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*.
- Little is known about this association in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.
- 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 + 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
  - Pulmonary embolism
  - Hospitalization
  - Emergency dept. visit
  - Hospice
  - Outpatient visits
  - Medicare payment
- Cox proportional hazards models were used for all outcomes except outpatient visits (Poisson 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.

Figure 1. Study Design

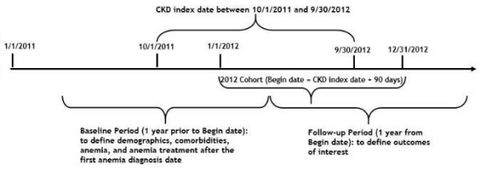
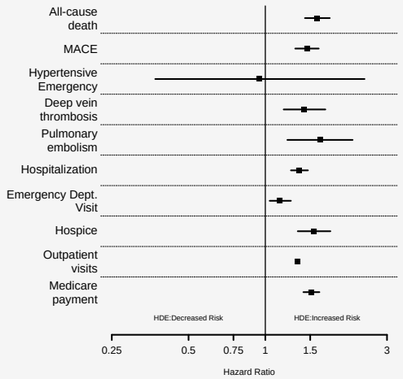


Table 1. Baseline Characteristics, Comorbidities, and Markers of Frailty in Stage 3-5 NDD-CKD Patients with Anemia: HDE vs. Non-HDE

	HDE	Non-HDE
Total N	1,290	11,611
Age category (%)		
66-69 yrs	10.4	12.8
70-74 yrs	23.0	21.5
75-79 yrs	28.1	26.9
80-85 yrs	38.4	38.8
Gender (%)		
Male	50.5	38.3
Female	49.5	61.7
Race (%)		
White	85.4	77.2
Black	10.2	16.7
Other	4.4	6.1
Comorbidities (%)		
ASHD	52.1	46.4
CHF	44.1	35.9
CVA/TIA	18.8	19.2
PVD	33.6	30.9
Cardiac (other)	38.9	32.5
COPD	33.6	28.3
GI	18.0	11.5
Liver disease	5.3	3.4
Dysrhythmia	44.0	36.6
Cancer	47.5	28.1
Diabetes	56.7	60.2
Hypertension	91.5	94.7
Markers of frailty (%)		
Durable medical equipment*	29.8	25.4
Home health & hospice	32.9	29.8
Depression or dementia	20.1	19.2
Hip fracture	1.1	1.8

*Bed, oxygen, wheelchair, walker, enteral nutrition. ASHD, atherosclerotic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; GI, gastrointestinal; HDE, high-dose erythropoiesis-stimulating agent; PVD, peripheral vascular disease.

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



MACE, major adverse cardiac event, including death.

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 percentile) were ≥75,630 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).
- HDE use was associated with a significant increase in cardiovascular and thrombo-embolic events relative to non-HDE patients.
- Furthermore, the risk of death was 60% higher among HDE patients (HR 1.60 [1.43-1.79]), and the risk of MACE was 46% higher (1.46 [1.31-1.62]) (Figure 2) 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 death, 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:
* Gilbertson DT, Peng Y, Arneson TJ, Dunning S, Collins AJ. Comparison of methodologies to define hemodialysis patients hyporesponsive to epoetin and impact on counts and characteristics. BMC Nephrol. 2013 Feb 20;14:44. doi: 10.1186/1471-2369-14-44.

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