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Prognostic Significance of Erythropoiesis-Stimulating Agent Dose Requirements in PIVOTAL and its Implications for the Potential Mechanisms of IV Iron Benefit in Maintenance Haemodialysis Patients

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Background

PIVOTAL (Proactive IV Iron Therapy in Haemodialysis Patients trial) has shown that high-dose iron given proactively is superior to a low-dose reactive strategy with respect to the primary end-point of all-cause mortality (ACM) or nonfatal myocardial infarction, stroke, or heart failure hospitalisation. The underlying mechanism(s) remain unclear. Whilst attenuations in erythropoiesis-stimulating agent (ESA) dose requirements might explain the results, it has yet to be determined whether temporal ESA doses related to PIVOTAL outcomes. Moreover, whether the benefits of high-dose iron could have arisen via mechanisms unrelated to ESAs and erythropoiesis, such as mitochondrial augmentation, is unknown. We hypothesised that lower monthly ESA doses would relate to better PIVOTAL outcomes, but that higher iron doses would still associate with better outcomes even after accounting for ESA doses or haemoglobin (Hb) levels.

Methods

We undertook a post-hoc analysis using the entire PIVOTAL cohort (n=2141, mean±SD age 63±15yrs, 65% male). Univariable then multivariable stepwise linear regression assessed intervariable relations. Cox proportional hazards survival analyses were conducted with monthly ESA doses, iron doses, or Hb levels as time-varying covariates. The relation between ESA dose and outcome was depicted with restricted cubic spline plots.

Results

Median[IQR] standardised ESA dose at baseline was similar in the proactive (8000[5000, 10000] IU/week) and reactive (8000[5000, 12000] IU/week) arms with higher doses related to higher C-reactive protein, body mass index, phosphate binder use, dialysis via a graft, and lack of hypertension (all P<0.05). Over a median follow-up of 24[10, 33] months, proactive patients had lower median (25,980[17320, 43300] vs. 34,640[25980, 56290] IU/month) and cumulative (63,2180[259800, 1163471] vs. 76,2080[329080, 1437560] IU, Fig A) ESA doses, higher cumulative iron doses (5900[3400, 8200] vs. 3400[1500, 5200]mg), and ΔTSAT (6[-1, 13] vs 0[-5, 7]%). Hb levels increased more rapidly in proactive patients. Greater ESA dose reductions correlated to greater increases in albumin, higher cumulative iron doses, and lower blood transfusion needs (all P<0.05) after adjustment for treatment assignment. Primary end-point and ACM events occurred in 658(31%) and 515(24%) patients. In the total population, monthly ESA dose (per 100,000 IU; HR 1.007, P=0.04), monthly iron dose (per 100mg; HR 0.79, P<0.0001), age (HR 1.03, P<0.0001), and diabetes (HR 1.84, P<0.0001) independently predicted the primary end-point. Median monthly ESA dose was also prognostic despite adjustment for median monthly iron dose, with doses below the median (34,640 IU/month) linked to better outcomes (Fig B, C). For ACM, monthly ESA dose (per 100,000 IU; HR 1.008, P=0.02), monthly iron dose (per 100mg; HR 0.83, P<0.0001), age (HR 1.04, P<0.0001), and diabetes (HR 1.63, P<0.0001) were

independently predictive. In separate Cox models, monthly iron dose remained predictive of the primary end-point and ACM after adjustment for monthly Hb, age, and diabetes.

Conclusion

Decreased ESA requirements are associated with better outcomes in PIVOTAL, but higher iron doses remained protective even after accounting for monthly ESA doses or Hb levels. This suggests that mechanisms beyond ESA dosing and erythropoiesis might have contributed to the benefits of iron.