

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Table S1. Urine toxicology evaluation of patients by inductively coupled plasma mass spectrometry.

Figure S1. Map showing the location of Supebeda.

Figure S2. X-ray of forearm and leg of patient 12 showing interosseous calcification suggestive of skeletal fluorosis.

Supplementary References.

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Long- Versus Short-Acting Erythropoiesis-Stimulating Agent Type and Mortality



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Most patients with end-stage kidney disease (ESKD) who are undergoing maintenance hemodialysis (HD) are affected by anemia and receive erythropoiesis-stimulating agents (ESAs) to maintain

hemoglobin levels in the target range. Long-acting ESAs, such as darbepoetin and epoetin beta pegol, have a longer half-life and thus can be administered less frequently than short-acting ESAs, such as epoetin

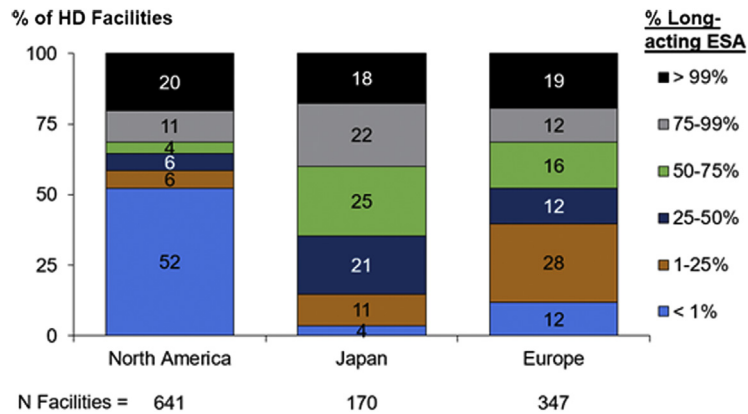


Figure 1. Hemodialysis (HD) facility level distribution of long-acting erythropoiesis-stimulating agent (ESA) use, where facilities are characterized based on the proportion of ESA users who were prescribed a long-acting (darbepoetin and epoetin beta pegol) rather than a short-acting (epoetin) ESA. North America includes the United States and Canada; Europe includes Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom.

alfa and epoetin beta, which can simplify nurses' work in HD centers and may contribute to better hemoglobin stability.^{1,2} Both long- and short-acting ESAs are used commonly in the maintenance HD setting, but head-to-head safety comparisons have been uncommon, with a meta-analysis of randomized trials yielding inconclusive results.³

A recent large, registry-based analysis in Japan found a higher mortality rate for long- versus short-acting ESAs,⁴ contradicting results from a previous U.S.-based cohort.⁵ The Japanese results caused some controversy and sparked renewed interest in this topic.^{6–9,S1} A subsequent large, event-driven randomized trial found no evidence of a mortality effect comparing epoetin beta pegol to epoetin and darbepoetin.^{S2} Given the potentially wide-reaching implications for patients, we used international data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) to compare mortality rates in patients prescribed a long- versus short-acting ESA.

METHODS

This analysis included data from 65,706 patients treated with HD enrolled in the DOPPS, a prospective cohort study of in-center HD patients, from phases 4 (2009–2011), 5 (2012–2015), and 6 (2015–2018) and from 10 countries across 3 regions: North America (the United States and Canada), Japan, and Europe (Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom). All patients prescribed an ESA at DOPPS enrollment were included in the analysis. The exposure variable was long-acting (darbepoetin and epoetin beta pegol) versus short-acting (epoetin) ESA prescription at DOPPS enrollment. The time-to-event outcome was all-cause mortality, with follow-up starting at DOPPS enrollment and ending at death, loss to

Table 1. Erythropoiesis-stimulating agent use and dose, by region

Characteristic	North America ^a	Japan	Europe ^b
Patients, <i>N</i>	48,118	5547	12,041
ESA type, %			
Epoetin	59	37	52
Darbepoetin	37	53	41
Epoetin beta pegol	4	9	7
Mean dose per week			
Epoetin, units	16,532	4807	9991
Darbepoetin, μ g	52	31	44
Epoetin beta pegol, μ g	42	27	42
Empirical dose conversion			
EPO:darbepoetin	320	153	228
EPO:epoetin beta pegol	390	181	240

EPO = epoetin alfa or beta; ESA = erythropoiesis-stimulating agent. Subcutaneous EPO was converted to intravenous EPO at a ratio of 1:15:1.^{S6}

^aThe United States and Canada.

^bBelgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom.

follow-up, 7 days after leaving the facility because of transfer or change in modality, or the administrative end of study phase, whichever occurred first.

For the primary time-to-event analysis, we used Cox regression, accounting for within-facility clustering using a robust sandwich covariance estimator. Models were stratified by DOPPS phase, country, and dialysis organization size (within the United States). Adjustment covariates included age, years on dialysis, sex, black race, catheter use, 13 comorbidities (Supplementary Table S1), albumin, creatinine, post-dialysis weight, transferrin saturation, ferritin, intravenous iron dose, and C-reactive protein (only in subanalyses of Japan and Europe, where it is routinely measured). We additionally adjusted for ESA dose to account for differences by ESA type; because the true conversion factors between long-acting and short-acting ESA doses remain unknown, we assessed the sensitivity of results to different assumptions. We also performed a facility preference-based instrumental

Table 2. Hazard ratio (95% confidence interval) for all-cause mortality comparing long- versus short-acting erythropoiesis-stimulating agents

Region	N	Long-acting, %	Model 1 unadjusted	Model 2 adjusted	Model 3 plus ESA dose
Overall	65,706	44%	0.99 (0.91–1.07)	0.93 (0.87–0.99)	0.94 (0.88–1.00)
By region					
North America	48,118	41%	1.01 (0.91–1.13)	0.91 (0.83–0.99)	0.93 (0.86–1.02)
Japan	5547	63%	1.29 (1.03–1.61)	1.15 (0.92–1.44)	1.10 (0.88–1.38)
Europe	12,041	48%	0.86 (0.78–0.96)	0.94 (0.85–1.03)	0.92 (0.84–1.02)

Cox regression models accounting for within-facility clustering using a using robust sandwich covariance estimator. All models stratified by Dialysis Outcomes and Practice Patterns Study phase, country, and dialysis organization size (within the United States). Model 2 adjusted for age, years on dialysis, sex, black race, catheter use, 13 comorbidities (Supplementary Table S1), albumin, creatinine, postdialysis weight, transferrin saturation, ferritin, and intravenous iron dose; an additional adjustment was made for C-reactive protein in Japan and Europe, where C-reactive protein is measured routinely.

variable analysis that can overcome potential unmeasured confounding. We repeated the analysis for each of the 3 regions.

RESULTS

Descriptive Data

In this DOPPS cohort of adult patients with in-center maintenance HD, the proportion of patients prescribed a long-acting ESA was 41% in North America, 63% in Japan, and 48% in Europe. In North America, patients prescribed a long- versus short-acting ESA tended to be older and more likely to dialyze with a catheter and had lower levels of albumin, creatinine, and hemoglobin (Supplementary Table S1). In Japan, patients prescribed a long- versus short-acting ESA were also older with lower levels of albumin and creatinine. In Europe, patient characteristics were generally balanced between the 2 groups. The proportion of HD facilities prescribing either long- or short-acting ESAs to >99% of ESA users was 71% in North America, 22% in Japan, and 31% in Europe (Figure 1). The mean epoetin doses (units per week) were 16,532 in North America, 4807 in Japan, and 9991 in Europe, and the respective empirical epoetin:darbepoetin conversion factors were 320:1, 153:1, and 228:1 (Table 1).

ESA Type and Mortality

Over a median (interquartile range [IQR]) follow-up of 14 (6–26) months, there were 12,254 deaths. The mortality rate per year was 0.15 in North America, 0.06 in Japan, and 0.15 in Europe. The mortality hazard ratio (HR; 95% confidence interval [CI]) for long- versus short-acting ESA was 0.99 (0.91–1.07) in the unadjusted model, 0.93 (0.87–0.99) after covariate adjustment, and 0.94 (0.88–1.00) after further adjustment for converted ESA dose (primary analysis). The adjusted HR (95% CI) for long- versus short-acting ESA was 0.93 (0.86–1.02) in North America, 1.10 (0.88–1.38) in Japan, and 0.92 (0.84–1.02) in Europe (Table 2). The HR (95% CI) in an instrumental variable analysis (first-stage F = 120) was 0.95 (0.88–1.04). The primary analysis used an epoetin:darbepoetin dose conversion factor of 250:1;

when varying the conversion factor used, the HR (95% CI) ranged from 0.89 (0.84–0.95) when using 350:1 to 1.00 (0.94–1.06) when using 150:1 (Supplementary Table S2).

DISCUSSION

In this large international cohort study, patients prescribed a long-acting ESA (i.e., darbepoetin or epoetin beta pegol) had a similar mortality rate as patients prescribed a short-acting ESA (i.e., epoetin). The estimated effect was $\leq 10\%$ in each of 3 regions—North America, Japan, and Europe—with the HR comparing long- versus short-acting ESA ranging from 0.92 to 1.10. Despite differences in approach to dosing between long- and short-acting ESAs, we found no evidence of a harmful effect of long- versus short-acting ESAs on mortality.

Our results are consistent with a previous analysis by Winkelmayer *et al.*,⁵ who found minimal differences in clinical outcomes between U.S. facilities that switched from epoetin to darbepoetin versus epoetin-only facilities. A recently published multicenter randomized clinical trial comparing epoetin beta pegol to epoetin and darbepoetin also found no evidence of a mortality effect.^{S2} While the study^{S2} compared a long-acting ESA (epoetin beta pegol) to a reference group that included both short-acting ESAs (epoetin) and a long-acting ESA (darbepoetin), unpublished results showed no difference in mortality comparing either epoetin beta pegol or darbepoetin to epoetin, though patients within the darbepoetin/epoetin reference group were not randomized to ESA type (personal communication; Francesco Locatelli, June 5, 2020).

In a recent study of Japanese registry data, Sakaguchi *et al.*⁴ found a 13% higher death rate in HD patients receiving long- versus short-acting ESAs. While our overall results (HR = 0.94) are in contrast with these findings, our Japan-DOPPS results (HR = 1.10) are comparable, albeit estimated with lower precision. This is not unexpected, because the Japan-DOPPS was designed to be a random subset of Japanese HD facilities. While other biologic mechanisms are

possible, the results from Sakaguchi *et al.*⁴ do not support a pathway via the longer-acting effects of these medications, because the mortality rate was higher in the darbepoetin versus epoetin beta pegol group, despite the latter's longer half-life. We also found a similar epoetin:darbepoetin dose ratio (153:1) in Japan-DOPPS as in Sakaguchi *et al.*,⁴ which was much smaller than what we observed in North America (320:1) and Europe (228:1). This is consistent with research showing that the conversion factor is greater at higher doses of epoetin.^{S3-S5} The primary reason for the lower conversion factor in Japan is likely to be a cap on the maximum reimbursable epoetin dose (9000 units/wk) while there is no cap for darbepoetin⁷; patients receiving a long-acting ESA tended to receive a greater amount of equivalent ESA on average, and long-acting ESAs may have been more likely used in patients with ESA hyporesponsiveness, leading to confounding by indication bias in both the Japan-DOPPS and Japanese registry analysis.⁴ In a follow-up letter to their original analysis, Sakaguchi *et al.*^{S1} showed that the observed effect was likely not attributable to the higher darbepoetin (vs. epoetin) doses. However, our international extension of the analysis provided no evidence of a harmful effect of long-acting ESA in other regions where epoetin doses are uncapped and darbepoetin doses were relatively lower, leaving the dose effect open as a possible explanation for the comparable results observed in Japan-DOPPS and by Sakaguchi *et al.*⁴ We acknowledge that the different results by region may also be related to physiologic or geographic differences in clinical practices.

Our study had some limitations. Residual confounding is possible because of the observational study design. However, because decisions regarding ESA type tend to occur at the HD facility level rather than the individual patient level, particularly in North America, where the potential for residual bias was greater because of a lack of C-reactive protein assessment, the risk of bias caused by confounding by indication (outside of Japan, where epoetin doses are capped) is low in our study; this is supported by the robust evidence from the facility preference-based instrumental variable analysis. Another limitation is the lack of a well-established dose conversion ratio from epoetin to darbepoetin or epoetin beta pegol. Because the empirical conversion ratios were different across regions, it was difficult to properly account for dose differences in the adjusted Cox model, and an alternative approach using standardized dose would be ineffective by artificially removing the link between ESA dose and type. While our results were sensitive to the conversion factor used, no results

outside of Japan were suggestive of a harmful effect of long- versus short-acting ESA. Our study also had some strengths. We used a large contemporary international cohort including patients with HD with a broad range of ESA doses and adjusted for numerous confounders to minimize potential residual bias.

Using international DOPPS data, we observed no evident difference in mortality rate between HD patients prescribed a long- versus a short-acting ESA, suggesting no increased mortality risk for long- versus short-acting ESAs.

DISCLOSURE

AK and BR are employees of Arbor Research Collaborative for Health, and FKP has a consultancy contract with Arbor Research Collaborative for Health, which administers the DOPPS. BR has received consultancy fees or travel reimbursement from AstraZeneca, GlaxoSmithKline, and Kyowa Kirin Co., all paid directly to his institution of employment. ZAM reports grants for CKD REIN and other research projects from Amgen, Astra Zeneca, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp and Dohme-Chibret, Sanofi-Genzyme, Lilly, Otsuka and the French government, as well as fees and grants to charities from Astellas, and Sanofi-Genzyme. FL is or was a member of an advisory board of Akebia, Amgen, Astellas, Astra Zeneca, Baxter, GSK, Mitsubishi, Roche, and Vifor Pharma, and has been a speaker at meetings supported by Amgen, Astellas, Bayer, Norgine, Roche, and Vifor Pharma. AC has received grants from Vifor Pharma and AB-Biotics, is or was a member of an advisory board of Astellas, GlaxoSmithKline, Vifor Pharma, Daiichi Sankyo, and Novo Nordisk, and has received speaker fees from Astellas, Amgen, Bayer, and Vifor Pharma. KN has received research grants from Chugai Pharmaceutical Co. and Kyowa Kirin Co. Ltd. KJJ has received speaker fees from Fresenius Medical Care. SL declared no competing interests.

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AUTHOR CONTRIBUTIONS

AK, BR, and ZM designed the study; AK analyzed the data and drafted the article; BR, ZM, FL, AC, FKP, KJ, SL, and KN revised the article; all authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Table S1. Patient characteristics, by ESA type and region.

Table S2. Sensitivity of results to different epoetin:darbepoetin conversion factors

Supplementary References.

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