Reviewer’s report

**Title:** The importance of iron in long-term survival of maintenance hemodialysis patients treated with epoetin-alpha and intravenous iron: analysis of 9.5 years of prospectively collected data

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**Reviewer:** Anatole Besarab

**Reviewer’s report:**

The authors analyzed their experience with EPO and iron in 1774 HD patients over a 9+ year period to determine the influence of epoetin alfa and iron on patient survival. The mean Hb achieved averaged 11.6 g/dL and mean iron parameters for TSAT and ferritin were within KDOQI guidelines (1997-2006) period. As in most observational data bases, survival was actually better at levels above those currently recommended by the FDA (10-12 g/dL) with a weak effect from epoetin but a strong interaction with iron. Survival was best at a relatively high Hb, moderate iron administration and iron sufficiency.

The new finding in this study is the strong positive effect of iron on survival which has not been previously examined by others using large data bases from FMC or DaVita. URDRS data those not have this kind of granularity with respect to iron parameters nor with respect to the other laboratory parameters that make up the “case-mix-inflammation” complex. Previous studies focused more on excluding a harmful effect of iron. This study is interesting but like all others can not separate practice effects (i.e. the way we manage iron and ESAs) from the effects of concurrent processes in our patients that determine their response to our therapy.

The variables analyzed often were averaged over years and the authors did not include any analysis of the degree of variability in Hb or the iron saturation or the ESA doses on survival. This should perhaps be looked at in another analysis as the authors indicate at the end of their discussion section?

The discussion is a bit disjointed and should be condensed by at least a third. At a minimum the importance of iron should be explicitly stated before jumping in with analysis of the subheadings.

A. Major
1. I take issue with the comment that the NHCT, CHOIR, and CREATE, and Canadian LV remodeling studies were “relatively short-term” or did not examine mortality explicitly. Mortality was part of the composite end point and the studies were designed to see a difference in end-points based on the “available best estimates” present at the time of the design.
2. The studies with CERA were designed to maximize iron sufficiency. The characterization that “few reports on the effects of EPO and newer ESAs have
addressed the need for adequate iron” is improper. The authors are however correct that the guidelines have been too cautious about “proper” iron usage. Ref 15 actually has to be taken in the context of other papers by this group of authors and it should be noted that maximal survival in the DaVita data set occurs at a ferritin of 900, above the current recommended upper limit. This paper specifically does not caution about iron use but makes the point that ferritin is a bad marker of actual iron stores.

3. In the discussion, the authors again refer to the absence of iron in the CKD RCTs but in all fairness, delivering iron in these patients (as in CAPF/CCPD) is quite different from HD patients. I think all comments regarding whether iron was not appropriately given in these trials is not germane in the presentation at hand and should be removed.

4. There is no specifics given about the iron or EPO algorithms used at the three dialysis units other than they conformed with guidelines and with external pressures from CMS. For instance was iron sufficiency maintained by a load-hold approach or by a maintenance iron regimen?

5. In the analysis we are told that EPO doses and iron doses were administered and we are told of a dose conversion when patients participated in equivalence studies using other ESAs. However we are not told whether the protocol was thrice weekly i.v. epoetin alfa administration ~99% OF THE TIME. If the later, since iron was administered ~ 1/3 as often as epoetin alfa, it appears that “maintenance” was practiced most of the time?

6. It is expected that certain parameters will not be normally distributed but presentation of mean values in table 2 allows the reader to determine which way the skewness points.

7. It also would be useful to see an overall Kaplan Meier survival curve. Based on the # of EPO doses give, the average weeks of participation is 80.1 weeks which is much lower than the actual median weeks of survival (or time to censure).

8. Comorbid conditions could have had better granularity if there were 3-4 subgroups rather than 2, i.e. no comorbid conditions, 1-2, 3-4, > 4. Since HIV had such a bad prognosis during the time of the study (i.e. pre HAART) wonder whether it should not have been looked at separately. Would the multivariate model results changed if there was more or less granularity?

9. The effect of iron dose per month is to me, in part, a comorbidity effect of underlying illness. Requirements for more than 455 mg/mo of Fe indicate ongoing losses (usually GI, on occasion vascular access) and of course would be confounding by indication. The now iron group may have had specific characteristics different from the other 3 groups. Was this specifically looked for?

10. Again, when looking at the survival curves for iron, TSAT, and ferritin, what this reviewer would want to see on each graph is the amount of iron given to each subgroup over the time at risk. For instance did the lowest serum iron and TSAT groups receive the most or least iron compared to the high groups. Similarly for serum ferritin.

11. I am not certain I understand what the authors mean by EPO alone had no
effect on survival [page 12. last paragraph]. Was the effect a positive or negative one?

12. I could find no presentation of table 7 perhaps it was inadvertently cut in the operation that reduplicated the problem under Minor comments, item 11.

13. I would delete the entire 3rd paragraph under “hemoglobin: except the first sentence and combine it with the first sentence of the next. That paragraph can be condensed to the last 2 sentences.

14. On page 15, the whole paragraph on cytokines can be reduced.

B. Minor

1. INTRO: 2nd paragraph of the Background is peripheral to the population studies and can be eliminated.

2. I do not have reference 19 in front of me so the authors should summarize the characteristics in this paper.

3. Most readers will not know what the omnibus test for interaction (page 9, line 6) is.

4. Could the ethnic distribution have been broken out as: white/black/Hispanic/other?

5. In table 4, unable to determine the absolute # of subject with the reference value compared to the other value. Please provide!

6. The difference in survival at 1000 days was 75% vs. 60% in the low vs. high EPO tertiles. This is a 20% difference. I would not characterize this as “rather small” [page 10 last line].

7. Figure 3 looks impressive but this phenomenon is well known at this point and the figure can be deleted.

8. Fig 7 and table 5

9. Fig 8 and table 6

10. Table 6 has no data in 2 of the cells.

11. At the bottom of page 13, the first 4 sentences of the paragraph are repeated into the next page. “The

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

For the past 5-10 years, I have been a consultant, received honoraria, and performed clinical studies for all of the major manufacturer’s of ESAs as well as
perenteral iron. These include Amgen, Affymax, Roche, Fibrogen, Watson, American Regent, AMAG Pharma.