Erythropoiesis-Stimulating Agent Hyporesponse Is Associated with Persistently Elevated Mortality among Hemodialysis Patients

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Introduction

- Anemia is highly prevalent among patients with end-stage renal disease (ESRD) and is associated with poor outcomes and mortality.[1] Renal anemia in patients with ESRD receiving hemodialysis (HD) is typically treated with both erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron.[2,3]
- Many HD patients with renal anemia do not respond optimally to ESA treatment (ie, are ESA hyporesponsive [ESAhr]). ESAhr patients are unable to achieve their targeted hemoglobin (Hb) concentration or require chronic high ESA doses to achieve their targets.[4]
- Prior studies have examined the association between ESAhr and outcomes among HD patients.[5-7]
- However, none have been conducted following 2011 changes to the US ESA labels and reimbursement policy, using recent data and a definition of ESAhr that is relevant to contemporary practice.

Objectives

- To determine a contemporary definition of ESAhr that is relevelant to current ESA dosing practices
- To study the association between ESAhr and mortality in HD patients

Methods

- Eligible patients were 18 years or older, non-veterans, receiving in-center HD at a large dialysis organization (LDO), and had a dialysis vintage ≥ 6 months to ensure stable ESA use.
- Point prevalence for various definitions of ESAhr was determined at the beginning of each consecutive calendar quarter (Q) during the study period (01 Jan 2012 - 31 Dec 2013) by dividing the number of patients meeting the definition criteria by the total number of patients eligible at the time.
- For associative analyses, the point prevalent cohort of eligible patients at the start of Q1 2012 were considered. Exposure status was assigned as ESAhr or non-ESAhr based on whether the patient met the operative definition of ESAhr (definition 4) at any point during Q1 2012. Patients were followed until the earliest of death, loss to follow-up (transfer of care, transplant, withdrawal from dialysis), or end of study (31 December 2013).
- ESA utilization was calculated monthly as the mean dose administered per dialysis session. Hemoglobin was determined as the mean of all measurements during the month. Deaths and missed dialysis treatments were assessed quarterly and expressed as rates (number of events during the quarter divided by cumulative time at risk).
- Associations of ESAhr status with ESA utilization and hemoglobin concentration were estimated using general estimating equation linear models with an identity link and Gaussian distribution. Models contained fixed-effects terms for exposure status, month, and 2-way exposure-by-month cross-product, the latter to account for differences over time in the association between exposure groups.
- Associations of ESAhr status with mortality and missed dialysis treatments were estimated using general estimating equation models using a log link and Poisson (mortality) or negative binomial (missed treatments) distribution.
- Adjusted models contained fixed-effects terms for covariates that differed significantly between exposure groups at baseline ($P < 0.10$).
  - In cases where adjusted models did not converge, changes in covariate adjustments were necessary on a model-by-model basis, based on the variables presumed to have the least influence on the final estimate.

Results

Table 1. Apparent Prevalence of ESAhr by Candidate ESAhr Definitions

Criteria	ESAhr Definition 1 Consecutive Hb measurements of < 10 g/dL [a]	2 Consecutive Hb measurements of < 9.5 g/dL [a]	3 ESA Dose > 7700 U/treatment	4 Meets criteria of definitions 1 and 3	5 Meets criteria of definitions 2 and 3
1Q 2012 (N = 98,972)	29,287 (29.6)	14,431 (14.6)	25,107 (25.4)	12,361 (12.5)	7590 (7.7)
2Q 2012 (N = 101,808)	28,195 (27.7)	13,681 (13.4)	24,956 (24.5)	11,975 (11.8)	7324 (7.2)
3Q 2012 (N = 103,058)	27,199 (26.4)	13,217 (12.8)	24,608 (23.9)	11,483 (11.1)	7109 (6.9)
4Q 2012 (N = 103,549)	25,884 (25.0)	12,425 (12.0)	23,340 (22.5)	10,537 (10.2)	6433 (6.2)
1Q 2013 (N = 103,899)	28,306 (27.2)	13,724 (13.2)	23,959 (23.1)	11,530 (11.1)	7138 (6.9)
2Q 2013 (N = 105,271)	27,475 (26.1)	13,134 (12.5)	23,542 (22.4)	11,117 (10.6)	6895 (6.6)
3Q 2013 (N = 106,998)	29,239 (27.3)	14,139 (13.2)	23,900 (23.4)	11,690 (10.9)	7267 (6.8)
4Q 2013 (N = 104,742)	23,465 (22.4)	11,265 (10.8)	23,290 (22.2)	9519 (9.0)	5901 (5.6)

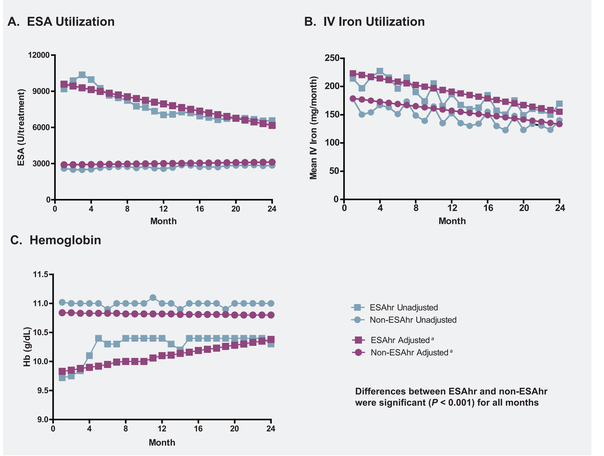
[a] Consecutive Hb measurements must have been separated by at least 14 days.
Abbreviation: ESAhr, erythropoiesis-stimulating agent hyporesponse; Hb, hemoglobin; Q, quarter

Table 2. Characteristics of ESAhr and Non-ESAhr Patients

		ESAhr N = 12,361	Non-ESAhr N=86,611	*P* Value
Age, years	mean ± SD median [p25, p75]	59.5 ± 14.9 60 [50, 70]	62.3 ± 14.8 63 [53, 73]	< 0.001
Sex				< 0.001
Female		47.8%	45.2%	
Race				< 0.001
White		32.4%	35.8%	
Black		45.8%	37.3%	
Hispanic		114.6%	18.6%	
Asian		3.3%	3.8%	
Unknown/missing		3.9%	4.5%	
Vascular access				< 0.001
Arteriovenous fistula		55.6%	62.1%	
Arteriovenous graft		23.2%	20.5%	
Central venous catheter		20.2%	14.2%	
Vintage, months				< 0.001
6-12 months		18.2%	20.1%	
≥ 13 months		81.9%	80.0%	
Postdialysis weight, kg	mean ± SD median [p25, p75]	79.8 ± 23.3 75 [64, 92]	79.8 ± 22.4 76 [64, 92]	0.87
Etiology of ESRD				< 0.001
Diabetes		43.9%	45.8%	
Hypertension		30.9%	31.1%	
Other		25.2%	23.1%	
Charlson comorbidity index score	mean ± SD median [p25, p75]	5.4 ± 2.0 5 [4, 7]	5.5 ± 1.9 6 [4, 7]	< 0.001
Cancer		3.1%	1.9%	< 0.001
Cerebrovascular disease		0.8%	0.7%	0.38
COPD, n (%)		5.0%	3.8%	< 0.001
Congestive heart failure		14.5%	12.0%	< 0.001
Coronary artery disease		7.6%	7.0%	0.01
Diabetes		68.6%	68.4%	0.53
Gastrointestinal bleeding		1.5%	1.0%	< 0.001
HIV/AIDS		0.9%	0.4%	< 0.001
Hypertension, n (%)		35.2%	32.4%	< 0.001
Peripheral vascular disease,		32.9%	2.7%	0.11
IV antibiotics		8.9%	4.3%	< 0.001
Serum albumin, g/dL	mean ± SD median [p25, p75]	3.89 ± 0.48 3.9 [3.60, 4.20]	4.06 ± 0.38 4.10 [3.90, 4.30]	< 0.001
Kt/V	mean ± SD median [p25, p75]	1.67 ± 0.31 1.64 [1.47, 1.84]	1.71 ± 0.31 1.68 [1.52, 1.87]	< 0.001
IV Vit D utilization, µg/treatment	mean ± SD median [p25, p75]	2.52 ± 2.82 1.85 [0.50, 3.50]	2.28 ± 2.54 1.69 [0.50, 3.21]	< 0.001
IV iron utilization, mg/month	mean ± SD median [p25, p75]	189 ± 209 200 [0, 200]	163 ± 172 200 [0, 200]	< 0.001
ESA utilization, U/treatment	mean ± SD median [p25, p75]	7993 ± 5515 7000 [3789, 11,825]	2731 ± 3120 1742 [677, 3723]	< 0.001
Parathyroid hormone, ng/mL	mean ± SD median [p25, p75]	547 ± 550 406 [258, 620]	472 ± 382 383 [256, 560]	< 0.001
Hemoglobin, g/dL	mean ± SD median [p25, p75]	10.1 ± 1.1 9.9 [9.3, 10.8]	11.2 ± 1.0 11.1 [10.6, 11.7]	< 0.001
Serum ferritin, ng/mL	mean ± SD median [p25, p75]	819 ± 499 737 [476, 1041]	783 ± 396 740 [510, 992]	< 0.001
Transferrin saturation, %	mean ± SD median [p25, p75]	31.6 ± 16.6 27.0 [21.0, 37.0]	33.6 ± 13.9 31.0 [24.0, 40.0]	< 0.001

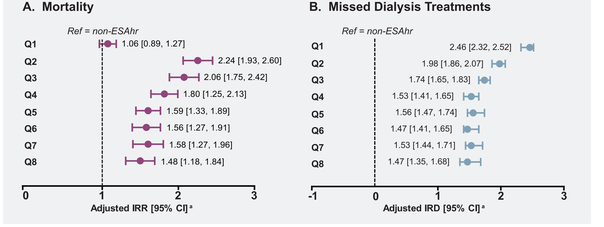
Abbreviations: AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; ESA, erythropoiesis-stimulating agent; ESAhr, ESA hyporesponse; HIV, human immunodeficiency virus; IV, intravenous; p25, 25th percentile; p75, 75th percentile; SD, standard deviation; Vit, vitamin

Figure 1. ESA Utilization, IV Iron Utilization, and Hemoglobin Levels among ESAhr and Non-ESAhr Patients



[a] Models were adjusted for covariates that differed significantly between exposure groups at baseline ($P < 0.10$); where models did not converge, changes in adjustment were made according to the relative clinical importance of covariates. Models for ESA and IV iron utilization were adjusted for baseline differences in sex, age, race, etiology of ESRD, dialysis vintage, vascular access, cancer, serum parathyroid hormone, albumin, and Charlson comorbidity index. Models for hemoglobin were adjusted for baseline differences in age, sex, race, etiology of ESRD, dialysis vintage, vascular access, cancer, parathyroid hormone, serum albumin, Charlson comorbidity index score, antibiotic use, peripheral vascular disease, hypertension, human immunodeficiency virus/acquired immune deficiency syndrome, gastrointestinal bleed, coronary artery disease, chronic obstructive pulmonary disease, and congestive heart failure.
Abbreviations: ESA, erythropoiesis-stimulating agent; ESAhr, ESA hyporesponse; Hb, hemoglobin; IV, intravenous.

Figure 2. Adjusted Associations between ESAhr, Mortality, and Missed Dialysis Treatments



[a] Adjusted for differences at baseline ($P < 0.10$) in age, sex, etiology of ESRD, vintage, vascular access, cancer, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, coronary artery disease, gastrointestinal bleeding, human immunodeficiency virus/acquired immune deficiency syndrome, peripheral vascular disease, intravenous antibiotic use, dry weight, serum ferritin, transferrin saturation, parathyroid hormone, serumalbumin, intravenous vitamin D utilization, and Charlson comorbidity index score.
Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; ESAhr, ESA hyporesponse; IRD, incidence rate difference; IRR, incidence rate ratio; ref, referent.

- The point prevalence of candidate definitions of ESAhr was assessed (Table 1). Definition 4 (ESA dose of > 7700 U/treatment and consecutive Hb measurements [separated by at least 14 days] < 10 g/dL) met the expected prevalence rate of approximately 10%[8,9] and was used to define ESAhr in all subsequent analyses.
- Compared to non-ESAhr patients, ESAhr patients were younger, more likely to be African American, more frequently used central venous catheters, less frequently used arteriovenous fistulae, and were more frequently treated with antibiotics (Table 2).
- ESAhr patients had significantly greater ESA and IV iron utilization (Figure 1A and 1B) and lower Hb concentrations (Figure 1C) compared to non-ESAhr patients at all times during follow-up.
- ESAhr was associated with a greater adjusted risk of mortality vs non-ESAhr in Q2 through Q8 of follow-up (Figure 2). Adjusted incidence rate ratios (IRR; 95% confidence interval [CI]) ranged from 2.24 (1.93, 2.60) in Q2 of follow up to 1.48 (1.18, 1.84) in Q8.
- ESAhr was also associated with a greater rate of missed dialysis treatments vs non-ESAhr. Adjusted incidence rate differences (IRD; 95% CI) ranged from 2.46 (2.32, 2.52) in Q1 of follow up to 1.47 (1.36, 1.68) in Q8.

Conclusions

- We identified a definition of ESAhr that is relevant to contemporary clinical practice and expected disease prevalence.
- Using this definition we show that ESAhr is potently and persistently associated with:
  - Increased ESA and IV iron use
  - Lower Hb concentrations
  - Elevated rates of mortality and missed dialysis treatments

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