturation of transferrin (TSat)/ferritin categories, hemoglobin categories, weekly erythropoietin (EPO) doses categories, change in EPO, interaction of TSat/ferritin categories and hemoglobin categories, albumin, creatinine, predialysis systolic BP, body weight, change in weight, vascular access type, noninfection-related hospitalization, and infection. Demographics and baseline comorbidity were included in the outcome models. HR, hazard ratio; 95% CI, 95% confidence interval.

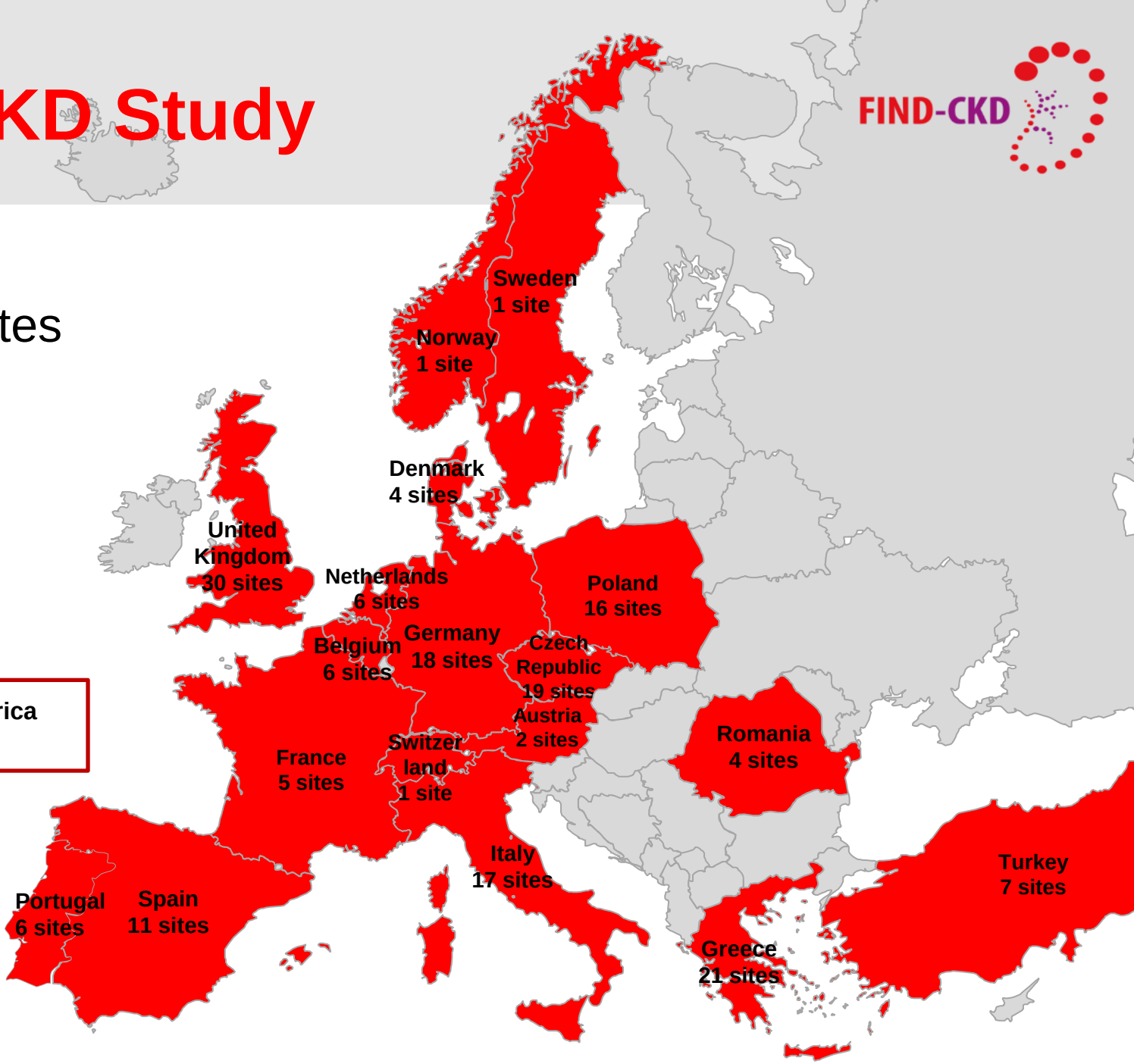
[a]Models were adjusted for all covariates included in all-cause and cardiovascular morality models, except recent infection.

[b]Global tests of iron exposure.

Miskulin et al, 2014.

FIND-CKD Study

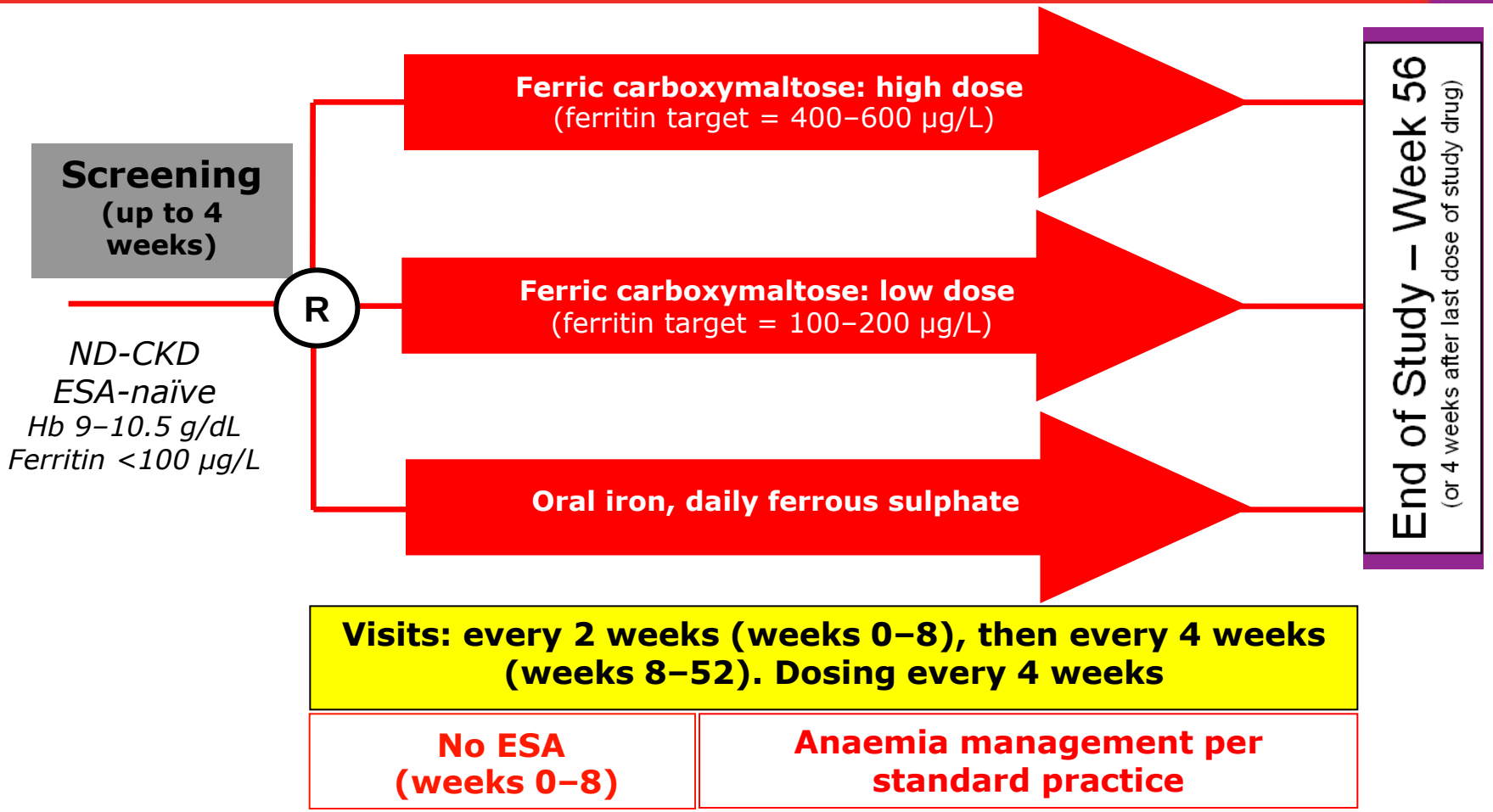
20 Countries
193 Active Sites



Australia
14 sites

United States of America
4 sites

The FIND-CKD trial



Primary objective: To evaluate the long-term efficacy of ferric carboxymaltose (using targeted ferritin levels to determine dosing) or oral iron to delay and/or reduce ESA use in ND-CKD patients with iron deficiency anaemia

Secondary objectives: To evaluate the ESA requirements, to evaluate the long-term safety and tolerability of iron therapy and evaluate the health resource and economic burden of the treatment of anaemia of ND-CKD

The rate of infections was identical for all three treatment arms

	High-ferritin ferric carboxymaltose (n=154)	Low-ferritin ferric carboxymaltose (n=150)	Oral iron (n=312)
Any adverse event, n (%)	126 (81.8)	130 (86.7)	255 (81.7)
Gastrointestinal disorders	32 (20.8)	38 (25.3)	128 (41.0)
Diarrhoea	15 (9.7)	11 (7.3)	45 (14.4)
Constipation	2 (1.3)	5 (3.3)	37 (11.9)
Nausea	9 (5.8)	7 (4.7)	15 (4.8)
Dyspepsia	2 (1.3)	3 (2.0)	17 (5.4)
Infections	**51 (33.1)**	**51 (34.0)**	**95 (30.4)**
Urinary tract infection	18 (11.7)	10 (6.7)	17 (5.4)
Nasopharyngitis	13 (8.4)	10 (6.7)	16 (5.1)
Influenza	4 (2.6)	8 (5.3)	7 (2.2)
General disorders and administration-site conditions	36 (23.4)	35 (23.3)	67 (21.5)
Peripheral oedema	21 (13.6)	21 (14.0)	29 (9.3)

Macdougall *et al. Nephrol Dial Transplant* 2014;29:2075–2084.

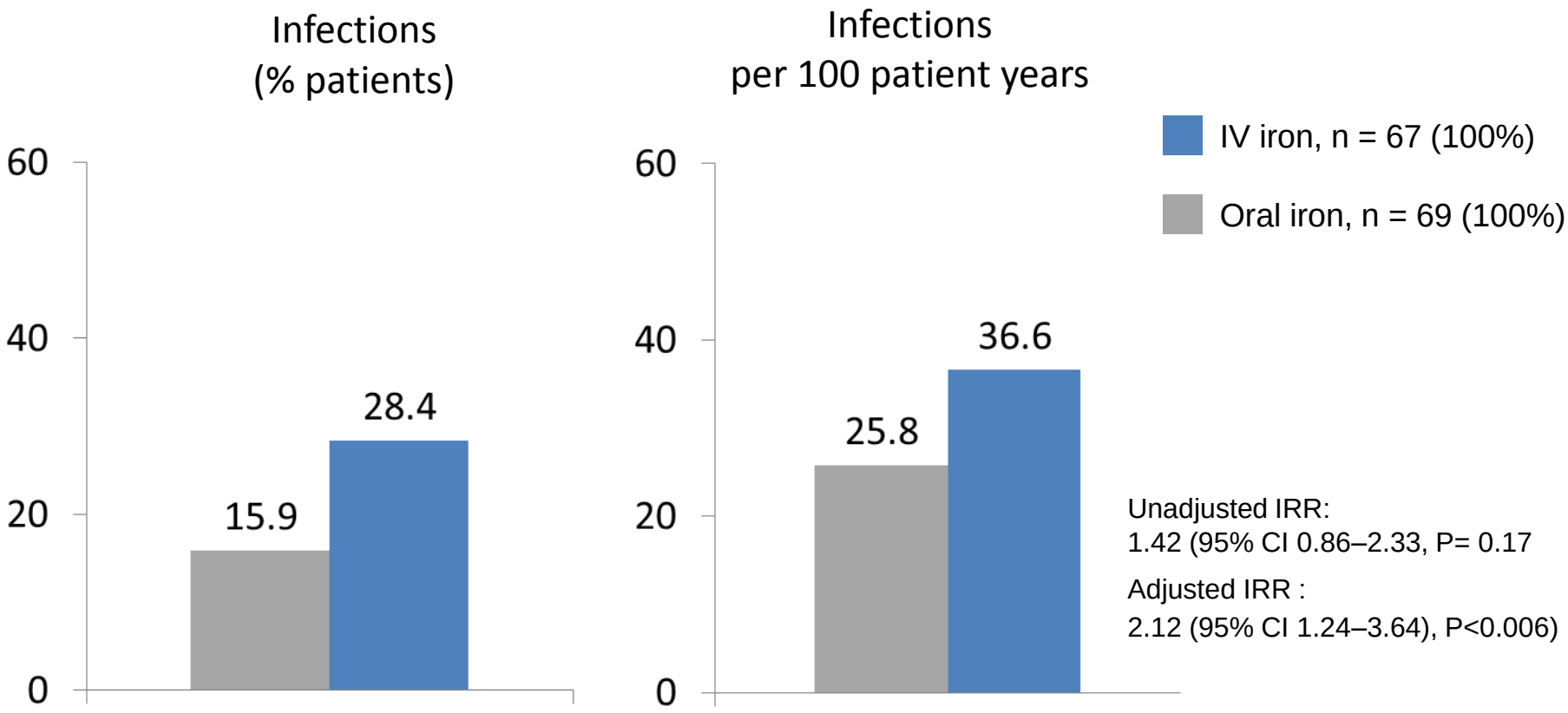
The rate of serious infections was identical for all three treatment arms

	High-ferritin ferric carboxymaltose (n=154)	Low-ferritin ferric carboxymaltose (n=150)	Oral iron (n=312)
Any serious adverse event*, %	25.3	24	18.9
Cardiac disorders, %	6.5	4.7	4.5
Acute myocardial infarction	1.3	0	1.3
Cardiac failure	0.6	0	1.0
Infections, %	**3.9**	**3.3**	**3.8**
Pneumonia	**0**	**0.7**	**1.3**
Injury, poisoning & procedural complications, %	2.6	2.0	2.6

- None of the serious adverse events in the ferric carboxymaltose treatment groups and one (0.3%) in the oral iron group were considered treatment related

Macdougall *et al. Nephrol Dial Transplant* 2014;29:2075–2084.

REVOKE:
Infection-related SAEs



- The **incidence of lung** and **skin infections** were increased between three- and fourfold in the IV iron group

Incidence Rate Ratio (IRR)

Agarwal et al. Kidney Int. 2015 Oct;88(4):905-14

Iron Management in CKD Conference

Steering Committee

Glenn Chertow, USA – Conference Co-Chair
Iain Macdougall, UK – Conference Co-Chair

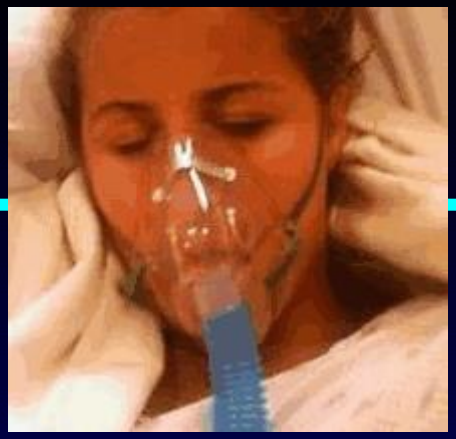
Iron Overload Co-Chairs
Kai-Uwe Eckardt, *Germany* & Dorine Swinkels, *Netherlands*

Inflammation & Oxidative Stress Co-Chairs
Peter Stenvinkel, *Sweden* & Christoph Wanner, *Germany*

Iron & Infection Co-Chairs
Gregorio Obrador, *Mexico* & Günter Weiss, *Austria*

Hypersensitivity Reactions to IV Iron Co-Chairs
Andreas Bircher, *Switzerland* & Carol Pollock, *Australia*

Reactions to IV iron

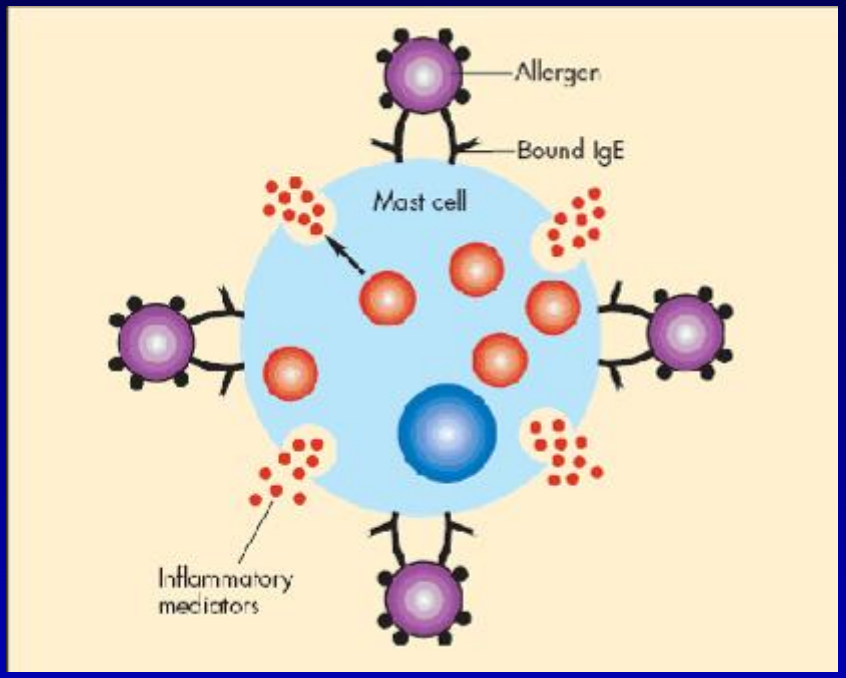


- **“Anaphylactic”**

– Ig-mediated

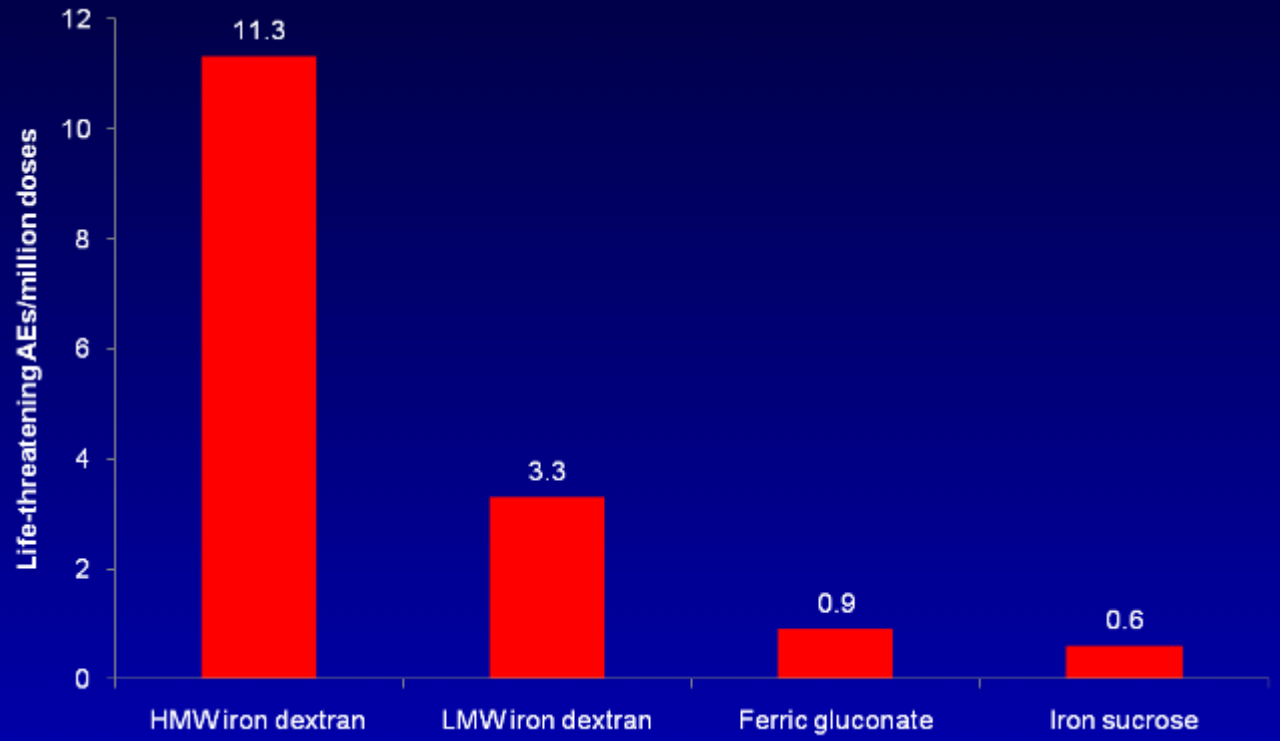
– release of histamine from basophils and mast cells

– vasoactive, haemodynamic, and respiratory effects



Life-threatening AEs higher with iron dextrans

- Life-threatening AEs (per 1,000,000 doses) occur at a rate of 11.3 for HMW iron dextran, 3.3 for LMW dextran, 0.9 for ferric gluconate and 0.6 for iron sucrose[1]



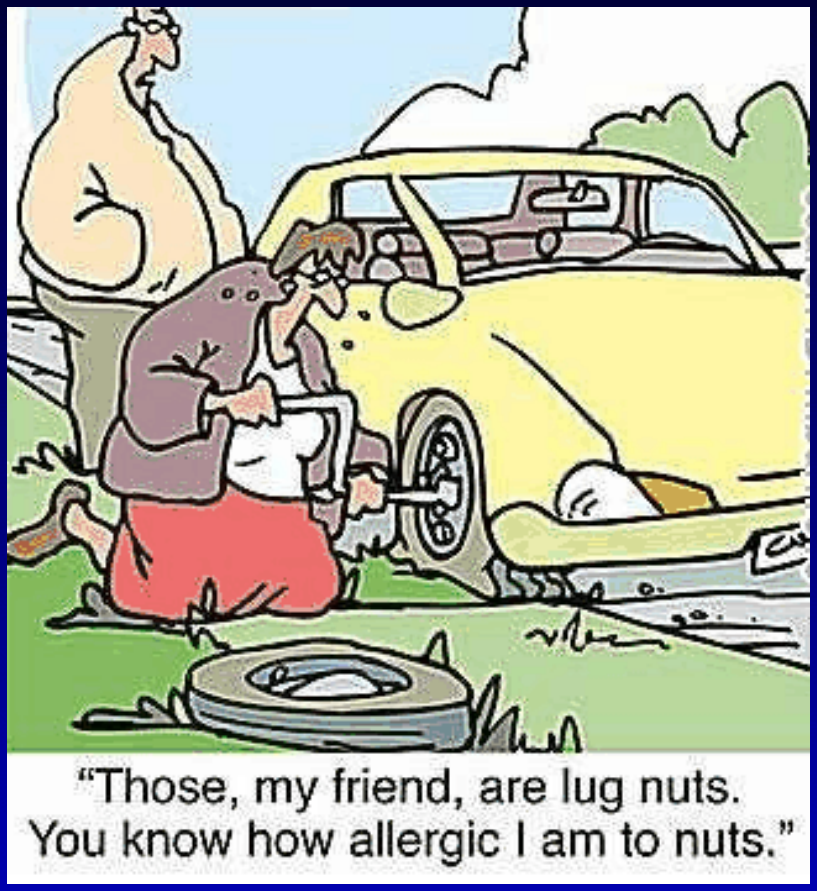
Data from the FDA on AEs occurring during 2001–2003 using 100 mg iron dose equivalent

1. Chertow GM *et al*. *Nephrol Dial Transplant* 2006;21:378–82.

Hypersensitivity reactions to IV iron

- **? ‘Labile’ iron**
- **? Complement-mediated**
  -- *CARPA reactions*

– vasoactive, haemodynamic, and respiratory effects



New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines

Press release

28/06/2013

New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has completed its review of intravenous iron-containing medicines used to treat iron deficiency and anaemia (low red-blood-cell counts) associated with low iron levels. The CHMP concluded that the benefits of these medicines are greater than their risks, provided that adequate measures are taken to minimise the risk of allergic reactions.

Intravenous iron medicines are used when iron supplements given by mouth cannot be used or do not work. All intravenous iron medicines have a small risk of causing allergic

Related information

- Intravenous iron-containing medicinal products: Article-31 referral

Contact point:

Monika Benstetter or Martin Harvey Allchurch
Tel. +44 (0)20 7418 8427
E-mail: press@ema.europa.eu

PIVOTAL

Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

- **UK multicentre prospective open-label 2-arm RCT of IV iron therapy in incident HD patients**

Lead investigator:	Iain Macdougall
Clinical Trial Manager:	Claire White
No of sites:	50
No. of patients:	2080
Commenced:	November 2013
Trial oversight:	Glasgow Clinical Trials Unit
Funder :	Kidney Research UK

This investigator-led clinical trial is supported through an unrestricted grant from
Vifor Fresenius Medical Care Renal Pharma

University of Glasgow

NHS Greater Glasgow and Clyde

THE RENAL ASSOCIATION founded 1950
UK Kidney Research Consortium : Renal Anaemia CSG

Kidney Research UK
Funding research to save lives

www.kidneyresearchuk.org
Registered Charity No: 252892 Registered Scottish Charity No. SC039245

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Study design

Incident new HD patients (0-12 mths)

On ESA

R

Proactive IV iron arm – IV iron 400mg/month

(withhold if ferritin>700 ug/l; TSAT>40%)

Reactive – minimalistic IV iron arm
(give IV iron if ferritin<200 ug/l; TSAT<20%)

Primary endpoint

Time to all-cause mortality or composite of MI, stroke, HF hosp

Up to 4 weeks screening

Total study period approximately 4 years *(event-driven)* – 2 years recruitment; 2-4 years follow-up per patient

Sample size: 2080 patients

Kidney Research UK
Funding research to save lives

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Primary endpoint

- Time to all-cause death or a composite of non-fatal cardiovascular events (MI, stroke, and HF hospitalisation)
  -- adjudicated by a blinded Endpoint Adjudication Committee

Secondary endpoints

- Incidence of all-cause death and a composite of myocardial infarction, stroke, and hospitalisation for heart failure as recurrent events.
- Time to (and incidence of) all-cause death
- Time to (and incidence of) composite cardiovascular event
- Time to (and incidence of) myocardial infarction
- Time to (and incidence of) stroke
- Time to (and incidence of) hospitalisation for heart failure
- ESA dose requirements
- Transfusion requirements
- EQ-5D QOL and KDQOL
- Vascular access thrombosis
- All-cause hospitalisation
- Infections; hospitalisation for infection

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

NETWORK OF SITES

King's College Hospital NHS
NHS Foundation Trust

England
Queen Elizabeth Hospital, Birmingham; Heartlands Hospital, Birmingham; Royal Free, London, King's College Hospital, London; Guy's & St Thomas', London; St Helier, Surrey; St George's, London; Royal Liverpool Hospital, University Hospital Aintree; Sheffield Teaching Hospital; Lister Hospital, Stevenage; Salford Royal Hospital, Manchester; Manchester Royal Hospital; Queen Alexandra Hospital, Portsmouth; Kent & Canterbury Hospital, Leicester General Hospital, Hull Royal Infirmary; Freeman Hospital, Newcastle; Churchill Hospital, Oxford; University Hospital of North Staffordshire, Stoke-on-Trent; Southmead Hospital, Bristol; Royal Cornwall Hospital; Nottingham City Hospital; Norfolk & Norwich Hospital; New Cross Hospital, Wolverhampton; Royal London Hospital; Wirral University Teaching Hospital; Royal Shrewsbury Hospital, Royal Devon & Exeter Hospital, Royal Preston Hospital, St James' Hospital, Leeds; Hammersmith Hospital, London; Royal Sussex Hospital, Brighton; Bradford Teaching Hospital; Coventry University Hospital; Southend University Hospital; Gloucestershire Royal Hospital; Derriford Hospital, Plymouth; Royal Berkshire, Reading

Wales
Morriston Hospital, Swansea; University Hospital, Cardiff

Scotland
Western Infirmary, Glasgow; Victoria Hospital, Kirkcaldy; Ninewells Hospital, Dundee; Royal Edinburgh Hospital

N. Ireland
Belfast City Hospital, Antrim Area Hospital;
Daisy Hill Hospital,Newry; Altnagelvin Hospital, Derry

Kidney Research UK
Funding research to save lives

Conclusions

- IV iron is a fantastic resource in replacing deficient iron stores
- Increasing evidence of positive effects beyond red cell production

But

- Laboratory and animal studies have produced a plethora of data on potential safety concerns of IV iron
- Further robust scientific evidence needed

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients