High Dose Erythropoiesis-Stimulating Agent Is Associated with Increased Healthcare Resource Utilization and Risk of Adverse Events in Non-Dialysis-Dependent Chronic Kidney Disease Patients

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Introduction

• High dose ESA (HDE), which may be considered a measure of ESA resistance, is associated with increased comorbidity, adverse events, and healthcare resource utilization (HRU) in hemodialysis patients. 2• Little is known about this association in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients. 1

We investigated this association in stage 3-5 NDD-CKD patients with anemia using 2011-2013 Medicare data.

Methods

• The study population consisted of stage 3-5 NDD-CKD patients with anemia and receiving treatment with ESAs, aged 66 years or older.
• Patients in 2012 were identified with a CKD index date between October 1, 2011, and September 30, 2012. As shown in Figure 1, the baseline period was 1 year before the index date. In 90 days used to define CKD, anemia, treatment, and comorbidity, a 1-year follow-up period was used to define clinical outcomes.
• CKD and anemia were defined from ICD-9-CM diagnosis codes on 1 or more inpatient claims or 2 or more outpatient claims on different dates within 365 days.
• HDE as a measure of ESA resistance was defined by an average monthly ESA dose above the 90th percentile of monthly doses, among patients receiving ESAs.

• Anemia treatment immediately following the diagnosis of anemia included use of ESAs, intravenous iron, and blood transfusion.
• Outcomes in the follow-up period included:
  - All-cause death
  - Major adverse cardiac events (MACE), defined as all-cause death or non-fatal myocardial infarction or non-fatal stroke
  - Hypertensive emergencies
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism
  - Hospitalization
  - Emergency dept. visit
  - Hospital
  - Outpatient visits
  - Medicare payment

• Cox proportional hazards models were used for all outcomes except outpatient visits (Poission regression) and Medicare payment (generalized linear model with log link and gamma distribution).
• Analyses were adjusted for patient demographics, comorbidities, intravenous iron use, red blood cell (RBC) transfusion, and CKD stage.

Results

• A total of 12,901 stage 3-5 NDD-CKD patients with anemia receiving ESAs were included (11.8% of all stage 3-5 NDD-CKD patients).
• HDE cut-points (90th percentiles) were $75,430 units for erythropoietin and $351 mcg for darbepoetin.
• HDE patients were more likely to be male, to be white, and to have a higher baseline comorbidity burden relative to non-HDE patients (Table 1). 1
• HDE use was associated with a significant increase in cardiovascular and thromboembolic events relative to non-HDE patients.
• Furthermore, the risk of death was 60% higher among HDE patients (HR 1.43 [1.39-1.47]), and the risk of MACE was 46% higher (1.46 [1.31-1.62]) relative to non-HDE patients.
• Medicare payments were 52% higher for HDE patients (1.52 [1.41-1.63]) relative to non-HDE patients.

Conclusions

• Anemia requiring HDE use in stage 3-5 NDD-CKD patients is associated with increased MACE, cardiovascular events, thromboembolic events, and HRU.
• Further research is needed to confirm these associations in other cohorts that include more precise data on hemoglobin measurement and ESA dose.

References:

Figure 2. Hazard Ratios: HDE vs. Non-HDE

Table 1. Baseline Characteristics, Comorbidities, and Markers of Frailty in Stage 3-5 NDD-CKD Patients with Anemia: HDE vs. Non-HDE

| Characteristic          | HDE (n = 12,901) | Non-HDE (n = 106,357) | p-Value
|-------------------------|------------------|-----------------------|--------
| Age (years)             | 77.2±10.9        | 77.2±10.9             | 0.979  |
| Gender                  | Male 58.4%       | Female 41.6%          |       |
| Race                    | White 80.4%      | Black 16.7%           | 0.001  |
| Hypertension            | 33.6%            | 18.0%                 | <0.001 |
| Diabetes                | 28.1%            | 10.4%                 | <0.001 |
| Dysrhythmia             | 18.8%            | 9.5%                  | <0.001 |
| GI                      | 4.4%             | 4.4%                  |       |
| Cardiac (other)         | 20.1%            | 24.7%                 | <0.001 |
| Heart failure (CHF)     | 9.0%             | 6.9%                  | <0.001 |
| Pulmonary disease        | 6.1%             | 5.1%                  | <0.001 |
| Depression or dementia  | 9.3%             | 4.8%                  | <0.001 |
| Markers of frailty       |                 |                      |        |
| 3 Medical visits         | 20.9±14.2        | 20.8±14.2             | 0.968  |
| Bed, oxygen, wheelchair  | 29.5±27.3        | 28.9±27.2             | 0.970  |
| Hospitalization         | 18.6±17.9        | 16.3±17.2             | <0.001 |
| Outpatient visits        | 18.3±17.5        | 14.7±16.1             | <0.001 |
| Medicare payment        | 43.2±40.8        | 39.4±39.4             | <0.001 |

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