Untangling the Association between Anemia Treatment and Stroke Risk in CKD

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Randomized, controlled trials (RCTs) of erythropoietin-stimulating agents (ESAs) suggest an association between ESA dose and stroke, but it remains unclear whether the causal pathway is the ESA dose itself, target hemoglobin (Hgb), achieved Hgb, or comorbidities that may lead to ESA hyporesponsiveness. The most striking association was seen in the Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease (TREAT) (1), which demonstrated 1.92 increased incidence of stroke (P<0.001) among anemic subjects treated with darbepoetin to target Hgb of 13.5 g/dl versus those treated with placebo (rescue therapy with darbepoetin for Hgb<9.0 g/dl). The publication of TREAT was followed by a change in the US Food and Drug Administration (FDA) label for all ESAs, with a black box warning of “serious adverse cardiovascular reactions and stroke when [these agents are] administered to target a hemoglobin level of greater than 11 g/dl; no trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks” (2). Previously, Farfrey et al. (3) performed an RCT examining full (target Hgb = 13.5–14.5 g/dl) versus partial (target Hgb =9.5–11.5 g/dl) anemia correction among patients on incident hemodialysis; patients treated to the higher Hgb target experienced more cerebrovascular disorders (P=0.05). More recently, the Reduction of Events by Darbepoetin in Heart Failure RCT of patients with systolic heart failure and anemia confirmed 1.94 relative risk (RR) of stroke (95% confidence interval [95% CI], 1.43 to 2.63) among darbepoetin-treated (versus placebo-treated) subjects who would have met inclusion criteria for TREAT (4). Although the Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR) study (5) did not demonstrate increased stroke risk among patients with nondialysis CKD treated with epoetin alfa to target Hgb of 13.5 versus 11.3 g/dl, occurrence of the primary composite cardiovascular end point, which included stroke, was higher in the high-Hgb target arm (hazard ratio [HR], 1.34; 95% CI, 1.03 to 1.74). A secondary analysis of CHOIR (6) noted that patients achieving their Hgb target had better outcomes than those who failed to do so. Among subjects in the higher-Hgb target arm who achieved the Hgb target, no increased risk was associated with the higher Hgb level. The greatest cardiovascular risk accrued to those subjects requiring the highest epoetin alfa doses, irrespective of the target Hgb arm.

A natural experiment occurred due to the more restrictive United States ESA label and changes in ESA reimbursement for patients on dialysis in the United States beginning in 2011. Patients aged 66 years or older who were incident to dialysis January 2008 through December 2009 were compared in a retrospective cohort study with those who were incident to dialysis July 2011 through June 2013. Those in the later cohort had a lower rate of ESA use (92% versus 72%) in the month of dialysis initiation; this gap decreased but remained significant over the 24-month follow-up period. By the end of the follow-up period, mean ESA dose was approximately 40% lower in the later cohort than the earlier cohort. The HR for stroke was 0.77 in the later cohort (95% CI, 0.64 to 0.93); interestingly, this was the lowest HR for any outcome assessed, including composite major cardiovascular events, acute myocardial infarction, all-cause mortality, hospitalization for heart failure, and venous thromboembolism. Because this analysis comes from Medicare claims, there are no Hgb data, but the rate of blood transfusion was higher in the later cohort (HR, 1.09; 95% CI, 1.07 to 1.12; P<0.001), suggesting lower achieved Hgb (7).

The secondary analysis of CHOIR (6) seems to favor higher ESA dose over higher achieved Hgb level as the mechanism for increased cardiovascular risk (including stroke) in the RCTs. Further exploration into the heterogeneity of ESA responsiveness through retrospective analyses has revealed a clear association between the failure to achieve target Hgb levels with escalating ESA doses and adverse outcomes, including shorter time to death (8). It remains unclear whether this association is the consequence of the inflammatory and other serious conditions that produce ESA hyporesponsiveness or if the high ESA doses administered in affected patients are directly toxic. Studies that dissociate Hgb from ESA dose are required to address this question.

In this issue of Kidney360, Mark et al. (9) report the results of a prespecified secondary analysis of stroke incidence in the Proactive IV Iron in Hemodialysis Patients (PIVOTAL) trial. PIVOTAL was an RCT of proactive versus reactive intravenous iron strategies

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in 2141 patients on incident hemodialysis (<12 months) receiving ESAs with a mean follow-up of 2.1 years. The proactive group received 400 mg dialysis iron sucrose monthly unless serum ferritin was >700 ng/ml or transferrin saturation was >40%. The reactive group received 0–400 mg intravenous iron sucrose monthly to maintain serum ferritin ≥200 ng/ml and transferrin saturation ≥20%. ESA dose was titrated to maintain Hgb of 10–12 g/dl. The primary outcomes of PIVOTAL were previously reported (10), revealing comparable Hgb levels in the two groups and 19% ESA dose reduction in the proactive intravenous iron group. The primary safety end point was the composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death assessed in a time to first event analysis. There was a significant decrease in the primary composite end point among patients treated with the proactive intravenous iron regimen in both the intention-to-treat (HR, 0.85; 95% CI, 0.73 to 1.00; \( P < 0.001 \)) and the per-protocol (HR, 0.85; 95% CI, 0.73 to 0.99; \( P < 0.001 \)) analyses. In this original analysis (10), the rate of stroke was similar in the two treatment arms (HR, 0.90; 95% CI, 0.56 to 1.44). Mark et al. (9) performed a multivariable analysis to identify risk factors for stroke. Women, diabetes, history of prior stroke at baseline, higher baseline systolic BP, lower serum albumin, and higher C-reactive protein were independently associated with stroke events during the study follow-up period. Of note, lower baseline Hgb was associated with stroke, although this may represent confounding by indication as such patients may have inflammatory conditions associated with ESA hyporesponsiveness. Mean Hgb level and ESA dose during the follow-up period were not associated with stroke events. These findings suggest that the inflammatory state that leads to higher ESA doses may be more responsible for stroke incidence than the ESA doses themselves because the ESA-sparing effect of proactive higher-dose intravenous iron did not decrease stroke incidence. The possibility remains that PIVOTAL was not sufficiently powered to demonstrate differences in stroke incidence between the two arms because first stroke events occurred in only 3.2% of the entire cohort. Because PIVOTAL randomized patients on hemodialysis in their first year on dialysis, it used a single iron preparation (iron sucrose), and the population was ethnically homogeneous (<10% Black), caution should be exercised in extrapolating these results to other populations.

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) are a novel class of agents for treatment of anemia that leverages the cellular hypoxia-sensing apparatus to induce the transcription of genes related to erythropoiesis, including those that code for erythropoietin and proteins related to iron absorption and transport (11). Six HIF-PHIs are under development worldwide, and some have been approved as of this writing in Japan, China, Chile, South Korea, and the European Union. Roxadustat was the first of these agents to complete its global phase 3 development program, and data on patients with nondialysis-dependent CKD and patients with dialysis-dependent CKD were submitted to FDA. The primary prespecified safety outcome for these studies was major adverse cardiovascular event (MACE), which includes stroke; pooled global phase 3 studies in patients with dialysis-dependent CKD revealed MACE noninferiority in comparison with epoetin. FDA performed a more detailed analysis of roxadustat safety as part of its new drug application in the United States (12); 1940 patients with dialysis-dependent CKD were treated with roxadustat, and 1940 patients were treated with epoetin, with durations of exposure of 89.2 and 100.7 weeks, respectively. Patients treated with roxadustat had a least squares mean higher Hgb level of 0.17 g/dl (95% CI, 0.08 to 0.26; \( P < 0.001 \)) at the primary efficacy end point over weeks 28–52. This is likely to be due to differences in roxadustat versus epoetin dosing protocols rather than differences in the inherent efficacy of the two agents. The RR of stroke in the pooled studies of patients with dialysis-dependent CKD was 1.04 (95% CI, 0.72 to 1.50) in the intention-to-treat analysis and 1.03 (95% CI, 0.68 to 1.55) in the on-treatment +7 days analysis (roxadustat versus epoetin). It is notable that other thrombotic complications were more frequent among roxadustat-treated patients with dialysis-dependent CKD in this analysis: deep venous thrombosis: RR, 3.9; vascular access thrombosis: RR, 1.5. It is unclear whether the risk of these thrombotic events was conferred by the higher achieved Hgb level among the roxadustat-treated patients or an inherent thrombogenic property of the drug or its class. Additional studies with significant statistical power to assess stroke risk between HIF-PHIs and ESAs with comparable achieved Hgb levels are awaited.

In conclusion, evidence regarding the contributions of Hgb level, ESA dose, and other comorbidities, such as inflammation, to stroke risk in patients on hemodialysis remains contradictory. ESA dose has been a regulatory target following the publication of TREAT (1), but the secondary analysis of PIVOTAL in this issue of Kidney360 (9) undermines this concept by demonstrating no decrease in stroke events among patients with 19% lower ESA dose and comparable achieved Hgb levels. More likely, as suggested by the secondary analyses of PIVOTAL (9) and CHOIR (6), stroke risk in patients on dialysis is driven more by the comorbidities that confound anemia treatment than by the anemia treatment itself. Alternatives to ESA treatment, such as HIF-PHIs, have yet to fulfill their promise as MACE- or stroke-sparing strategies. In the absence of evidence to the contrary, it appears prudent to pursue Hgb targets <11.5 g/dl in ESA-treated patients and to limit ESA dose escalation in patients whose comorbidities blunt ESA responsiveness.

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