Consultancy, honoraria, research grant income:-

- Vifor Pharma
- Vifor FMC Renal Pharma
- Pharmacosmos
- Takeda
- AMAG
- FibroGen
- Astellas
- Glaxo Smith Kline
- Bayer
- Rockwell
- Keryx
- Noxxon
- Pieris
- Amgen
- Janssen Cilag
- Roche

(No employment, stock ownership, legal expert witness)
Conference Overview and Objectives

To develop a greater understanding of the role of iron therapy in the management of anemia in patients with chronic kidney disease

-- benefits *versus* risks

-- balance between ESA therapy and iron
CKD Anaemia Management

- Transfusions
- IV Iron
- ESAs

KDIGO
Pre-1990

**Transfusions**

1990 - 2009

**Transfusions**

**ESAs**

**IV Iron**

Post-TREAT

**Transfusions**

**ESAs**

**IV Iron**

**KDIGO**
What do we know about IV iron?

- Enhances the erythropoietic response to ESA therapy
  -- increased Hb response
  -- reduced ESA doses (economic, safety)

- Widespread variability in IV iron usage worldwide

- Very limited robust clinical data on safety
  -- iron overload
  -- oxidative stress / cardiovascular toxicity
  -- infections
  -- hypersensitivity reactions

Reduced ESA use with IV iron in dialysis patients

### Haemoglobin, ESA, and IV iron use in dialysis units in the US (1992–2004)

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 77,347)</td>
<td>(n = 89,815)</td>
<td>(n = 100,540)</td>
<td>(n = 109,685)</td>
<td>(n = 121,133)</td>
<td>(n = 140,227)</td>
<td>(n = 157,960)</td>
<td></td>
</tr>
<tr>
<td><strong>Hemoglobin (g/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-&lt;11</td>
<td>9.7 ± 1.0</td>
<td>10.1 ± 1.0</td>
<td>10.5 ± 1.0</td>
<td>10.9 ± 0.8</td>
<td>11.5 ± 1.0</td>
<td>11.7 ± 1.0</td>
<td>11.8 ± 0.9</td>
</tr>
<tr>
<td>≤11-≥12</td>
<td>49,471 (64.0)</td>
<td>58,160 (64.8)</td>
<td>54,345 (54.1)</td>
<td>48,704 (44.4)</td>
<td>27,398 (22.6)</td>
<td>23,507 (16.8)</td>
<td>18,775 (11.9)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>4,453 (5.8)</td>
<td>10,411 (11.6)</td>
<td>23,452 (23.3)</td>
<td>40,642 (37.1)</td>
<td>49,005 (40.5)</td>
<td>60,484 (43.1)</td>
<td>65,070 (41.2)</td>
</tr>
<tr>
<td>Missing/unknown</td>
<td>404 (0.5)</td>
<td>1,071 (1.2)</td>
<td>3,194 (3.2)</td>
<td>4,599 (4.2)</td>
<td>30,482 (25.2)</td>
<td>42,073 (30.0)</td>
<td>60,336 (38.2)</td>
</tr>
<tr>
<td><strong>Total ESA use/mo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>23,125 (29.9)</td>
<td>19,988 (22.3)</td>
<td>18,973 (18.9)</td>
<td>15,506 (14.1)</td>
<td>14,244 (11.8)</td>
<td>14,085 (10.0)</td>
<td>13,631 (8.6)</td>
</tr>
<tr>
<td>0-≤28,000 units</td>
<td>31,676 (41.0)</td>
<td>31,786 (35.4)</td>
<td>29,336 (29.2)</td>
<td>32,791 (29.9)</td>
<td>28,866 (23.8)</td>
<td>33,586 (24.0)</td>
<td>36,514 (23.1)</td>
</tr>
<tr>
<td>28,000-≤58,000 units</td>
<td>18,884 (24.4)</td>
<td>27,234 (30.3)</td>
<td>31,298 (31.1)</td>
<td>35,219 (32.1)</td>
<td>36,086 (29.8)</td>
<td>41,957 (29.9)</td>
<td>46,233 (29.3)</td>
</tr>
<tr>
<td>&gt;58,000 units</td>
<td>3,662 (4.7)</td>
<td>10,807 (12.0)</td>
<td>20,933 (20.8)</td>
<td>26,169 (23.9)</td>
<td>41,937 (34.6)</td>
<td>50,599 (36.1)</td>
<td>61,582 (39.0)</td>
</tr>
<tr>
<td><strong>Iron use (yes)</strong></td>
<td>258 (0.3)</td>
<td>22,601 (25.2)</td>
<td>36,781 (36.6)</td>
<td>63,678 (58.1)</td>
<td>75,385 (62.2)</td>
<td>83,718 (59.7)</td>
<td>113,03 (71.6)</td>
</tr>
</tbody>
</table>

*Note: Values expressed as mean ± SE or number (percent). Hemoglobin in g/dL may be converted to g/L by multiplying by 10.*
What do we know about IV iron?

- Enhances the erythropoietic response to ESA therapy
  - increased Hb response
  - reduced ESA doses (economic, ?safety)

- Widespread variability in IV iron usage worldwide

- Very limited robust clinical data on safety
  - iron overload
  - oxidative stress / cardiovascular toxicity
  - infections
  - hypersensitivity reactions
Mean Ferritin Trends by Country
– DOPPS 2-5 (2002-2012)
Ferritin Distribution by Country
– DOPPS 5 (2012) –

Ferritin (ng/mL)

- US
- Ger
- UK
- Swe
- A/NZ
- Bel
- GCC
- Spa
- Ita
- Can
- Fra
- Jpn

Patient Percentile
- 95th
- 75th
- 50th
- 25th
- 5th

N Pts =
- US 2728
- Ger 427
- UK 301
- Swe 387
- A/NZ 352
- Bel 343
- GCC 439
- Spa 467
- Ita 325
- Can 355
- Fra 35
- Jpn 1151
What do we know about IV iron?

- Enhances the erythropoietic response to ESA therapy
  - *increased Hb response*
  - *reduced ESA doses (economic, ?safety)*

- Widespread variability in IV iron usage worldwide

- Very limited robust clinical data on safety
  - *iron overload*
  - *oxidative stress / cardiovascular toxicity*
  - *infections*
  - *hypersensitivity reactions*
Breakout Questions

A. Iron overload – chairs: Kai-Uwe Eckardt (DE), Dorine Swinkels (NL)

- What is the cause of iron deficiency in CKD patients?
- What is the usual iron loss in non-dialysis (ND), hemodialysis (HD), and peritoneal dialysis (PD) patients?
- What doses of iron are required to compensate for the patients' iron losses?
- What are the benefits of iron supplementation in CKD patients? What are the effects on Hb? What are the non-anemia related effects (heart, respiration)? Does the type of iron salt or iron complex make a difference? Oral/IV? Cost-effectiveness?
- What is the cause of iron overload in CKD patients treated with iron? Does iron overload depend on the type of iron salt/complex, on oral or IV administration?
- What is the definition of iron overload in a CKD setting? Is there a threshold?
- How best to diagnose iron overload in a CKD setting? What laboratory tests? Is there a threshold? Do we need to control lab tests for the inflammatory status? MRI scanning?
- How best to guide decisions on initiation, maintenance and discontinuation of iron supplementation in CKD patients? What laboratory tests? MRI scanning (and what exact MRI-methodology)? SQUID? Do these decisions depend on the patient group (ND, HD or PD), gender, co-treatment with ESA, or co-morbidities (cardiovascular disease, chronic liver disease-hepatitis C, inflammation)?
- What are short and long term effects of iron accumulation in various tissues and cells in CKD patients in terms of documented iron overload (biopsy, MRI; cellular distribution), morphological changes (e.g. fibrosis), or non-invasive measures of atherosclerosis (NIMA)?
- How does iron accumulation affect organs on a functional level? (e.g., liver, heart, pancreas, bone, kidney). Does iron supplementation contribute to CKD progression?
- How does iron accumulation affect long term outcome measures (events, mortality)?
134 HD patients
- Hb < 11 g/dl
- Ferritin = 500–1200 ug/l
- TSAT < 25%
- EPO dose >225 IU/kg/wk or >22,500 IU/wk

Coyne et al. JASN 2007; 18: 975-984.
2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):

- an increase in Hb concentration without starting ESA treatment is desired and
- TSAT is $\leq 30\%$ and ferritin is $\leq 500\, \text{ng/ml} \ (\leq \SI{500}{\mu g/l})$

2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):

- an increase in Hb concentration or a decrease in ESA dose is desired and
- TSAT is $\leq 30\%$ and ferritin is $\leq 500\, \text{ng/ml} \ (\leq \SI{500}{\mu g/l})$
Monitoring iron overload by MRI?

B. Inflammation and oxidative stress – chairs: Christoph Wanner (DE), Peter Stenvinkel (SE)

- What methods are best to estimate oxidative stress in the clinical setting?
- Do IV iron compounds aggravate oxidative stress and/or inflammation?
  - If so, can antioxidants blunt the pro-oxidative effects of iron supplementation?
- What is the role of free circulating iron: can iron compounds adequately be bound and metabolized when given intravenously?
- Are there differences in the pro-oxidative and pro-inflammatory potential among different iron compounds? Data under consideration: laboratory, animal, observational or RCT
- Is there a difference in the oxidative stress potential between iron originators vs iron similars (i.e., iron generic follow-ons)?
- Does IV dose and administration time matters among different iron compounds in respect of causing oxidative stress and inflammation?
- Is there any evidence that iron compounds promote atherogenesis and cardiovascular disease?
  - Are there subgroups of patients that may be at risk?
  - How does iron therapy link to vascular calcification? Effects of iron on FGF23?
- What are the consequences of increased hepcidin and ferritin levels during inflammation?
- IV iron and risk of malignancy, CVD and diabetic nephropathy
Iron and oxidative stress

Fe$^{3+}$ \rightarrow Fe$^{2+}$

Fenton reaction

OH$^{-}$ radical

ROS

macromolecules, e.g. membrane lipids

lipid-derived free radicals

atherosclerosis
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.

Correlation between iron dose and CCA-IMT in patients <60 years

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, Wilheminespital, Vienna, Austria

Total peroxides (µmol/l)

A                B                C               D

200
150
100
50
0

**
***

KDIGO

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.

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

**Probability of Mortality**

(Adjusted Hazard Ratio ± 95% CI)

<table>
<thead>
<tr>
<th>Cumulative 6 month iron dose (mg)</th>
<th>0 - 700</th>
<th>700 - 1000</th>
<th>1000 - 1800</th>
<th>&gt; 1800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>&lt; 3.0</td>
<td>3.0 - &lt; 3.5</td>
<td>3.5 - &lt; 4.0</td>
<td>4.0 - &lt; 4.5</td>
</tr>
</tbody>
</table>

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

Association between IV iron and all-cause and CV mortality

Associations between IV iron dose and mortality

Hazard Ratio (95% CI)

HD for ACM per 100 mg/mo higher = 1.02 (95% CI = 1.00-1.05), p = 0.05

% of observations (35)

Average Monthly IV Iron Dose (mg/mo)

KDIGO
C. Iron and infections – chairs: Guenter Weiss (AT), Greg Obrador (MX)

- What is the impact of iron supplementation on host immune function?
- How could IV iron exacerbate the risk of infections? (e.g., neutrophil killing potential; bacterial proliferation)
- Is it a real or just a theoretical risk? – laboratory data; animal data; observational data; RCT data
- What is the evidence in favor or against an association between IV iron and infection in predialysis and dialysis patients?
- Is there an increased risk of infection with different iron formulations including new ones?
- Is there an increased risk of infection with different dosing strategies (bolus versus maintenance)?
- What type of infections should we be concerned about? (e.g., bacterial, fungal, viral, or parasitic)
- Is there an increased risk of infection associated with iron overload derived from blood transfusions?
IV iron decreases neutrophil killing capacity

**IV iron and infection**

_Hoen B et al (2002)_

- Prospective study of 985 HD patients
- Risk factors for bacteraemia analysed
- IV iron administration does not significantly ↑ the risk of bacteraemia in chronic HD patients
Associations between IV iron dose and mortality

Hazard Ratio (95% CI)

HR for ACM per 100 mg/mo higher = 1.02 (95% CI = 1.00-1.05), p = 0.05

% of observations (35)

Average Monthly IV Iron Dose (mg/mo)

0 1-99 100-199 200-299 300-399 ≥400

KDIGO
D. Hypersensitivity reactions – chairs: Andreas Bircher (CH), Carol Pollock (AU)

- What are the characteristics of a drug hypersensitivity reaction? What are the risk factors for these reactions (e.g., asthma, atopy, previous drug hypersensitivity, previous iron hypersensitivity) and how should these reactions be diagnosed and classified?
- What are the differences in propensity to hypersensitivity reactions between the different formulations of IV iron?
- Does the incidence of hypersensitivity translate into a cost effective recommendation for the use of any IV iron formulation use over another?
- What is the pathogenesis of immediate reactions to IV iron? Are they immune mediated?
- Are some of the reactions to IV iron caused by ‘free’ iron in the circulation?
- What is the difference between ‘free’ iron, ‘labile’ iron, and ‘non-transferrin-bound’ iron?
- How commonly do reactions to IV iron occur?
- How often are these reactions serious or life-threatening?
- Are there differences in the risk of reactions to IV iron between the various iron preparations?
- How should reactions to IV iron be treated?
- How should patients with previous reactions to IV iron be managed in the future? What is the utility of a test dose? Can another formulation be used and if so, what additional testing might be required?
- How can such adverse drug reactions be better documented?
IV Iron Salts / Colloids → Carbohydrates

1940s
Goetsch (1946)
IV colloidal Fe(OH)_3 for anaemia. Severe toxic reactions in patients: ‘preclude use for therapeutics’

Nissim 1947
Use of IV iron saccharide

1950s
IV iron sucrose
Launched in Switzerland

IM iron dextran (Imferon) → IV

1980s
Iron oxyhydroxide core
Carbohydrate shell

Anaphylaxis DEATH

Hamstra (1980)
Anaphylactoid adverse events (AEs) to iron dextran are ‘serious and unpredictable’. Leads to black box label and test dose

Hypersensitivity reactions to IV iron

- **Anaphylactic**
- **Anaphylactoid**

- vasoactive, haemodynamic, and respiratory effects
- role of histamine release from basophils and mast cells