

## **Intravenous iron dosing and infection risk in hemodialysis patients: a pre-specified secondary analysis of the PIVOTAL trial**

Iain C. Macdougall<sup>1</sup>, Sunil Bhandari<sup>2</sup>, Claire White<sup>1</sup>, Stefan D. Anker<sup>3</sup>, Kenneth Farrington<sup>4</sup>, Philip A. Kalra<sup>5</sup>, Patrick B. Mark<sup>6</sup>, John J. V. McMurray<sup>6</sup>, Chante Reid<sup>1</sup>, Michele Robertson<sup>7</sup>, Charles R.V. Tomson<sup>8</sup>, David C. Wheeler<sup>9</sup>, Christopher G. Winearls<sup>10</sup>, Ian Ford<sup>7</sup> on behalf of the PIVOTAL investigators and committees

<sup>1</sup>Department of Renal Medicine, King's College Hospital, Denmark Hill, London, UK; <sup>2</sup>Hull University Teaching Hospitals NHS Trust and Hull York Medical School, Hull, UK; <sup>3</sup>Division of Cardiology and Metabolism, Department of Cardiology (CVK); and Berlin-Brandenburg Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin Berlin, Germany; <sup>4</sup>Lister Hospital, Stevenage, UK, and University of Hertfordshire, Hertfordshire, UK; <sup>5</sup>Salford Royal Hospital, Salford, UK; <sup>6</sup>British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; <sup>7</sup>Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK; <sup>8</sup>Freeman Hospital, Newcastle upon Tyne, UK; <sup>9</sup>University College London, London, UK and George Institute for Global Health, Sydney; <sup>10</sup>Oxford Kidney Unit, The Churchill, Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

A complete list of the Proactive IV irOn Therapy in haemodiAlysis patients (PIVOTAL) investigators and committee members is provided in the Supplementary Appendix / at the end of the paper.

**Running title:** Infections with IV Iron in PIVOTAL

**Keywords:** chronic kidney disease; hemodialysis; intravenous iron; infections; randomized trial

Corresponding author: Professor Iain Macdougall

Address: Department of Renal Medicine, King's College Hospital, London SE5 9RS, UK

Telephone: +44-203-299-6233

E-mail: [iain.macdougall11@gmail.com](mailto:iain.macdougall11@gmail.com)

## **Significance statement**

Previous experimental and observational data have raised concerns that intravenous iron could increase the risk of infections. In the PIVOTAL trial, 2141 hemodialysis patients were randomized to either a high-dose or a low-dose intravenous iron regimen, and there was no evidence of an increased incidence of infection when analyzed as ‘All infections’, ‘Hospitalization for infections’, and ‘Death from infection’. Given the potential cardiovascular benefits seen in PIVOTAL, this analysis provides reassurance for administering higher doses of IV iron than are currently given in many units worldwide.

## **Abstract**

### **Background**

There are concerns about an increased risk of infections with intravenous iron. The PIVOTAL trial randomized 2141 patients undergoing maintenance hemodialysis for end-stage kidney failure to a high-dose or a low-dose intravenous iron regimen, with a primary composite outcome of all-cause death, heart attack, stroke, or heart failure hospitalization. Comparison of infection rates between the two groups was a pre-specified secondary analysis.

### **Methods**

Secondary endpoints included any infection, hospitalization for infection, and death from infection; cumulative event rates were calculated for all three endpoints. The interaction between IV iron dose and vascular access (fistula versus catheter) was also interrogated.

### **Results**

There was no difference in event rates (63.3 per 100 patient years high-dose versus 69.4 low-dose) for “all infections” (46.5% versus 45.5%; HR 0.98; CI 0.87, 1.11; p=0.80) and hospitalization for infection (HR 0.99; CI 0.82, 1.16; p=0.92) between the two groups. Compared to patients with an arteriovenous fistula, patients dialyzing via a catheter had a higher incidence of having any infection, hospitalization for infection, or fatal infection, but there was no impact of IV iron dosing on these outcomes.

## **Conclusions**

Infection rates were identical in the high-dose and low-dose IV iron groups. There was a strong association between the risk of a first cardiovascular event and a recent infection. There were no consistent relationships between iron dose, ferritin/TSAT and risk of infection.

## INTRODUCTION

Intravenous iron is widely used to treat iron deficiency, either when oral iron has failed to correct an iron deficit or is causing unacceptable side-effects. Furthermore, in patients receiving maintenance hemodialysis<sup>1</sup> and in those with heart failure,<sup>2</sup> it has become incorporated into standard-of-care. However, there are safety concerns with this treatment.<sup>3</sup> Because this mode of administration bypasses the normal physiological hepcidin-regulated process of iron absorption from the gut,<sup>4</sup> there is the potential for iatrogenic iron overload, which is associated with an increased infection risk. There have also been concerns about the potential for intravenous iron to exacerbate infections more acutely (notably gram negative organisms, mycobacteria, fungi, *Yersinia* sp), both by enhancing bacterial proliferation and by reducing natural defense mechanisms.<sup>5</sup> Several studies have shown that within hours of intravenous administration, there is a reduction in bacterial killing by neutrophils.<sup>6</sup> Observational studies examining the relationship between intravenous iron administration and infections have produced conflicting results.<sup>7-10</sup> Whilst some support an increased risk,<sup>7,8</sup> others do not.<sup>9,10</sup> A meta-analysis of 78 randomized controlled trials of intravenous iron compared to oral iron or no iron supplementation for treatment of anemia or prevention of blood transfusion suggested that intravenous iron was associated with a significantly higher incidence of infection compared with either oral iron or no iron supplementation amongst 4400 patients in 24 studies (RR; 95% CI): 1.33; 1.10-1.64).<sup>11</sup> A subsequent meta-analysis in dialysis patients found no association between an increased incidence of infection with intravenous iron, although this included only four studies, all of which were small and of short duration.<sup>12</sup>

The Proactive IV irOn Therapy in hemodiALysis patients (PIVOTAL) study, the largest randomized controlled trial of iron therapy in any patient population,<sup>13</sup> provided an ideal

opportunity to examine infection risk with two different treatment strategies with intravenous iron. In this trial, the safety and efficacy of a proactive, high-dose intravenous iron regimen, compared with a reactive, low-dose intravenous iron regimen, were examined in 2141 hemodialysis patients, followed up for a median of 2.1 years (maximum 4.4 years). Although the primary endpoint was a composite of all-cause death and non-fatal cardiovascular events, key safety secondary endpoints focused on infection risk. The statistical analysis plan pre-specified analysis of the infection secondary endpoints.<sup>13</sup>

## **METHODS**

A full description of the study methods, including the study protocol and statistical analysis plan has previously been reported,<sup>13, 14</sup> and is available at NEJM.org.<sup>13</sup> In brief, 2141 patients were randomized to a high-dose (400 mg monthly, with a cut-off ferritin of 700 µg/L and/or TSAT of 40%) or a low-dose (0 to 400 mg monthly) iron regimen. Importantly, the protocol instructed investigators to withhold iron if the patient developed a new infection deemed sufficient to contraindicate the use of intravenous iron. In such cases, iron therapy was resumed when the investigator judged it safe. Patients with active infection at the time of recruitment were also excluded from the trial. Follow-up was for a median of 2.1 years (maximum 4.4 years). The median cumulative iron dose at one year was 3.8 g in the high-dose arm and 1.8 g in the low-dose arm. The median monthly iron doses in the respective groups were 264 mg versus 145 mg.<sup>13</sup>

Safety secondary endpoints included (i) any infection, (ii) hospitalization for infection, and (iii) death from infection. Any infection was determined from investigator judgement, and included patients with mild respiratory, urinary, or catheter infections not considered severe enough to

require hospitalization, but also including all infections causing hospitalization or death. Hospitalization for infection was defined as an admission to hospital caused by an episode of infection, and lasting  $\geq 24$  hours. Death from infection was determined from the investigator serious adverse event reports, and was adjudicated by the study endpoint adjudication committee.

### ***Rates of infectious events***

Event rates (overall percentages and per 100 patient years) were calculated split by randomized treatment group for each of these infection endpoints, adjusting for the competing risk of death. Cumulative incidence plots were also constructed for each of these endpoints.

### ***Impact of dialysis catheter versus arteriovenous fistula***

Because infection rates (usually *Staphylococcus* sp.) are more common in patients using dialysis catheters compared with those relying on native arteriovenous fistulae,<sup>15</sup> the association between type of vascular access and infection rates was also examined. Type of vascular access was recorded monthly on the electronic case record form during the trial. To simplify the analysis, vascular access was recorded as ‘catheter at baseline and for every month of the study follow-up’ versus ‘arteriovenous fistula at baseline and for every month of the study follow-up’, thus excluding any patients who had periods using a catheter and periods using a fistula. Cumulative incidence functions were determined for each endpoint adjusting for the competing risk of death.

### ***Association between iron dose, most recent ferritin and TSAT levels, and infectious event***

We created time-varying covariates specifying at a given point in time the most recent iron dose and the current total iron dose. We then determined the association between each of these variables and the outcome of a first infection in a time varying Cox regression model separately in each treatment group adjusting for baseline stratification variables defined by diabetes status, time on dialysis and vascular access status. These analyses were repeated for the outcome of hospitalized infection. The analysis for iron dose and infectious event was repeated for most recent ferritin and TSAT levels.

### ***Association between a recent infection and risk of a first cardiovascular event***

The association between a recent infection and risk of a first cardiovascular event was investigated using infection in the previous 30 days as a time-varying covariate, in a Cox regression model adjusted for treatment group and baseline stratification variables (defined by diabetes status, time on dialysis and vascular access status). (Figure 1). Cardiovascular events were adjudicated by the trial endpoint adjudication committee blinded to the treatment assignment. The analysis was repeated for infections requiring hospitalization, and for any infection. Results reported included hazard ratios, 95% confidence intervals and p-values.

### ***Characterization/Identification of infectious agent***

In the vast majority of infections reported, particularly those not requiring hospitalization, (but also, for example, in patients hospitalized for pneumonia), no causal infectious agent was identified via culture of fluid, tissue or blood. Infections were classified according to main organ primarily involved. Where an infectious agent was identified, these were subdivided into Gram-

positive bacteria, Gram-negative bacteria, viruses, and fungi or parasites. Further data on specific organisms was also recorded when available.

## RESULTS

### *Rates of infectious events*

For ‘All infection episodes’, there were 508 first events (46.5%) in the proactive high-dose arm versus 477 first events (45.5%) in the reactive low-dose arm (HR 0.98; CI 0.87, 1.11; p=0.80) (Figure 2). This represented an incidence of 63.3 per 100 patient years for the high-dose arm versus 69.4 per 100 patient years for the low-dose arm. Corresponding results for ‘Hospitalizations for infections’ were 323 first events (29.6%) in the proactive high-dose arm versus 307 first events (29.3%) in the reactive low-dose arm (HR 0.99; CI 0.82, 1.16; p=0.92). For ‘Death from infections’, there were 46 events (4.21%) in the proactive high-dose arm versus 41 first events (3.91%) in the reactive low-dose arm (HR 1.04; CI 0.69, 1.59; p=0.84).

Cumulative event curves for ‘all infection episodes’ were not distinguishable between the high-dose versus low-dose treatment assignment arms (Figure 3). 20% of the patients had a first event within the first 6 months, 40% had a first event by 1.5 years, and by 3.5 years, 60% of patients had an infection episode. For ‘hospitalized infections’, 20% of the patients had a first event within the first year, and 40% had a first event by 3.5 years, with no evidence of a difference

between the two groups. For ‘fatal infections’, the event rate was low with no evidence of a difference between the groups, with most deaths occurring after one year of follow-up.

### ***Infection rates for dialysis catheter versus arteriovenous fistula patients***

Of the 2141 patients in the study, 260 had a dialysis catheter throughout the entire study period, compared with 946 patients who had an arteriovenous fistula throughout the duration of the study. Cumulative event curves for each of the three infection endpoints are shown in Figure 4.

As might be expected, compared to patients with an arteriovenous fistula, patients with a catheter had a higher incidence of having any infection (HR: 1.57; 95% CI: 1.27 - 1.94;  $p < 0.001$ ), a higher incidence of hospitalization for an infection (HR: 1.60; 95% CI: 1.22 - 2.09;  $P < 0.001$ ), and a higher risk of having a fatal infection (HR 2.33; 95% CI: 1.28 - 4.25;  $p < 0.001$ ).

When the risk of infections with ‘catheter only’ versus ‘fistula only’ was compared in relation to the treatment assignment arm, no differences were seen. Thus, patients who were dialyzed on a catheter throughout the entire period of the study had a similar risk of contracting an infection with high-dose iron versus low-dose iron; the same is true for patients dialyzing on an arteriovenous fistula for the entire study (Figures 5 and 6), and this held true for all three infection endpoints.

### ***Association between indices reflecting iron status and infectious event/outcome***

There was no evidence of an association between iron status and infection outcomes. The hazard ratios, 95% CIs, and p-values are given per 100 unit higher ferritin level and per 5 unit higher TSAT level (Table 1).

### ***Association between a recent infection and risk of a first cardiovascular event***

In the time-updated covariate-adjusted analysis, there were strong associations between the risk of a first cardiovascular event and any infection in the previous 30 days (HR 2.83, 95% CI 2.04, 3.92,  $p < 0.0001$ ); the same was true for hospitalization for infection (HR = 2.74, 95% CI 1.54, 4.88,  $p = 0.0006$ ).

### ***Characterization of infectious agent***

In total, there were 1837 documented infection episodes for any infection. Grouped by organ involvement, 40.2% were of the respiratory tract; 19.4% unclassified; 20.3% skin and soft tissue and 12.3% urinary tract related. A total of 144 episodes had an organism identified (64 Gram-positive; 58 Gram-negative; and 22 viral). For those infections leading to hospitalization, there was a total of 1130 episodes: 39.4% respiratory; 15.7% sepsis (no specific organ characterized); 8.6 % soft tissue or skin and 11.7% unclassified. In this case there were a total of 97 events (23 Gram-positive; 32 Gram-negative; 39 viral; and 3 fungal/parasitic). Hence, where the infectious agent was identified, similar proportions of Gram-positive organisms, Gram-negative organisms, and viral agents were seen (Figure 7).

## DISCUSSION

The PIVOTAL trial showed no impact of the higher dosing intravenous iron protocol on infection incidence in a large hemodialysis population. Despite the high-dose iron arm receiving more than double the dose of intravenous iron over the first year and nearly double the median monthly intravenous iron dose overall, no increase in infection incidence was observed, compared with the low-dose iron group. Three infection endpoints were assessed ('All infections', 'Hospitalizations for infections', and 'Fatal infections'), and the consistency of the findings across all of these provides reassurance that there is no impact of administering higher doses of intravenous iron on incidence of infections.

These findings are at variance with multiple reports in the experimental literature suggesting that iron might enhance bacterial and fungal proliferation,<sup>5</sup> and also reduce bacterial defense mechanisms.<sup>6</sup> Using the same IV iron preparation that was used in PIVOTAL (iron sucrose), Deicher et al<sup>6</sup> found that within the first two hours of dialysis, the percentage of *E. coli* killed by neutrophils significantly decreased in the group randomized to IV iron versus no iron. Observational studies examining the relationship between IV iron administration and infections have produced conflicting results, with some for, and others against, an association.<sup>7-10</sup> Several previous reports have indicated that patients dialyzing via a catheter have a greatly enhanced infection risk compared to those using an arteriovenous fistula.<sup>15</sup> Similar findings were obtained in PIVOTAL, with significant increases in all three infection endpoints. However, the trial also allowed us to examine whether there was any impact of iron dosing on the infection risk in relation to vascular access. In both subpopulations of patients (catheter only and fistula only), there was no impact of iron dosing on the incidence of infection across all three endpoints; this

may be reassuring for certain subsets of vulnerable patients such as the frail elderly dialyzing via long-term catheters.

The design of the study also allowed us to examine whether there was any association between an infection episode and the subsequent cardiovascular event, which has been reported in a number of observational studies outside the dialysis setting.<sup>16-18</sup>

An analysis of the ARIC (Atherosclerosis Risk in Community) study,<sup>16</sup> for example, showed that both inpatient and outpatient infections appeared to be a trigger for a cardiovascular event. In 1312 incident coronary heart disease and 727 incident stroke cases, the 30 days odds ratio for the event following an inpatient infection was 8.39 (4.92-14.41) and outpatient infection 2.69 (2.14-3.37) compared to a control period.

In a non-dialysis CKD prospective cohort study (Canadian Study of Prediction of Risk and Evolution to Dialysis, Death and Interim Cardiovascular Events Over Time; CanPREDDICT), Cheikh Hassan et al<sup>17</sup> found that infection (i.e. positive culture, use of antibiotics, or hospitalization for infection) was associated with an increased risk of cardiovascular events, end-stage kidney disease and mortality (median follow-up 3.5 years).

In the PIVOTAL trial, we confirmed this association in a hemodialysis population randomized to two different IV iron regimens. The strengths of this analysis include the creation of a model capturing only infection episodes within the previous 30 days, and using data collected prospectively via an electronic case record form and via adjudicated cardiovascular endpoints. As with all the previous studies examining this association, this does not prove causality. An alternative explanation is that patients at risk of a future cardiovascular event are more susceptible to infections, although this has less biological plausibility.

The lack of any impact of the exploratory analysis of iron dose on infection risk is perhaps no surprise. Since there was no effect overall in the randomized study, it would perhaps have been surprising to have found any significant association in these analyses. The same is true with the analysis of iron markers on infection risk. Because the randomized treatment induced significant differences in ferritin and TSAT between the groups and there was no difference in infections, there is no evidence of a causal relationship between ferritin concentrations or TSAT and infection. Hence, any associations in the analyses can be attributed to reverse causality (during inflammatory states, the serum ferritin increases as an acute phase protein, and the transferrin saturation is reduced). Infection leads to raised ferritin and reduced TSAT, and hence one might have expected a recent raised ferritin or lower TSAT observed during an evolving infection to be associated with an increased risk of subsequent infection. Given a possibly longer delay in hospital admission after the initial onset of infection, the association might be stronger in hospitalized infection.

The strengths of this study include the study design (randomized controlled), the prospective data capture via an electronic database on a monthly basis, and the adjudication of cardiovascular events by an independent committee blinded to the treatment assignment. There are, however, a few limitations to the study. The first is that this is a secondary analysis and not the primary aim of the study, albeit the analysis was pre-specified. Although this is the largest randomized trial of iron in any patient population, it was conducted in a cohort of patients receiving hemodialysis. This is a very specific group of patients, with different infection risks and profiles from other patient groups. Given the incidence of infection in this group of patients, it was a good way to test the hypothesis of iron treatment on the risk of infection, but extrapolating the findings to other patient populations may not be justified. The follow-up, although adequate, also does not

allow extrapolation of results beyond the study period (median follow up 2.1 years; maximum follow-up 4.4 years). We acknowledge that only 56% of the population could be included in the analysis comparing patients with ‘Fistula only’ versus ‘Catheter only, and therefore there may potentially be issues with a lack of power to be certain of this finding. Finally, the study does not exclude the possibility that even higher doses of IV iron could be harmful in exacerbating infections, as has recently been found in an observational study.<sup>8</sup>

Nevertheless, the clarity of the findings across all three infection endpoints, as well as the closeness of the hazard ratios to 1.0 provides reassurance that patients recently starting hemodialysis exposed to an IV iron regimen of 400 mg of iron sucrose monthly, maintaining ferritin concentrations around 600-700 µg/L, were not at increased risk of infections compared to the less intensive iron strategy. Given the potential cardiovascular benefits seen in PIVOTAL,<sup>13</sup> this analysis provides further support for administering higher doses of IV iron than are currently given in many units worldwide.

**Authors’ Contributions:** I.C.M. conceived the study, contributed to the study design and statistical analysis plan, and developed the first draft of the manuscript, which was critically reviewed and revised by the other authors. All other authors contributed to the study design and statistical analysis plan. M.R. and I.F. provided biostatistical support.

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### **Disclosure Statements**

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kept abreast of the progress of the trial via regular study reports and newsletters. Vifor Fresenius Medical Care Renal Pharma Ltd also provided iron sucrose for the trial, free of charge.

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## Appendix

### PIVOTAL trial sites and investigators

#### England

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*Basildon & Thurrock Hospital*, Basildon: Georgia Winnett; *Bradford Teaching Hospital*, Bradford: Habib Akbani; *Churchill Hospital*, Oxford: Christopher Winearls; *City General Hospital*, Stoke-on-Trent: Julie Wessels; *Coventry University Hospital*, Coventry: Waqar Ayub; *Derriford Hospital*, Plymouth: Andrew Connor; *Freeman Hospital*, Newcastle: Alison Brown; *Gloucestershire Royal Hospital*, Gloucestershire: Jim Moriarty; *Guy's & St Thomas' Hospital*, London: Paramit Chowdury; *Hammersmith Hospital*, London: Megan Griffiths; *Heartlands Hospital*, Birmingham: Indranil Dasgupta; *Hull Royal Infirmary*, Hull: Sunil Bhandari; *Kent & Canterbury Hospital*, Canterbury: Timothy Doulton; *King's College Hospital*, London: Iain Macdougall; *Leicester General Hospital*, Leicester: Jonathan Barratt; *Lister Hospital*, Stevenage: Enric Vilar; *Manchester Royal Infirmary*, Manchester: Sandip Mitra; *New Cross Hospital*, Wolverhampton: Babu Ramakrishna, Johann Nicholas; *Norfolk & Norwich Hospital*, Norwich: Calum Ross; *Northern General Hospital*, Sheffield: Arif Khwaja; *Nottingham City Hospital*, Nottingham: Matt Hall; *Queen Alexandra Hospital*, Portsmouth: Adam Kirk; *Queen Elizabeth Hospital*, Birmingham: Stuart Smith, Mark Jesky, Clara Day; *Royal Berkshire Hospital*, Reading: Bassam Alchi; *Royal Cornwall Hospital*, Cornwall: Jon Stratton; *Royal Devon & Exeter Hospital*, Exeter: Helen Clarke; *Royal Free Hospital*, London: Stephen Walsh; *Royal Liverpool Hospital*, Liverpool: Rebecca Brown; *Royal London Hospital*, London: Kieran McCafferty; *Royal Preston Hospital*, Preston: Laurie Solomon; *Royal Shrewsbury Hospital*, Shrewsbury: Suresh Ramadoss, Babu Ramakrishna; *Royal Sussex Hospital*, Brighton: Kolitha Basanyake, Sarah Lawman; *Salford Royal Hospital*, Manchester: Phil Kalra; *Southend University Hospital*, Southend: Gowrie Balasubramaniam; *Southmead Hospital*, Bristol: Albert Power; *St George's Hospital*, London: Debasish Banerjee; *St Helier Hospital*, Carlshalton: Pauline Swift; *St James' Hospital*, Leeds: Matt Wellberry-Smith; *University Hospital*, Aintree: Christopher Goldsmith; *Wirral University Teaching Hospital*, Wirral: Thomas Ledson

#### Wales

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*Morriston Hospital*, Swansea: Ashraf Mikhail; *University Hospital*, Cardiff: Ruth Benzimra

#### Scotland

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*Ninewells Hospital*, Dundee: Samira Bell, Alison Severn; *Royal Infirmary of Edinburgh*, Edinburgh: John Neary; *Victoria Hospital*, Kirkcaldy: Arthur Doyle; *Western Infirmary*, Glasgow: Peter Thomson

## ***N. Ireland***

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*Altnagelvin Hospital*, Derry: Girish Shivashankar; *Antrim Area Hospital*, Antrim: Stephanie Bolton, Michael Quinn; *Belfast City Hospital*, Belfast: Peter Maxwell; *Daisy Hill Hospital*, Newry: John Harty

## **PIVOTAL Committees and Coordinating groups**

### **Steering Committee**

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Iain Macdougall (chair), Ian Ford (biostatistician), Stefan Anker, Sunil Bhandari, Ken Farrington, Phil Kalra, John McMurray, Charlie Tomson, David Wheeler, Christopher Winearls

### **Endpoint Adjudication Committee**

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John McMurray (chair), Eugene Connolly, Pardeep Jhund, Michael MacDonald, Patrick Mark, Mark Petrie, Matthew Walters

### **Independent Data Monitoring Committee**

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Alan Jardine (chair), Janet Peacock (biostatistician), Chris Isles, Donal Reddan

### **Independent Data and Biostatistical Centre, Robertson Centre for Biostatistics, University of Glasgow**

Ian Ford, Heather Murray, Kirsty Wetherall, Sharon Kean, Claire Kerr, Sarah Boyle, Robbie Wilson, Jane Aziz, Eleanor Dinnett, Amanda Reid, Claire Burton, Ross Clarke, Neil Hillen

### **Clinical Coordinating Centre, King's College Hospital, London**

Iain Macdougall, Claire White, Chante Reid, Sadiq Andani

## Legends to Figures

**Figure 1.** Schematic representation of the methodology used in the analysis of the association between a recent infection and risk of a first cardiovascular event. Infection in the previous 30 days was used as a time-varying covariate, in a Cox regression model adjusted for treatment group and baseline stratification variables (diabetes status, time on dialysis and vascular access status). Scenarios for 4 different patients shown. (CV = cardiovascular; Pt = Patient).

**Figure 2.** Comparison of number and percentage of events (\*expressed as hazard ratio), and number of recurrent events per 100 patient-years (†expressed as a rate ratio), for ‘All infections’ and ‘Hospitalization for infection’, and number and percentage of fatal infections (\*expressed as hazard ratio), between the high-dose intravenous iron group and the low-dose iron group.

**Figure 3.** Comparison of cumulative event curves between the high-dose intravenous iron group and the low-dose iron group for ‘All infections’, ‘Hospitalization for infection’, and ‘Death from infection’.

**Figure 4.** Comparison of cumulative event curves between patients dialyzing on a fistula only for the whole study versus those dialyzing on a catheter only for ‘All infections’, ‘Hospitalization for infection’, and ‘Death from infection’.

**Figure 5.** Comparison of cumulative event curves between patients dialyzing on a fistula only for the whole study versus those dialyzing on a catheter only for ‘All infections’, ‘Hospitalization for infection’, and ‘Death from infection’, shown separately for the high-dose group versus the low-dose group.

**Figure 6.** Forest plot showing hazard ratios and interaction P values for ‘All infections’ and ‘Hospitalization for infection’ for all subjects in the trial, and separated according to patients dialyzing on a fistula only for the whole study versus those dialyzing on a catheter only. Data are adjusted for stratification variables (vascular access, diabetic status, and time on dialysis).

**Figure 7.** Proportion of causal infectious organisms for all patients randomized in PIVOTAL where an infectious agent was identified.

Figure 1.

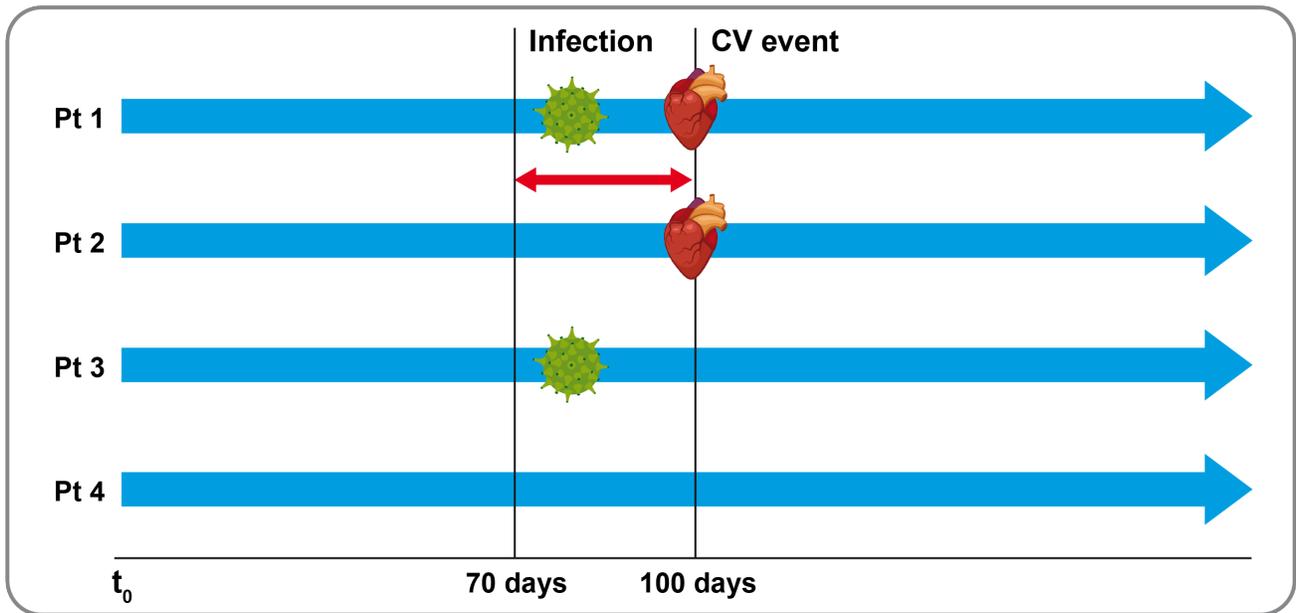


Figure 2.

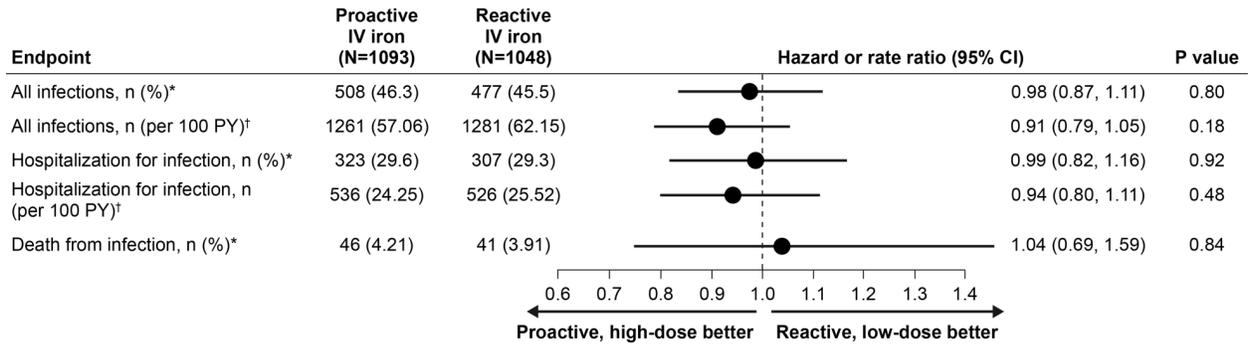


Figure 3.

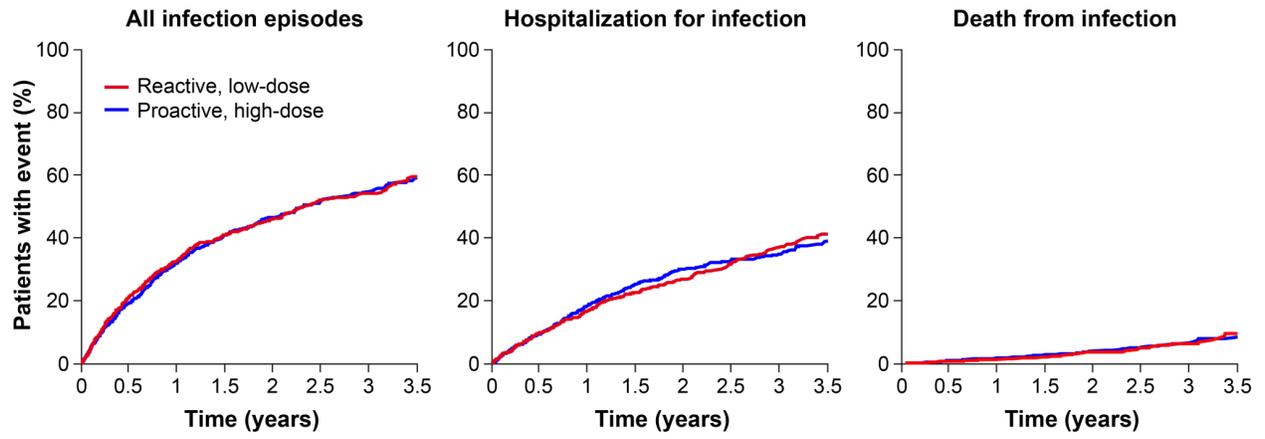


Figure 4.

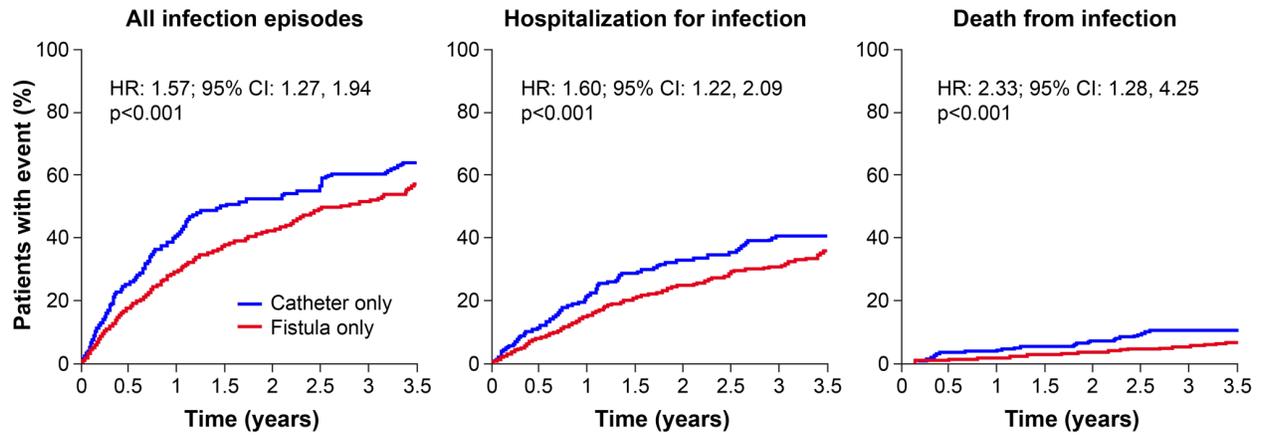


Figure 5.

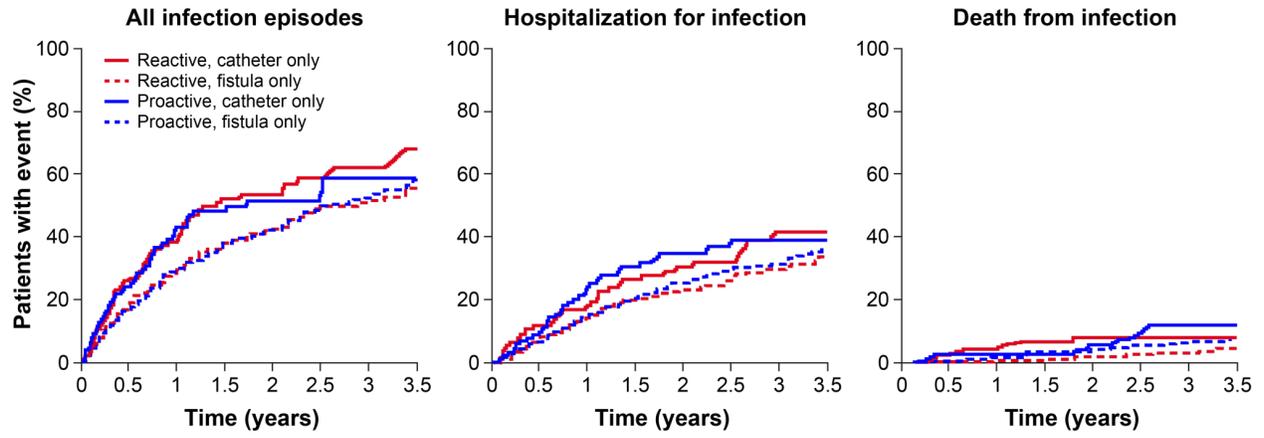


Figure 6.

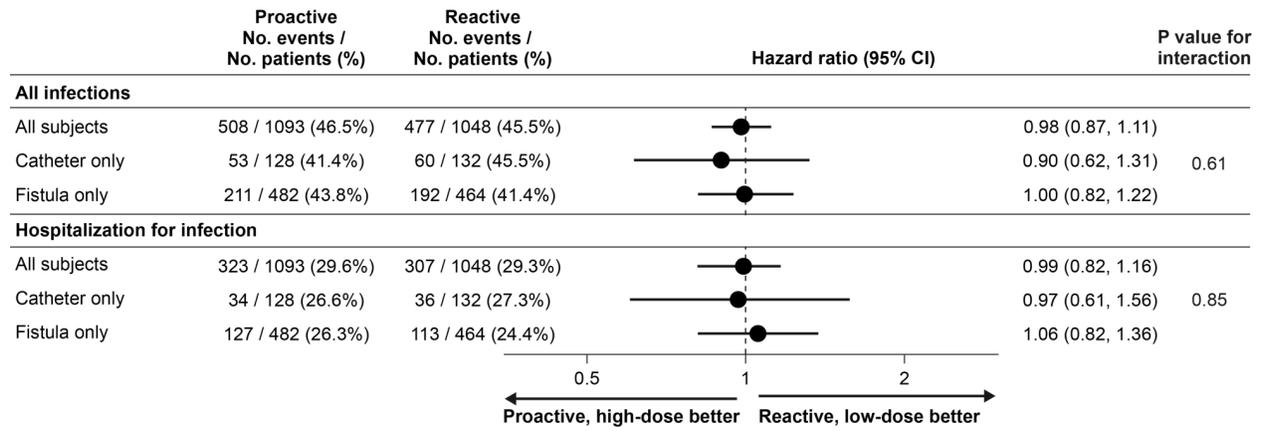
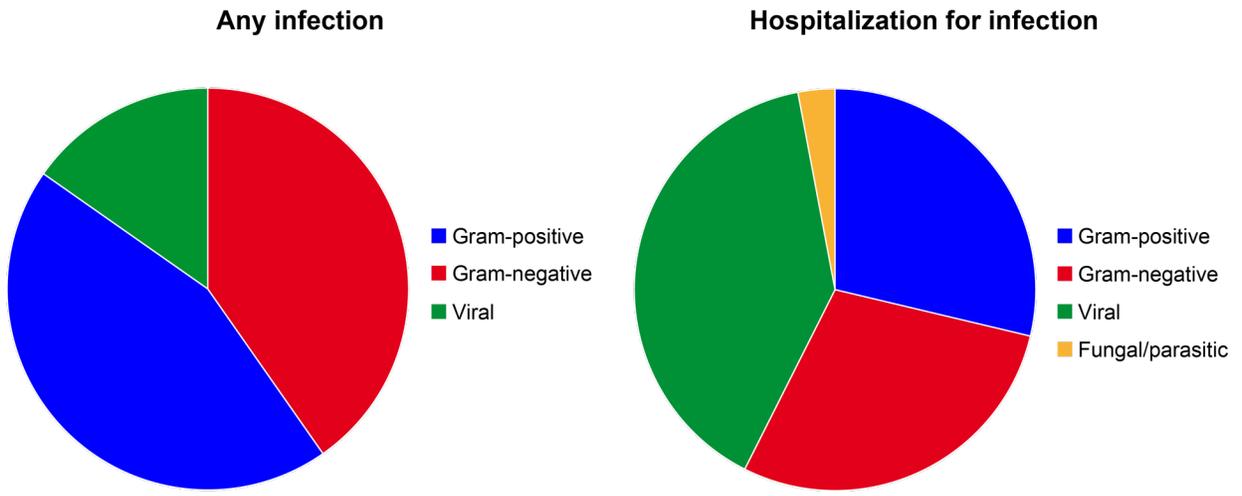


Figure 7.



**Table 1. Characteristics of patients at baseline by vascular access type**

<b>Variable</b>	<b>All subjects (n=2141)</b>	<b>Catheter at baseline (n=877)</b>	<b>Fistula/graft at baseline (n=1264)</b>	<b>P-value</b>
Age (years)	62.8 ( 15.01)	61.2 ( 15.69)	63.9 ( 14.41)	<0.001
Males	1398 ( 65.30%)	556 ( 63.40%)	842 ( 66.61%)	0.124
<b>Ethnicity</b>				
White	1698 ( 79.31%)	662 ( 75.48%)	1036 ( 81.96%)	<0.001
Black	190 ( 8.87%)	98 ( 11.17%)	92 ( 7.28%)	
Asian	185 ( 8.64%)	79 ( 9.01%)	106 ( 8.39%)	
Other	68 ( 3.18%)	38 ( 4.33%)	30 ( 2.37%)	
Duration of dialysis treatment (months)*	4.8 ( 2.83, 8.22)	4.3 ( 2.66, 7.11)	5.3 ( 2.98, 8.96)	<0.001
AF	164 ( 7.66%)	60 ( 6.84%)	104 ( 8.23%)	0.236
Heart failure	86 ( 4.02%)	36 ( 4.10%)	50 ( 3.96%)	0.863
Hypertension	1557 ( 72.72%)	609 ( 69.44%)	948 ( 75.00%)	0.005
hyperlipidaemia	535 ( 24.99%)	197 ( 22.46%)	338 ( 26.74%)	0.079
PVD	187 ( 8.73%)	83 ( 9.46%)	104 ( 8.23%)	0.319
MI	184 ( 8.59%)	64 ( 7.30%)	120 ( 9.49%)	0.075
Stroke	176 ( 8.22%)	69 ( 7.87%)	107 ( 8.47%)	0.621
Diabetes	950 ( 44.37%)	403 ( 45.95%)	547 ( 43.28%)	0.220
<b>Smoking status</b>				
Current	249 ( 11.63%)	111 ( 12.66%)	138 ( 10.92%)	0.466
Former	545 ( 25.46%)	220 ( 25.09%)	325 ( 25.71%)	
Never	1347 ( 62.91%)	546 ( 62.26%)	801 ( 63.37%)	
Weight (kg)	82.1 ( 20.96)	80.3 ( 21.16)	83.3 ( 20.73)	0.001
BMI (kg/m <sup>2</sup> )	28.7 ( 6.91)	28.2 ( 6.95)	29.1 ( 6.86)	0.003
SBP(mmHg)	144.7 ( 23.68)	147.6 ( 24.28)	142.8 ( 23.06)	<0.001
DBP(mmHg)	73.6 ( 14.80)	75.8 ( 15.16)	72.1 ( 14.36)	<0.001
Haemoglobin (g/L)	105.6 ( 13.74)	104.3 ( 13.98)	106.4 ( 13.50)	<0.001

Variable	All subjects (n=2141)	Catheter at baseline (n=877)	Fistula/graft at baseline (n=1264)	P-value
Ferritin(ug/L)*	216.0 (133.00, 304.00)	204.0 (127.00, 294.00)	225.0 (137.00, 312.00)	0.010
TSAT (%)*	20.0 ( 16.00, 24.00)	19.0 ( 15.00, 23.00)	20.0 ( 16.00, 24.00)	<0.001
CRP (mg/L)*	6.0 ( 3.70, 14.00)	6.5 ( 4.00, 14.00)	6.0 ( 3.50, 14.00)	0.331
Standardised monthly ESA dose*	8000.0 (5000.0, 12000)	8000.0 (6000.0, 12000)	6000.0 (4000.0, 10000)	0.006
Primary Cause of Kidney Disease				
Hypertension	235 ( 10.98%)	88 ( 10.03%)	147 ( 11.63%)	0.001
Diabetic Nephropathy	712 ( 33.26%)	319 ( 36.37%)	393 ( 31.09%)	
Glomerular Disease	394 ( 18.40%)	171 ( 19.50%)	223 ( 17.64%)	
Tubulointerstitial Disease	201 ( 9.39%)	83 ( 9.46%)	118 ( 9.34%)	
Renovascular Disease	147 ( 6.87%)	55 ( 6.27%)	92 ( 7.28%)	
Other	129 ( 6.03%)	59 ( 6.73%)	70 ( 5.54%)	
Polycystic Kidney Disease	117 ( 5.46%)	29 ( 3.31%)	88 ( 6.96%)	
Unknown	206 ( 9.62%)	73 ( 8.32%)	133 ( 10.52%)	
Proactive Randomised Treatment	1093 ( 51.05%)	449 ( 51.20%)	644 ( 50.95%)	0.910

- *For categorical variables number and percentage are reported*
- *For continuous variables mean and standard deviation are reported except for variables with an asterisk where median and inter-quartile range are presented*

**Table 2. Association between iron dose; ferritin; TSAT and risk of infection**

Association analyzed	Reactive low-dose iron group			Proactive high-dose iron group		
	HR	95% CI	P value	HR	95% CI	P value
Most recent IV iron dose (per 100 mg) and any infection	1.03	0.96, 1.10	0.41	1.02	0.97, 1.06	0.45
Current total IV iron dose (per 100 mg) and any infection	1.00	0.98, 1.01	0.42	1.00	0.99, 1.01	0.50
Most recent ferritin (per 100 $\mu\text{g/L}$ ) and any infection	1.04	0.98, 1.10	0.16	0.97	0.93, 1.01	0.12
Most recent TSAT (per 5%) and any infection	0.90	0.85, 0.96	0.0007	0.97	0.92, 1.01	0.15
Most recent IV iron dose (per 100 mg) and hospitalized infection	1.00	0.92, 1.08	0.95	1.05	0.99, 1.10	0.11
Current total IV iron dose (per 100 mg) and hospitalized infection	1.00	0.99, 1.02	0.45	1.00	0.99, 1.01	0.53
Most recent ferritin (per 100 $\mu\text{g/L}$ ) and hospitalized infection	1.08	1.03, 1.14	0.001	0.95	0.90, 1.00	0.037
Most recent TSAT (per 5%) and hospitalized infection	0.88	0.82, 0.95	0.0009	0.92	0.87, 0.98	0.0056