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IV iron dosing and infection risk in the PIVOTAL trial: a pre-specified secondary analysis

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Introduction

For the last three decades, numerous reports have raised concerns on the likelihood of increased risk of infections with IV iron administration, although the evidence has been obtained largely from laboratory studies and observational data. The Proactive IV irOn Therapy in haemodiALysis patients trial (PIVOTAL) compared the benefit/risk ratio of regular high-dose versus low-dose IV iron in haemodialysis patients, with the primary composite outcome of all-cause death, heart attack, stroke, or heart failure hospitalisation. One of the pre-specified secondary analyses was comparison of infection rates between the two groups.

Methods

2141 patients were randomised to a high-dose (400 mg monthly, with a cut-off ferritin of 700 ug/L and/or TSAT of 40%) or a low-dose (0 to 400 mg monthly) iron regimen. Follow-up was for a median of 2.1 years (maximum 4.4 years). Safety secondary endpoints included any infection, hospitalisation for infection, and death from infection. Cumulative event rates were calculated for all these three endpoints. 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. Time-varying covariates were also used to investigate the associations between iron dose, ferritin, and TSAT for first incidence of infection and for first hospitalisation for infection.

Results

There was no difference in cumulative event rates for any infection between the two groups (HR 0.98; CI 0.87, 1.11; p=0.80) (Figure). There were a 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 hospitalised infection (HR = 2.74, 95% CI 1.54, 4.88, p = 0.0006). There was no association between iron dose and risk of infection in either group, and no consistent association between serum ferritin or TSAT, and the risk of infection.

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 the risk of infection.