Unexpected Medical Consequences of Revised ESA Label in Non-Dialysis-Dependent Chronic Kidney Disease Patients with Anemia

Suying Li,[1] Haifeng Guo,[1] Shaum Kabadi,[2] Sean Zhao,[2] Trudy Pendergraft,[2] Louise Sargent Heuer,[2] Yi Peng,[1] Wendy St. Peter,[1] and David T. Gilbertson[1]

[1]Chronic Disease Research Group, Minneapolis, MN; [2]AstraZeneca, Wilmington, DE.

Introduction

- In 2011, the US Food and Drug Administration revised labeling for erythropoiesis-stimulating agent (ESA) treatment in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.
- A hemoglobin target of 10-12 g/dL was replaced by guidance to initiate therapy when hemoglobin fell to <10 g/dL (ref).
- To the best of our knowledge, little is known about the impact of anemia treatment patterns and associated medical outcomes in stage 3-5 NDD-CKD patients with anemia before and after 2011.

Objective

- To examine changes in anemia treatment, comorbidities, and outcomes after the ESA label change in NDD-CKD patients.

Methods

- The study population consisted of Medicare stage 3-5 NDD-CKD patients with anemia aged 66 years or older. Patients were selected for two study cohorts:
  - 2008 cohort: consisting of patients identified from 2007-2009 claims;
  - 2012 cohort: consisting of patients identified from 2011-2013 claims.
- 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. The design was similar for 2008 cohort.
- 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.
- Anemia treatment immediately following the diagnosis of anemia included use of ESAs, intravenous iron, and red blood cell (RBC) transfusion.
- Outcomes in the follow-up period included:
  - All-cause death
  - Major adverse cardiac event (MACE): all-cause death or non-fatal myocardial infarction or non-fatal stroke
  - Hypertensive emergencies (HE)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- To compare differences in patient's characteristics and use of treatment between 2008 and 2012, standardized differences (STD) were calculated.
- To compare risk of outcomes between 2008 and 2012, Cox regressions were used, adjusted for demographics, comorbidity, and CKD stages.

Figure 1. Study Design

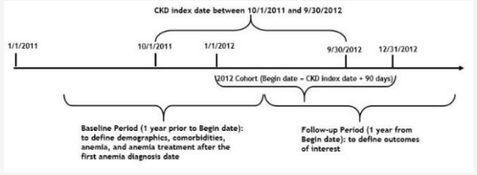
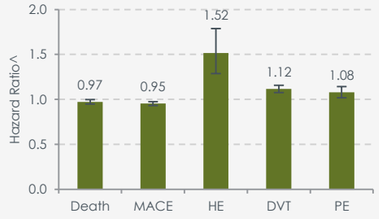


Table 1. Baseline Characteristics, Comorbidity, and Anemia Treatment in Stage 3-5 NDD-CKD Patients with Anemia: Comparing 2008 and 2012

	2008	2012	Standardized difference
Total N	71,744	109,251	
Age, %			
66-69 yrs.	14.2	14.2	-0.1
70-74 yrs.	22.7	23.1	0.8
75-79 yrs.	27.7	27.1	-1.4
80-85 yrs.	35.3	35.6	0.6
Female, %	53.0	53.7	1.4
Race, %			
White	81.0	80.2	-2.0
Black	13.4	14.0	1.5
Other	5.6	5.8	1.0
Comorbidity, %			
ASHD	51.6	52.2	1.4
CHF	40.8	40.5	-0.6
CVA/TIA	21.5	23.6	5.2
PVD	33.4	35.6	4.6
Anemia treatment, %			
ESA	29.4	12.7	-41.9
IV iron	6.3	6.7	1.7
RBC transfusion	21.3	22.2	2.2
Any	45.1	34.0	-22.9

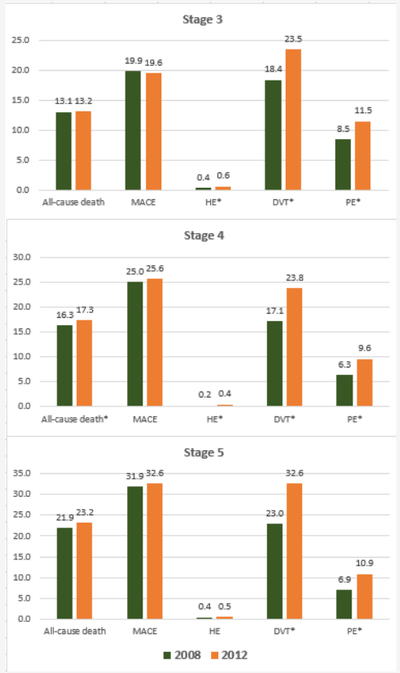
ASHD, atherosclerotic heart disease; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; ESA, erythropoiesis-stimulating agent; IV, intravenous; PVD, peripheral vascular disease; RBC, red blood cell.
Any: ESA, IV iron, or transfusion

Figure 3. Adjusted Hazard Ratio of Adverse Events during Follow-up in Stage 3-5 NDD-CKD Patients with Anemia, 2012 Cohort vs. 2008 Cohort



^All results are statistically significant.
DVT, deep vein thrombosis; HE, hypertension emergency; MACE, major adverse cardiac event including all-cause death; PE, pulmonary embolism.

Figure 2. Unadjusted Event Rates per 100 Patient-Years in Stage 3-5 NDD-CKD Patients with Anemia, by CKD Stage



* P-value < 0.05
DVT, deep vein thrombosis; HE, hypertension emergency; MACE, major adverse cardiac events including all-cause death; PE, pulmonary embolism.

Results

- Totals of stage 3-5 NDD-CKD patients with anemia were 71,744 in 2008 and 109,251 in 2012. There was no significant difference in baseline characteristics between 2008 and 2012. However, the percentage of patients receiving ESAs in 2012 was significantly lower than in 2008 (**Table 1**).
- In each CKD stage, the unadjusted rates of HE, DVT, and PE were statistically higher in 2012 than in 2008 patients (**Figure 2**).
- After adjusting for patient demographics, comorbidity, and CKD stage, patients in 2012 had the same risk of death or MACE, but higher risk of HE, DVT, and PE in 1 year, compared with patients in 2008 (**Figure 3**).

Limitations

- Anemia was defined by diagnosis codes due to lack of hemoglobin values in the database.
- There may be confounding given some differences between unadjusted and adjusted results.
- Causal relationships can't be inferred from the observational study.

Conclusions

- While the intent of the 2011 ESA label change was to improve safety, a reduction in all-cause death and MACE has not yet been observed in stage 3-5 NDD-CKD patients.
- After the 2011 ESA label change, there was an unexpected increase in risk of HE, DVT, and PE in stage 3-5 NDD-CKD patients.

Reference

- U.S. Food and Drug Administration. FDA modifies dosing recommendations for Erythropoiesis-Stimulating Agents. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm260670.htm . 6-24-2011. 9-18-2014.

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