Management of Anaemia in HD patients – what has PIVOTAL taught us?

Iain C. Macdougall

on behalf of the PIVOTAL Study Group

Renal Unit, King’s College Hospital, London, UK
Conflicts of Interest

**Research Support:** Akebia, Astellas, GSK, Vifor Pharma

**Lecturing:** Akebia, Astellas, FibroGen, Pharmacosmos, Vifor Pharma

**Consulting activities:** Akebia, AMAG, GSK, Vifor Pharma
Hi Iain,

I would die for if you could talk about iron therapy at the Heidelberger Nephrologishes Seminar, 4th-6th April 2019 in Heidelberg. Do you think that you can talk at that moment in time about the UK study that you are chairing and that will come to its end right now? If the data are still confidential in April 2019, there may be no use for that subject.

You have been at that CME meeting, the largest of its kind in Germany, attracting about 700 nephros

Take care  Hans
Management of Anaemia in HD

ESA therapy

IV iron
Normal hemoglobin level in patients with chronic kidney disease and anemia

A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Abstract

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

The New England Journal of Medicine

ORIGINAL ARTICLE

EPOETIN ALFA IN CHRONIC KIDNEY DISEASE...
Outcome trials of ESA therapy

1998

NHCT


Stopped early

Normal Hematocrit

1998 2006 2009

CHOIR


Harm

CREATE

3Drüeke T, et al. NEJM 2006;355:2071–84

No benefit

TREAT


No benefit/harm
EPO has non-erythropoietic actions

High EPO levels

↑ VSMC [Ca^{2+}]_{i}
↑ RAS activation
↑ ET-1
↑ Thromboxane
↓ Prostacyclin
↑ ADMA
↓ NO

Hypertension

VSMC proliferation
EC proliferation
Angiogenesis

Blood access stenosis
Proliferative retinopathy
Vascular remodeling
Tumor growth

↑ Platelet production
↑ Platelet activity
↑ E selectin
↑ P selectin
↑ vWF
↑ PAI-1

Thrombosis

IV iron improves haemoglobin


IV iron reduces EPO doses

Fig 2. Mean rHuEPO dose at every month of follow-up in the two study groups. Squares indicate the intravenous group; diamonds indicate the oral group. *P < 0.05.

IV iron reduces ESA doses

Haemoglobin, ESA, and IV iron use in US dialysis patients (1992–2005)

Table 2. Hemoglobin, Erythropoiesis-Stimulating Agent, and Iron Use Trends, 1992 to 2004 (even years shown)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<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>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td></td>
<td></td>
<td></td>
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</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>
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<tr>
<td>≥11-&lt;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>
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<tr>
<td>Missing/unknown</td>
<td>23,019 (29.8)</td>
<td>20,173 (22.5)</td>
<td>19,549 (19.4)</td>
<td>15,740 (14.4)</td>
<td>14,248 (11.8)</td>
<td>14,163 (10.1)</td>
<td>13,779 (8.7)</td>
</tr>
<tr>
<td>Total ESA use/mo</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-&lt;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-&lt;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>
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<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>Iron use (yes)</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 (52.2)</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.
Safety in iron management.

Fischbene S.

Abstract
Intravenous (IV) iron therapy has become an integral part of hemodialysis management during the past several decades, and the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines recognize that most patients undergoing hemodialysis will require IV iron therapy on a regular basis to reach target hemoglobin (Hgb) levels. There are now three IV iron compounds available in the United States: iron dextran, sodium ferric gluconate, and iron sucrose. Although all have been proven effective for increasing Hgb/chemostimulated levels, recent data show differences in their relative safety profiles. During the past two decades, more than 30 deaths have been attributed to the use of IV iron dextran. The two newer compounds available in the United States, sodium ferric gluconate and iron sucrose, have more favorable safety profiles, with the largest prospective safety comparison to date showing sodium ferric gluconate to be similar to placebo in the incidence of serious anaphylactoid-type reactions. This article reviews safety data surrounding the IV iron therapies.

Iron toxicity: relevance for dialysis patients.

Fischbene S., Mathew A, Vaziri ND.

Abstract
Iron deficiency is common among patients with advanced kidney disease, particularly those requiring hemodialysis. Intravenous iron is a convenient treatment to supplement iron and is widely used among hemodialysis patients. Its efficacy is well established, and with treatment, hemoglobin levels rise and erythropoiesis-stimulating agent dose requirements are reduced. However, the safety of intravenous iron with respect to patient-centered outcomes has not been adequately studied. A variety of studies have indicated potential safety concerns, but most have been of small numbers of patients and with endpoints studied that have unclear clinical relevance. In this study, issues related to iron toxicity are reviewed.

Balance of Benefit and Risk in Intravenous Iron Treatment in Chronic Kidney Disease.

Fischbene S.

Abstract
Iron supplementation is an important aspect of treatment for hemodialysis patients, with most administration by an intravenous route. As with any drug, decisions as to treatment are most meaningful when benefits and risks are weighed in the context of the individual patient's clinical characteristics. In this article, knowledge of benefits and risks of intravenous iron are reviewed.
Iron deficiency anemia in chronic kidney disease: Uncertainties and cautions.

Author information

Abstract
Anemia in chronic kidney disease is common and iron deficiency is an important cause. To repair iron-deficiency anemia, replacement of iron is needed. Iron can be replaced either by the oral route or by the intravenous route. In a meta-analysis, 5 of the 6 trials were short-term, 1 to 3 months, and compared to oral iron, the mean increase in hemoglobin with intravenous iron was only 0.31 g/dL. However, one of the studies included in this meta-analysis was 6 months long and had a mean decline in hemoglobin of 0.52 g/dL, associated with intravenous iron administration. Given the short duration of most of the clinical trials comparing oral with intravenous administration of iron the long-term safety of these modes of administration of supplemental iron could not be assessed. Regular use of iron by the oral route is associated with mostly minor complications such as black stools, constipation, and abdominal discomfort. In contrast, intravenous administration of iron may lead to severe adverse events such as anaphylaxis and, as a more recent randomized trial has suggested, delayed complications such as infections and cardiovascular disease. Delayed complications of repeated intravenous iron use are difficult to recognize at an individual level therefore patients who have had recent cardiovascular events or are infected, intravenous iron should probably be avoided. Balancing safety and efficacy would require clinical judgment because if size may not fit all we have better data to support the liberal use of parenteral iron.

Safety of intravenous iron in hemodialysis patients.

Author information

Abstract
Among end-stage renal disease patients maintained by hemodialysis, anemia has been managed primarily through erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron. Following concerns about the cardiovascular (CV) safety of ESAs and changes in the reimbursement policies in Medicare’s ESRD program, the use of IV iron has increased. IV iron supplementation promotes hemoglobin production and reduces ESA requirements; yet there exists relatively little evidence on the long-term safety of iron supplementation in hemodialysis patients. IV iron can induce oxidative stress and is also essential in bacterial growth, leading to concerns about IV iron use and risk of CV events and infections in hemodialysis patients. Existing randomized controlled trials provide little evidence about safety due to insufficient power and short follow-up; recent observational studies have been inconsistent, but some have associated iron exposure with increased risk of infections and CV events. Given the widespread use and potential safety concerns related to IV iron, well-designed large prospective studies are needed to assess the potential benefits and risks.

Understanding iron: promoting its safe use in patients with chronic kidney failure treated by hemodialysis.

Author information

Abstract
Although judicious use of intravenous iron preparations is an indispensable part of anemia treatment in hemodialysis patients, their excessive and indiscriminate use can have insidious but serious adverse consequences. With recent implementation of the bundling reimbursement policy, use of intravenous iron preparations in the hemodialysis population has markedly increased. Excessive use of these agents potentially can exacerbate oxidative stress, inflammation, endothelial dysfunction, cardiovascular disease, and iron deficiency and potentially increases the risk of infections in this patient population. Most of these adverse effects are mediated by iron-catalyzed generation of reactive oxygen species and the resultant cellular injury and dysfunction. This review is intended to provide an overview of the nature and mechanisms of the adverse effects of iron overload and call for the judicious use of these vitally important products.
Concerns about IV iron

- Increased oxidative stress
- Increased atherogenesis
- CV toxicity
- Inflammation
- Immune dysfunction
- Cellular toxicity
- Increased infections
Iron and oxidative stress

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

Fenton reaction

$OH^-$ radical

ROS

macromolecules, e.g. membrane lipids

lipid-derived free radicals

atherosclerosis
Iron increases oxidative stress

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.

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

George R. Bailie¹, Maria Larkina², David A. Goodkin², Yun Li²,³, Ronald L. Pisoni², Brian Bieber², Nancy Mason⁴, Lin Tong², Francesco Locatelli⁵, Mark R. Marshall⁶, Masaaki Inaba⁷ and Bruce M. Robinson²,³

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

- All-cause mortality (ACM)
- CV related mortality (CVM)
- Infection related mortality (IM)

Average Monthly IV Iron Dose (mg/mo)

- 0 (35)
- 1-99 (13)
- 100-199 (21)
- 200-299 (17)
- 300-399 (5)
- ≥400 (9)
Association of IV Iron Dose with Mortality

Ferritin and IV Iron Use in DOPPS

Mean Serum Ferritin (ng/mL)

Mean IV Iron Dose (mg/month)

Considerations and Challenges in Defining Optimal Iron Utilization in Hemodialysis

David M. Charytan,* Amy Barton Pai,† Christopher T. Chan,*,† Daniel W. Coyne,*‡ Adriana M. Hung,*,*** Csaba P. Kovacs,† and Steven Fishbane,*†† on behalf of the Dialysis Advisory Group of the American Society of Nephrology

*Renal Division and †Nephrology Division, Departments of Medicine and ‡Pharmacy Practice, Brigham & Women’s Hospital, Boston, Massachusetts; †Albany College of Pharmacy and Health Sciences, Albany, New York; ‡Toronto General Hospital, University Health Network, Ontario, Canada; ***Washington University, Saint Louis, Missouri; **Vanderbilt University Medical Center, Nashville, Tennessee; ††University of Tennessee Health Science Center, Memphis, Tennessee; and †‡Hofstra North Shore-LIJ School of Medicine, Great Neck, New York

questions regarding effects on mortality, cardiovascular outcomes, infections, and tissue deposition, and in vitro experiments support the notion that IVI exacerbates oxidative stress, inflammation, and endothelial dysfunction.29,83 Despite clear clinical ramifications, data remain insufficient to make firm recommendations regarding the maximum single, weekly, or cumulative dose of IVI or to support a particular limit of iron indices above which iron administration is clearly contraindicated. Given current levels of exposure to IVI, these data raise the possibility of large-scale harm to dialysis patients from current practices. However, it remains unclear whether reducing IVI use would actually improve cardiovascular or infectious outcomes or conversely whether it would potentially increase influences on ESRD care.

The case of IVI thus appears to represent an undesirable paradigm in which initial studies and an imperfect evidence base without appropriate RCTs and guideline-based practices (potentially not appropriate for individual patients) have converged with financial incentives to dialysis units, Medicare quality parameters, and the potential for rapid adoption given the dominance of large and medium dialysis organizations to quickly drive drug utilization well beyond the space in which the risk-versus-benefit ratio has been adequately defined. Caution is needed, especially (although not exclusively) in anemia management, in which recent definitive RCTs had divergent results from earlier, encouraging observational studies.1,4,84 Performed the needed studies to define

The highest priority should be given to RCTs, like the PIVOTAL study,55 that are designed to compare the effect of conservative and liberal strategies of IVI administration, to compare the safety of bolus and maintenance dosing strategies, and to understand the utility of standard or novel biomarkers of iron stores for detecting iron deficiency and avoiding iron overload and iron-related morbidity in hemodialysis (Table 3). These trials must be powered to detect differences in mortality, cardiovascular events, infections, and hospitalizations. Given the larger size of the hemodialysis population as well as the greater losses of blood and higher utilization of iron in hemodialysis compared with peritoneal dialysis, priority should be given to studies of the hemodialysis population. Nevertheless,
IRON MANAGEMENT IN CKD

KDIGO 2014 Controversies Conference
San Francisco, 27–30 March, 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 management in chronic kidney disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference

Iain C. Macdougall¹, Andreas J. Bircher², Kai-Uwe Eckardt³, Gregorio T. Obrador⁴, Carol A. Pollock⁵,⁶, Peter Stenvinkel⁷, Dorine W. Swinkels⁸, Christoph Wanner⁹, Günter Weiss¹⁰, and Glenn M. Chertow¹¹; for Conference Participants¹²

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

Proactive IV iron Therapy in hemodialysis patients
PIVOTAL Steering Committee
Iain Macdougall, Claire White, Stefan Anker, Sunil Bhandari, Kenneth Farrington, Philip Kalra, John McMurray, Heather Murray, Charles Tomson, David Wheeler, Christopher Winearls, Ian Ford

Endpoint Adjudication Committee (chair: John McMurray)

Independent Data Monitoring Board (chair: Alan Jardine)

Kidney Research UK (Elaine Davies; Michael Nation)

Vifor Fresenius Medical Care Renal Pharma Ltd (Sandra Wächter)

Editorial support from Adam Perahia NorthStar Strategic Consulting
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**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**
Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

**Hypothesis:** Proactive, high-dose IV iron would be non-inferior to reactive, low-dose IV iron for the outcome of all cause mortality and cardiovascular events in haemodialysis patients.

Prospective Randomised, Open label, Blinded Endpoint (PROBE) design

Eudra CT: 2013-002276-25
**Trial Design**

**Screening:** ≤4 weeks

**Follow-up period with monthly visits**

**Median (maximum) follow-up:** 2.1 (4.4) years

---

Proactive, high-dose IV iron arm (n=1093)

- IV iron 400 mg/month (withhold if ferritin >700 µg/L; TSAT >40%)

Reactive, low-dose IV iron arm (n=1048)

- IV iron only administered if ferritin <200 µg/L or TSAT <20%

≥631 primary endpoint events (i.e., all-cause mortality, MI, stroke, or HF hospitalization)

- New to HD (0-12 months)
- On ESA
- Ferritin <400 µg/L
- TSAT <30%

n=2589

R

n=2141
Statistical analysis

**Event rate:** Assumed 3 year event rate of 40% in placebo group and 10% loss to follow-up (including transplantation).

**Sample size:** Proposed sample size of 2080.

**Power:** 631 primary outcome events required to exclude non-inferiority of a hazard ratio of 1.25 with 80% power.

Superiority testing if non-inferiority confirmed.

Eudra CT: 2013-002276-25
## Outcomes

### Primary
- Composite of nonfatal MI, nonfatal stroke, hospitalization for HF, or all-cause death, analyzed as time-to-first event

### Secondary (efficacy)
- MI, stroke, hospitalization for HF, and deaths (first + recurrent events)
- All-cause death
- First composite CV event (MI, stroke, and hospitalization for HF)
- Fatal or nonfatal MI
- Fatal or nonfatal stroke
- Hospitalization for HF
- ESA dose requirements
- Transfusion requirements
- Quality-of-life measures

### Secondary (safety)
- Vascular access thrombosis
- All-cause hospitalization
- Hospitalization for infection
- Infection episodes

### Tertiary
- Cumulative dose of iron
- Hemoglobin concentration
- Serum ferritin concentration
- Platelet count
- Serum albumin concentration
- TSAT
**Patient Disposition**

Assessed for eligibility (n=2589) → Excluded (n=448)

Randomized (n=2141)

Randomized to reactive, low-dose IV iron Intention-to-treat (ITT) population (n=1048)

Per-protocol (PP) population (n=1038)
- Excluded (n=10)
  - Current malignancy (n=7)
  - Elevated serum ferritin (n=3)

Incomplete follow-up (n=631)
- Death (n=269)
- Transplant (n=187)
- Moved to home dialysis (n=36)
- Moved to peritoneal dialysis (n=17)
- Lost to follow-up (n=78)
- Withdrew from study (n=44)

Included in ITT analysis (n=1048)
Included in PP analysis (n=1038)
Included in safety analyses (n=1048)

Randomized to proactive, high-dose IV iron Intention-to-treat (ITT) population (n=1093)

Per-protocol (PP) population (n=1080)
- Excluded (n=13)
  - Current malignancy (n=12)
  - Elevated serum ferritin (n=1)

Incomplete follow-up (n=592)
- Death (n=246)
- Transplant (n=184)
- Moved to home dialysis (n=45)
- Moved to peritoneal dialysis (n=13)
- Lost to follow-up (n=62)
- Withdrew from study (n=42)

Included in ITT analysis (n=1093)
Included in PP analysis (n=1080)
Included in safety analyses (n=1093)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proactive, High-Dose IV Iron (N=1093)</th>
<th>Reactive, Low-Dose IV Iron (N=1048)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, year</td>
<td>62.7 (14.9)</td>
<td>62.9 (15.1)</td>
</tr>
<tr>
<td>Male sex</td>
<td>65.0%</td>
<td>65.6%</td>
</tr>
<tr>
<td>Median (LQ, UQ) dialysis vintage, month</td>
<td>4.9 (2.8, 8.4)</td>
<td>4.8 (2.8, 8.1)</td>
</tr>
<tr>
<td>Vascular access</td>
<td></td>
<td></td>
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<tr>
<td>Dialysis catheter</td>
<td>41.1%</td>
<td>40.8%</td>
</tr>
<tr>
<td>Arteriovenous fistula/graft</td>
<td>58.9%</td>
<td>59.2%</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8.8%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73.6%</td>
<td>71.9%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25.3%</td>
<td>24.6%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>8.4%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>8.9%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>7.8%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45.2%</td>
<td>43.5%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>13.3%</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

P=0.03
# Baseline Characteristics (cont’d)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proactive, High-Dose IV Iron (N=1093)</th>
<th>Reactive, Low-Dose IV Iron (N=1048)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body-mass index — kg/m², mean (SD)</td>
<td>28.5 (7.1)</td>
<td>29.0 (6.7)</td>
</tr>
<tr>
<td>Systolic BP — mm Hg, mean (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>145 (24)</td>
<td>145 (24)</td>
</tr>
<tr>
<td>Diastolic BP — mm Hg, mean (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>74 (14)</td>
<td>74 (15)</td>
</tr>
<tr>
<td>Hemoglobin — g/dL, mean (SD)</td>
<td>10.6 (1.4)</td>
<td>10.5 (1.4)</td>
</tr>
<tr>
<td>Serum ferritin — μg/L, median (LQ, UQ)</td>
<td>214 (132, 305)</td>
<td>217 (137, 301)</td>
</tr>
<tr>
<td>TSAT — %, median (LQ, UQ)</td>
<td>20 (16, 24)</td>
<td>20 (16, 24)</td>
</tr>
<tr>
<td>CRP — mg/L, median (LQ, UQ)</td>
<td>6.0 (3.3, 13.9)</td>
<td>7.0 (4.0, 15.0)</td>
</tr>
<tr>
<td>ESA dose — IU/wk, median (LQ, UQ)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8000 (5000, 10,000)</td>
<td>8000 (5000, 12,000)</td>
</tr>
<tr>
<td>ACE inhibitor/ARB at baseline</td>
<td>25.3%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Phosphate binders at baseline</td>
<td>36.0%</td>
<td>40.9%</td>
</tr>
</tbody>
</table>
Baseline ESA

- Darbepoetin alfa: 53.6%
- Epoetin alfa: 25.1%
- Epoetin beta: 17.3%
- Epoetin theta: 0.3%
- Methoxy polyethylene glycol-epoetin beta: 3.7%
Cumulative Iron Dose

Mean Cumulative IV Iron (mg)

Time from Randomization (months)

Proactive, high-dose iron

Reactive, low-dose iron

Median cumulative doses at 1 year: 3.8 g vs 1.8 g

Median monthly doses: 264 mg vs 145 mg

$P < 0.001$
Serum Ferritin Concentration

Proactive, high-dose iron

Reactive, low-dose iron

$P < 0.001$
(Treatment effect)

Mean Ferritin (μg/L) Proactive, high-dose iron

Time from Randomization (months)
Cumulative ESA Dose

Median monthly doses reduced by 19.4%

Mean Cumulative ESA Dose (1000 IU)

Proactive, high-dose iron

Reactive, low-dose iron

P<0.01

Median monthly doses reduced by 19.4%
Death, MI, Stroke, or HF Hospitalization
(Primary Endpoint)

Hazard ratio, 0.85 (95% CI, 0.73–1.00)
Noninferiority $P<0.001$
Superiority $P=0.04$

Proactive, high-dose iron
Reactive, low-dose iron
Subgroup Analysis: Primary Endpoint

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Proactive, High-Dose Iron</th>
<th>Reactive, Low-Dose Iron</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no. of events/total no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants</td>
<td>320/1093 (29.3)</td>
<td>338/1048 (32.3)</td>
<td>0.85 (0.73–1.00)</td>
<td></td>
</tr>
<tr>
<td>Duration of dialysis treatment at enrollment</td>
<td></td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>&lt;5 months</td>
<td>139/499 (27.9)</td>
<td>146/487 (30.0)</td>
<td>0.88 (0.69–1.11)</td>
<td></td>
</tr>
<tr>
<td>≥5 months</td>
<td>181/594 (30.5)</td>
<td>192/561 (34.2)</td>
<td>0.84 (0.68–1.03)</td>
<td></td>
</tr>
<tr>
<td>Dialysis access</td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Dialysis catheter</td>
<td>137/452 (30.3)</td>
<td>159/432 (36.8)</td>
<td>0.77 (0.61–0.97)</td>
<td></td>
</tr>
<tr>
<td>AV fistula</td>
<td>183/641 (28.6)</td>
<td>179/616 (29.1)</td>
<td>0.93 (0.76–1.14)</td>
<td></td>
</tr>
<tr>
<td>Baseline diabetes</td>
<td></td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Yes</td>
<td>182/490 (37.1)</td>
<td>193/453 (42.6)</td>
<td>0.83 (0.67–1.01)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>138/603 (22.9)</td>
<td>145/595 (24.4)</td>
<td>0.90 (0.71–1.13)</td>
<td></td>
</tr>
</tbody>
</table>

0.6 0.7 0.8 0.9 1.0 1.1 1.2
Proactive, High-Dose Better Reactive, Low-Dose Better
Primary Endpoint Components\textsuperscript{a}
as Recurrent Events

Death from any cause, MI, stroke, and hospitalization for HF.

Recurrent events plotted in the form of mean frequency functions using the method of Ghosh and Lin (\textit{Biometrics}. 2000;56:554-562.).

Rate ratio, 0.77 (95\% CI, 0.66–0.92)  
\(P=0.0027\)

\textsuperscript{a}Death from any cause, MI, stroke, and hospitalization for HF.

Recurrent events plotted in the form of mean frequency functions using the method of Ghosh and Lin (\textit{Biometrics}. 2000;56:554-562.).
Death from Any Cause

Hazard ratio, 0.84 (95% CI, 0.71–1.00)
P=0.054
## Subgroup Analysis: All-cause Death

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Proactive, High-Dose Iron</th>
<th>Reactive, Low-Dose Iron</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of dialysis treatment at enrollment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 months</td>
<td>246/1093 (22.5)</td>
<td>269/1048 (25.6)</td>
<td>0.74 (0.57–0.96)</td>
<td>0.84 (0.71–1.00)</td>
</tr>
<tr>
<td>≥5 months</td>
<td>143/594 (24.1)</td>
<td>153/561 (27.3)</td>
<td>0.94 (0.74–1.18)</td>
<td></td>
</tr>
<tr>
<td><strong>Dialysis access</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis catheter</td>
<td>102/452 (22.6)</td>
<td>127/432 (29.4)</td>
<td>0.74 (0.57–0.96)</td>
<td>0.84 (0.65–1.10)</td>
</tr>
<tr>
<td>AV fistula</td>
<td>144/641 (22.5)</td>
<td>142/616 (23.1)</td>
<td>0.94 (0.74–1.18)</td>
<td>0.86 (0.66–1.11)</td>
</tr>
<tr>
<td><strong>Baseline diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>138/490 (28.2)</td>
<td>149/453 (32.9)</td>
<td>0.83 (0.66–1.05)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>108/603 (17.9)</td>
<td>120/595 (20.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Cardiovascular Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Proactive, High-Dose IV Iron (N=1093) n (%)</th>
<th>Reactive, Low-Dose IV Iron (N=1048) n (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal or nonfatal MI, fatal or nonfatal stroke, or hospitalization for HF</td>
<td>149 (13.6)</td>
<td>168 (16.0)</td>
<td>0.80 (0.64–1.00)</td>
<td>0.049</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>78 (7.1)</td>
<td>102 (9.7)</td>
<td>0.69 (0.52–0.93)</td>
<td>0.015</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>34 (3.1)</td>
<td>35 (3.3)</td>
<td>0.90 (0.56–1.44)</td>
<td>0.663</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>51 (4.7)</td>
<td>70 (6.7)</td>
<td>0.66 (0.46–0.94)</td>
<td>0.023</td>
</tr>
</tbody>
</table>
Fatal or nonfatal MI

Hazard ratio, 0.69 (95% CI, 0.52–0.93)
P = 0.015

Numbers at risk:
Proactive  1093  819  574  202  30
Reactive  1048  753  517  196  22
Fatal or nonfatal stroke

Hazard ratio, 0.90 (95% CI, 0.56–1.44)
P = 0.663

Numbers at risk:
Proactive: 1093, 831, 600, 219, 33
Reactive: 1048, 778, 546, 213, 22
Heart failure hospitalisation

Hazard ratio, 0.66 (95% CI, 0.46–0.94)
P = 0.023

Numbers at risk:
Proactive 1093 834 586 215 32
Reactive 1048 768 532 205 22
Hemoglobin Concentration

Proactive, high-dose iron

Reactive, low-dose iron

$P<0.001$ through month 12
(Treatment effect)
Blood Transfusions

Hazard ratio, 0.79 (95% CI, 0.65–0.95)

$P=0.014$
## Safety

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Proactive, High-Dose IV Iron (N=1093) n (%)</th>
<th>Reactive, Low-Dose IV Iron (N=1048) n (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular access thrombosis</td>
<td>262 (24.0)</td>
<td>218 (20.8)</td>
<td>1.15 (0.96–1.38)</td>
<td>0.12</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>651 (59.6)</td>
<td>616 (58.8)</td>
<td>1.01 (0.90–1.12)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hospitalization for infection</td>
<td>323 (29.6)</td>
<td>307 (29.3)</td>
<td>0.99 (0.82–1.16)</td>
<td>0.92</td>
</tr>
<tr>
<td>Infection episodes</td>
<td>508 (46.5)</td>
<td>477 (45.5)</td>
<td>0.98 (0.87–1.11)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Proactive, High-Dose Better

Reactive, Low-Dose Better
Conclusions

In patients undergoing maintenance HD, a proactive, high-dose regimen of IV iron (relative to a reactive, low-dose regimen):

• Significantly reduced the risk of the primary outcome of death or nonfatal CV events
• Reduced the risk of MI and hospitalization for HF
• Was associated with a significant benefit in a recurrent event analysis
• Reduced ESA dose (19.4%) and transfusion rate (21%)
• Did not cause an increased risk of infection or hospitalization