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ORIGINAL RESEARCH ARTICLE

Comparative Safety of Originator and Biosimilar Epoetin Alfa Drugs: An Observational Prospective Multicenter Study

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Abstract

Background Erythropoiesis-stimulating agents (ESAs) are biological molecules approved for the treatment of anemia associated with chronic renal failure. Biosimilars were licensed for use in Europe in 2007.

Aim This study aimed to compare the safety profile of biosimilars with respect to the reference product in a nephrology setting.

Methods A prospective study was conducted in four Italian regions between 1 October 2013 and 30 June 2015. The study population included patients aged ≥ 18 years undergoing hemodialysis and treated with epoetins as per the clinical practice of the participating centers. The two comparison cohorts included patients treated with either an originator or a biosimilar epoetin alfa. Each patient was followed up until occurrence of any safety outcome of interest (grouped into three major categories), switch to a different ESA product, transplant or peritoneal dialysis, death, or end of the study period, whichever came first.

Results Overall, 867 subjects were included in the study (originator: $N=423$; biosimilar: $N=444$). Biosimilar users were older than originator users (median age of 76 vs 64 years, respectively), more frequently affected by arrhythmia (29.3 vs 22.5%), and less frequently candidates for transplantation (3.8 vs 18.2%). Cox-regression analysis showed no increase in risk of safety outcomes in biosimilar users, even after adjusting for confounding factors: 1.0 (95% confidence interval [CI] 0.7–1.3) for any outcomes; 1.1 (95% CI 0.7–1.8) for problems related to dialysis device; 0.9 (95% CI 0.6–1.5) for cardio- and cerebro-vascular conditions; 0.9 (95% CI 0.6–1.5) for infections.

Conclusion This study confirms the comparable safety profiles of originator and biosimilar epoetin alfa drugs when used in patients receiving dialysis.

G. Stoppa and C. D'Amore contributed equally to this work.

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Key Points

We carried out an observational study to compare the safety of originator epoetin alfa and biosimilars in patients receiving dialysis.

The two cohorts of users were largely overlapping in the time-to-events: approximately 25% of users experienced a safety outcome within 6 months of observation and 40% within 1 year.

Both unadjusted and adjusted estimates did not show any difference in the safety outcomes between the two cohorts.

Even though relevant to the clinical setting of dialysis, our findings provide further reassurance about the use of biosimilars in clinical practice.

1 Introduction

Biosimilars represent one of the main factors contributing to the economic sustainability of health systems. Savings on pharmaceutical expenditure originate only partly from the lower price of biosimilars. In fact, a larger effect is obtained when the originators are forced to reduce their prices, in order to counter the increased prescriptions of biosimilars. The significant advantage for patients and communities is that financial resources may be more efficiently allocated to other uses, in particular making innovative medicines available to patients [1].

This positive outcome could be hampered by uncertainty about the comparability process conducted to obtain marketing authorization for biosimilars. Despite the stringent regulatory requirements and the high standard of evidence required in the approval process [2], scientific societies and even regulators have expressed concerns regarding the safety and effectiveness of biosimilars [3, 4].

Providing prescribers with information about the rigorous steps of the approval process, as well as acquiring new evidence from clinical practice in order to corroborate the data obtained in the pre-registration phase, is essential for overcoming this resistance. Moreover, given the production process specificity of biological drugs, ongoing verification that the comparative risk–benefit profile of originator drug and biosimilars remains unchanged over the years is useful.

Erythropoiesis-stimulating agents (ESAs) are one of the first therapeutic categories in which biosimilars became available. Although biosimilar ESAs were licensed for use in Europe in 2007 in the nephrology setting, their prescription has been relatively limited for many years. For instance, at the beginning of 2013, when the present study was planned, in Italy biosimilar products represented only 10.6% of the doses of the entire ESA category, and 20.7% of those of epoetin alfa [5].

Given the large number of patients, nephrology is one of the clinical areas that might increase the diffusion of biosimilars because physicians have not only to choose which product is to be preferentially used in naïve patients, but also to decide whether switching between different products—both originators and biosimilars—carries an additional risk for patients. To this end, contributing additional data derived from current practice was deemed helpful. Therefore, a post-authorization observational study aimed at comparing the efficacy and safety of ESA products in patients undergoing dialysis treatment (ESAVIEW) was conducted in four Italian regions with the financial support of the Italian Medicines Agency [6]. The main objective of the study was to compare the safety of originator versus biosimilar epoetin alfa drugs in patients with chronic kidney disease (CKD).

2 Methods

2.1 Study Design and Population

This observational, multicenter, prospective cohort study was conducted in 26 hospitals of four Italian regions (Veneto, Liguria, Molise, and Sardegna) between 1 October 2013 and 30 June 2015. The study population included all adult (≥ 18 years) CKD outpatients undergoing hemodialysis at least twice a week and who were treated with epoetins as per the clinical practice of the participating hospitals. The study population comprised both prevalent users (patients already on ESAs before inclusion in the study) and incident users (patients starting the use of ESA at inclusion). Each patient was followed for 12 months after the first (index) visit. Patients were excluded if they were involved in other clinical studies or did not provide inform consent.

2.2 Data Collection

Trained monitors were in charge of collecting information from the clinical charts and recording it in a web-based database. For each patient, the following baseline data were collected: age and gender; dry weight; primary kidney disease; dialysis frequency and type of vascular access; previous renal transplant and/or inclusion on the transplant list; comorbidities; investigation tests; and drugs. For more details on the baseline comorbidities considered in the study, refer to Online Resource 1 (see electronic supplementary material [ESM]). The study monitors updated some of the baseline data (e.g., dialysis frequency, inclusion on the transplant list) and the results of investigation tests on a monthly basis.

2.3 Definition of Drug Exposure

Patients were classified as users of originator (Eprex®) or biosimilar (Binocrit® or Retacrit®) epoetin alfa based on the ESA received at index visit. Date of administration, drug authorization code, and number of dosage units were recorded for each patient at every visit. Patients were considered as incident (new) users of epoetins if they were not already on treatment at the index visit (no information was collected to distinguish between 'never users' before the first visit and patients who had already received prescriptions of epoetins in the past).

2.4 Study Outcomes

Clinicians were expected to detail in the clinical records any adverse event that was reported by the patient and observed by the attending physician. Moreover, reasons

for any emergency department visit or hospitalization were recorded as adverse events. The study monitors coded the safety outcomes according to the Medical Dictionary for Regulatory Affairs (MedDRA; version 7.0). MedDRA provides a hierarchy for summarizing symptoms or diagnoses: coding of the events was carried out at each visit using the preferred term level.

Starting from individual safety outcomes, three major categories were agreed between the participating nephrologists and the research group in order to provide clinically meaningful grouping with a sufficient number of events. The three categories were 'Problems related to the dialysis device' (i.e., arteriovenous fistula site complications, catheter-related complications, and infections of the vascular access), 'Cardio and cerebrovascular events' (i.e., coronary heart disease, arrhythmia, heart failure, cerebrovascular events, peripheral arterial occlusive disease, hemorrhage, and thrombosis), and 'Infections' (i.e., pneumonia/respiratory tract infections, sepsis, and other infections). Arrhythmia was included as an outcome only if not reported at baseline. Heart failure and coronary heart disease were considered as events if not preexisting at baseline. A clinical chart reporting a bypass/stent for patients with coronary heart disease or a worsening heart condition in case of heart failure and myocardial infarction was accepted as a safety event. Online Resource 2 (see ESM) provides additional details about the study outcomes.

2.5 Follow-Up

All patients were followed-up from the date of the index visit until the first of the following events: (i) any of the study outcomes; (ii) switch to a different ESA product; (iii) transplant or peritoneal dialysis; (iv) death; (v) end of the study period (12 months after the index visit).

2.6 Statistical Analysis

Characteristics of users of originator or biosimilar drugs were described through a $\chi 2$ test for categorical variables and a Mann–Whitney test or *t* test for continuous variables.

Survival curves by ESA exposure status were made using the Kaplan–Meier technique and compared using the log-rank test.

The Cox proportional hazard model was used to compare the incidence rates of each outcome in the two cohorts and to estimate crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). All missing data were excluded from the analysis. The following baseline characteristics of patients were considered and tested as potential confounders: age and gender; diagnosis leading to the renal failure; selected comorbidities retrieved at any time prior to the index visit; number of dialysis sessions per week; iron supplementation; number of drugs taken by the patient (other than iron supplementation). We adopted a stepwise procedure (significance for input 0.05 and removal 0.1) to select the characteristics to be included in the model for the risk adjustment.

The same analysis was conducted focusing only on incident users of epoetins. We also carried out three ancillary analyses comparing the two groups with regard to the last available hemoglobin (Hb) measurement, the need for transfusion during follow-up, and the occurrence of death during the entire 12-month period.

The statistical analysis was performed using STATA software (version 11.2; StataCorp LP, College Station, TX, USA).

3 Results

3.1 Study Population

Overall, 1278 patients were treated with ESAs and were eligible for the study; 411 patients were excluded, mainly because they received other ESAs (i.e., darbepoetin alpha, Aranesp®; methoxy polyethylene glycol-epoetin beta, Mircera®; epoetin beta, Neorecormon®), all without biosimilars in the Italian market (Fig. 1).

Among the remaining 867 patients included in the analysis, 423 (48.8%) received the originator epoetin and 444 (51.2%) the biosimilar ones (almost all subjects [440] received the Binocrit® product). Patients on treatment with biosimilars were older than the originator users (76 vs 64 years) (Table 1) and were more frequently affected by arrhythmia (29.3 vs 22.5%) and diabetes mellitus (34.9 vs 28.6%) at baseline. Originator users more frequently had arteriovenous fistula (75.4 vs 61.9%) and previous renal transplant (14.2 vs 3.8%), they were more often on a waiting list for transplant (18.2 vs 3.8%), and had received dialysis for a longer time (36 vs 28 months).

We found no difference in the proportion of patients requiring iron supplementation at baseline, or in levels of Hb: 10.8 mg/dL and 10.9 mg/dL in users of biosimilar and originator epoetins, respectively.

3.2 Study Outcomes

The median duration of observation was slightly longer for patients receiving biosimilars (10.5 vs 8.5 months). Overall, 274 patients (31.6%) experienced at least one of the safety outcomes: 123 (29.1%) occurred among originator users and 151 (34.0%) among biosimilar users. The most frequent events were infections (100/867; 11.5%), followed by cardio and cerebrovascular conditions (92/867; 10.6%) and by problems related to the dialysis device (85/867; 9.8%).

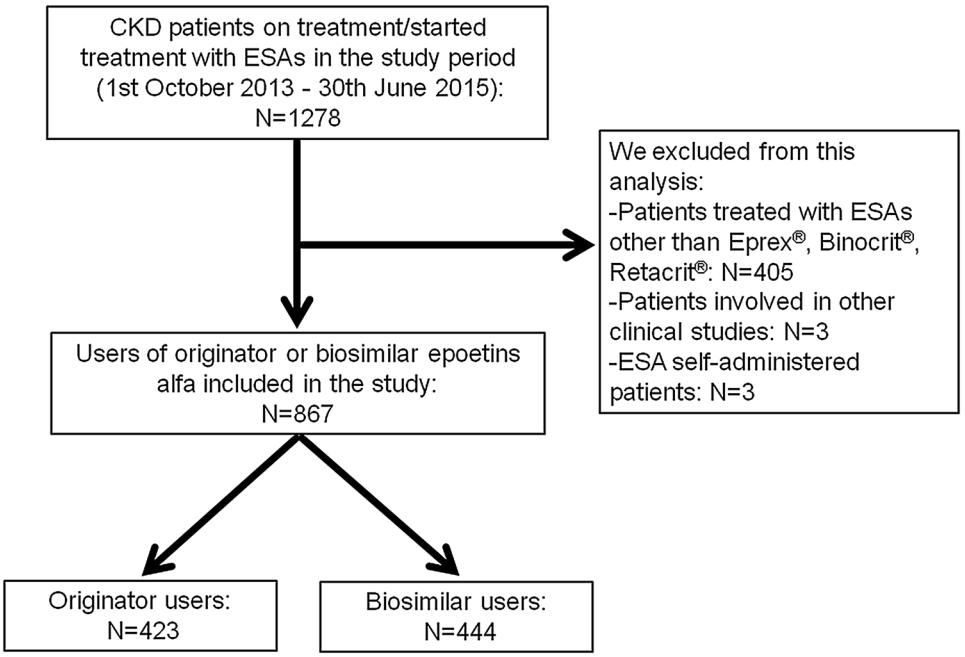

Fig. 1 Flow diagram of patients enrolled in the study. *CKD* chronic kidney disease, *ESA* erythropoiesis-stimulating agents

The two cohorts were largely overlapping regarding time to events (Fig. 2). Approximately 25% of users had an event within 6 months of observation and 40% within 1 year. Moreover, no differences in the survival probability were highlighted when separately considering the three categories of events (Fig. 2).

Neither unadjusted nor adjusted estimates showed any difference in the study outcomes (Table 2). After adjusting for confounding factors, the HR estimates were 1.0 (95% CI 0.7–1.3) for any outcomes; 0.9 (95% CI 0.6–1.5) for infections; 0.9 (95% CI 0.6–1.5) for cardio and cerebrovascular conditions; and 1.1 (95% CI 0.7–1.8) for problems related to the dialysis device. No statistically significant association was found for the individual outcomes within each category of events (Table 2).

3.3 Subgroup and Ancillary Analyses

Since our study cohort was mainly composed of prevalent users (about 88% of the study population), we also restricted the analysis to incident users ($n = 102$). The results were similar to those observed in the whole population, with 33 patients (32.4%) experiencing at least one safety outcome and no statistically significant difference between biosimilar and originator epoetin users (adjusted HR: 0.4; 95% CI 0.1–1.1).

An ancillary analysis was also carried out to evaluate the differences in the number of patients needing transfusions: 46 (10.3%) and 52 (12.3%) in the originator and biosimilar cohorts, respectively. With regard to the Hb level at the last measurement during follow-up, which can be considered as an indicator of quality of care, the average Hb was 11.0 mg/dL in the biosimilar cohort and 11.1 mg/dL in the originator one.

During the 12-month follow-up, 127 deaths occurred in the study population (14.6%). In an intention-to-treat analysis, the adjusted HR was 1.3 (95% CI 0.8–2.1) when comparing biosimilar with originator users.

4 Discussion

4.1 Comparison with Previous Studies

The results from this study confirm the similarity in terms of safety between originator epoetin alpha and biosimilars when used in patients with CKD receiving dialysis. Specifically, no difference emerged between the two cohorts of users with regard to any kind of adverse events.

Phase III equivalence studies have been carried out in patients with CKD to obtain marketing authorization. These studies showed that biosimilars were therapeutically equivalent to the comparator epoetin alfa in changing mean absolute Hb; the two products also had a comparable safety profile in the intravenous treatment of anemia with regard to adverse events, serious adverse events, and death [7, 8].

Completed and ongoing observational post-authorization studies provide important additional information in a real-world setting under conditions of greater heterogeneity of patients and clinical practices [9]. PASCO I and EPO-PASS were single-arm studies designed to investigate the incidence of adverse events of epoetin alfa biosimilars; these studies

Table 1 Characteristics of patients included in the study

Characteristics	Originator $N=423$ (%)	Biosimilar $N=444$ (%)	p value
Prevalent users	377 (89.1)	388 (87.4)	0.4
Incident users	46 (10.9)	56 (12.6)	
Gender			
Male	270 (63.8)	273 (61.5)	0.5
Female	153 (36.2)	171 (38.5)	
Age, years (median; IQR)	(64; 53–75)	(76; 68–81)	<0.05
Age classes, years			
≤60	158 (37.4)	55 (12.4)	
61–70	101 (23.9)	79 (17.8)	<0.05
71–80	109 (25.8)	186 (41.9)	
≥81	55 (13.0)	124 (27.9)	
Dry weight, kg (mean ± SD)	68.1 ± 16.2	68.0 ± 14.9	0.9
Dialysis duration, months (median; IQR)	(36; 15–82)	(28; 11–66)	0.002
Previous renal transplant	60 (14.2)	17 (3.8)	<0.05
Previous peritoneal dialysis	40 (9.5)	40 (9.0)	0.8
Vascular access			
Arteriovenous fistula	319 (75.4)	275 (61.9)	
Venous catheter	81 (19.1)	155 (34.9)	<0.05
Not specified	23 (5.4)	14 (3.2)	
Dialysis sessions per week			
Two	26 (6.1)	44 (9.9)	
Three	382 (90.3)	390 (87.8)	0.07
Not specified	15 (3.5)	10 (2.3)	
Waiting list for transplant			
Yes	77 (18.2)	17 (3.8)	
No	329 (77.8)	423 (95.3)	<0.05
Not specified	17 (4.0)	4 (0.9)	
Diagnosis leading to renal failure			
Diabetic nephropathy	66 (15.6)	61 (13.7)	0.4
Glomerulonephritis	56 (13.2)	45 (10.1)	0.2
Polycystic kidney disease	34 (8.0)	33 (7.4)	0.7
Hypertensive nephropathy	6 (1.4)	11 (2.5)	0.3
Nephropathy NOS	109 (25.8)	136 (30.6)	0.1
Other nephropathy	152 (35.9)	158 (35.6)	0.9
Comorbidities			
Hypertension	320 (75.7)	330 (74.3)	0.7
Vascular disease	167 (39.5)	188 (42.3)	0.4
Diabetes mellitus	121 (28.6)	155 (34.9)	0.05
Heart failure	97 (22.9)	118 (26.6)	0.2
Coronary heart disease	96 (22.7)	102 (23.0)	0.9
Arrythmia	95 (22.5)	130 (29.3)	0.02
Cerebrovascular disease	75 (17.7)	76 (17.1)	0.8
Valvular heart disease	19 (4.5)	16 (3.6)	0.5
Prescription drugs			
Number of prescription drugs per patient (mean ± SD)	8.3 ± 4.9	7.9 ± 4.4	0.2
Iron supplementation	120 (28.6)	127 (28.6)	0.7
Hemoglobin[a] (mean ± SD)	10.9 ± 1.2	10.8 ± 1.3	0.7
Epoetin dosage at the study start, IU (mean ± SD)	5957 ± 3447	5426 ± 3176	0.02

IQR interquartile range, *NOS* not otherwise specified, *SD* standard deviation

[a]The 2 weeks preceding or following the index visit were accepted as baseline measurement (measurement was available for 279 patients in the originator cohort and 307 patients in the biosimilar one)

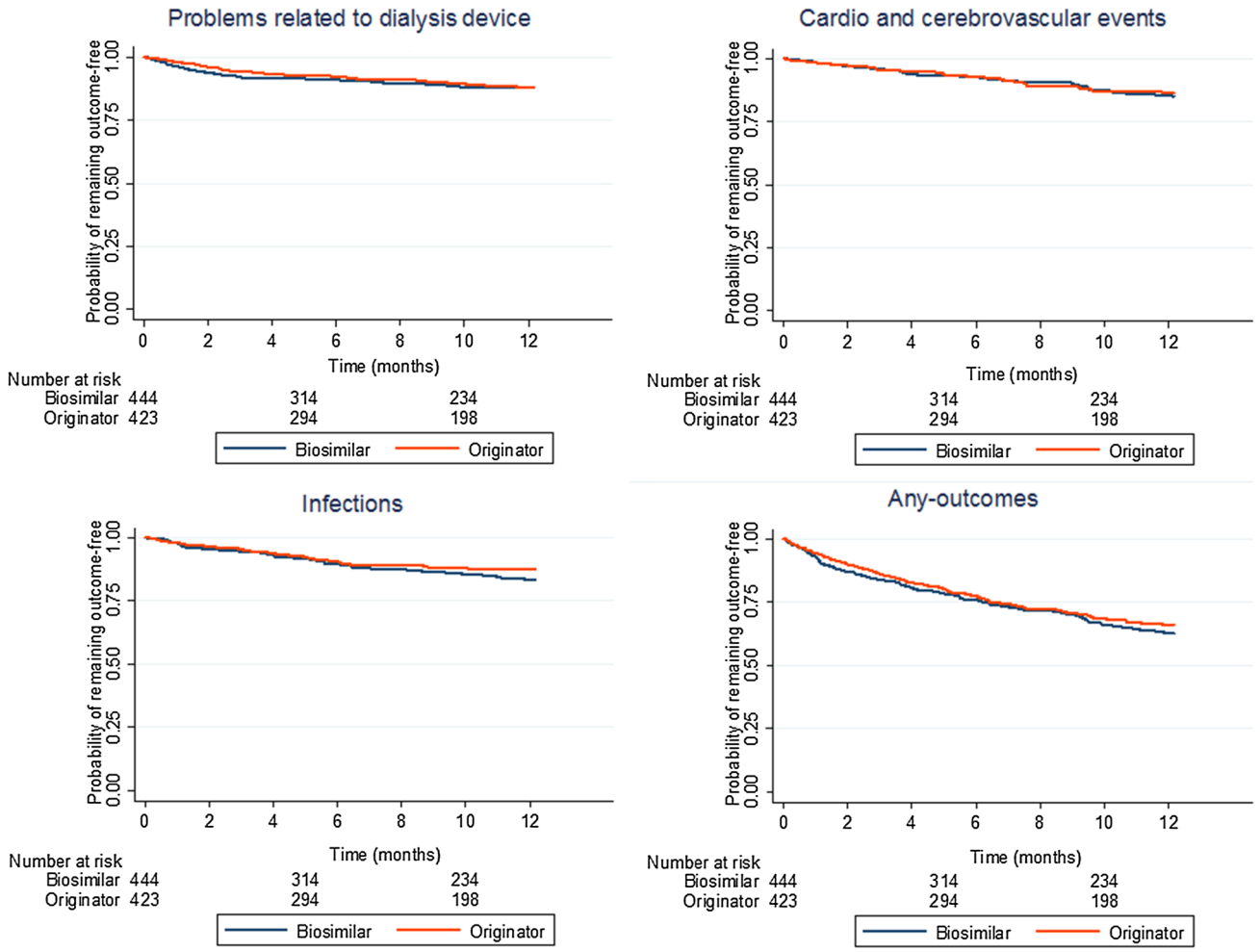

Fig. 2 Kaplan–Meier survival analysis for outcomes grouped into three major categories and considered all together

ascertained that their safety profiles were in line with other ESAs and with the data from pre-marketing studies [10, 11]. In particular, the PASCO I study was conducted for up to 1 year among patients with renal anemia treated with an intravenous epoetin biosimilar [10]. The median age was similar to our findings, while other characteristics such as the proportion of patients with diabetes or cerebrovascular diseases differed significantly. We found a similar frequency of fistula and shunt malfunction (about 10% of patients); the differences observed in relation to other events may be due to different inclusion criteria. With regard to EPO-PASS, our study had a comparative design (enabling a direct comparison between epoetin alpha drugs), focused on more severe patients (CKD patients without dialysis were not included), and had a longer follow-up (12 vs 6 months) [11].

A recent large observational study based on the record linkage of different regional databases (the Electronic Therapeutic Plan Register, the Health Care Assistance File, the Mortality Information System, and the Hospital Information System of the Lazio Region) did not find any difference between originator epoetin alfa and biosimilars on relevant effectiveness and safety outcomes measured during the follow-up period in patients with CKD [12]. In this study, comparing the occurrence of a composite outcome (including all-cause mortality, blood transfusion, major cardiovascular events, and blood dyscrasia), the adjusted HR was 1.02 (95% CI 0.78–1.33). However, only a small number (154: 1.9%) of the 8161 CKD patients included had received an epoetin alfa biosimilar; moreover, even though many potential confounders were taken into account, limited clinical information was available at baseline (e.g., dry weight, comorbidities, iron supplementation) because of the retrospective study design. In our study, we observed the same estimates in a population of biosimilar users that was almost three times larger and for which individual clinical information was recorded at baseline and during the 1-year follow up by means of an ad hoc case report form. A recently published comparative study (involving 57 and 47 patients who received originator and biosimilar epoetins, respectively) found that both groups of products were equally effective and safe for the

Table 2 Frequency distribution of safety outcomes by ESA exposure status

	Originator	Biosimilar	Unadjusted HR 95% CI	Adjusted HR[a] 95% CI
Person-months	3295	3668		
Any outcomes	123	151	1.1 (0.9–1.4)	1.0 (0.7–1.3)
Infections	42	58	1.3 (0.9–1.9)	0.9 (0.6–1.5)
Other infections	18	30	1.5 (0.8–2.7)	1.3 (0.7–2.4)
Respiratory infections	15	17	1.0 (0.5–2.1)	1.0 (0.5–2.1)
Sepsis	9	11	1.1 (0.5–2.7)	0.9 (0.3–2.2)
Cardio and cerebrovascular events	42	50	1.1 (0.7–1.6)	0.9 (0.6–1.5)
Bleeding	15	13	0.8 (0.4–1.6)	0.9 (0.4–2.0)
Arrhythmia	3	12	3.2 (0.9–11.3)	3.2 (0.9–11.3)
Peripheral ischemia	6	9	1.4 (0.5–3.9)	0.9 (0.3–2.5)
Cerebral accident	6	6	0.9 (0.3–2.7)	0.6 (0.2–2.0)
Coronary disease	6	4	0.6 (0.2–2.1)	0.7 (0.2–2.9)
Thrombosis	6	3	0.4 (0.1–1.8)	0.7 (0.2–3.2)
Heart failure	0	3		
Problems related to dialysis device	39	46	1.1 (0.7–1.7)	1.1 (0.7–1.8)
Vascular complications of the fistula	26	34	1.2 (0.7–2.0)	1.1 (0.6–2.1)
Localized infections	8	6	0.7 (0.2–2.0)	0.6 (0.2–1.8)
Vascular complications of the catheter	5	6	1.1 (0.3–3.6)	1.5 (0.4–5.4)

CI confidence interval, *ESA* erythropoiesis-stimulating agents, *Hb* hemoglobin, *HR* hazard ratio

[a]HRs were adjusted for age, vascular access, vascular disease, cerebrovascular disease, heart failure, diabetes, diabetic and hypertensive nephropathy, glomerulonephritis and epoetin dosage at the study start. Hb levels at baseline were not included in the final model since no difference in the two cohorts of users was observed

treatment of anemia in patients with CKD [13]. However, in the cohort treated with one of the originator epoetins, only six patients were receiving epoetin alpha, thus limiting the transferability of the comparison between originator epoetin alpha and biosimilars.

We found that patients who received biosimilars were significantly older, with more comorbidities, and were more likely not to be included on the transplant waiting list than those treated with the originator. This partly reflects the results shown in other studies where patients receiving biosimilar ESAs were slightly older and with more comorbidities such as diabetes [1, 13]. These observations may suggest that doctors who are concerned with the benefit–risk profile of biosimilars might preferentially select the originators to treat younger and healthier patients.

4.2 Implications for Clinical Practice and Health Systems

The European Medicines Agency (EMA) was the first regulatory authority in 2005 to clarify the general principles to be applied to a biological medicinal product claiming to be similar to another one already on the market [14]. However, the evaluation of biosimilar medicines for authorization purposes by the EMA does not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. Consequently, any recommendations for switching are within the remit of the EU member states [15].

The issue of biosimilar use is still a matter of debate, at least in Italy: the various scientific societies [3], patient associations [16], and political authorities [4, 17] operating at the local level express different positions, therefore contributing to the caution of clinicians. For instance, while our study was ongoing in 2014, the Italian Society of Pharmacology (SIF) published a working paper suggesting the need to carry out additional studies gathering real-life data on the comparative safety and efficacy of originator and biosimilar ESAs [3]. Moreover, Italian consumption data showed a modest use of biosimilar epoetins, which accounted for only 37% of the total defined daily dose per 1000 inhabitants per day in 2016, although an increase of 20% was observed from 2015 to 2016 [18].

Our study involved only four Italian regions, accounting for about 15% of the Italian population. However, there is no reason to expect that any clinical characteristics associated with the geographical area would modify the estimated safety of the epoetin originator and biosimilars. Therefore, the findings of our study should contribute to reassuring physicians about the equivalence of the epoetin alfa originator and biosimilars. The analysis of the available evidence accumulated during almost 10 years of use, in addition to post-authorization

studies and spontaneous reports, may help scientific societies in making clearer statements about the equivalence of the two products. More generally, studies aimed at comparing originator and biosimilar drugs, far from being redundant, will reinforce the credibility of the approval process of any biosimilar and thus boost confidence in their use.

The study had a limited power to detect a difference between the two formulations in terms of incidence of rare events such as hypersensitivity reactions (e.g., pure red cell aplasia [PRCA]). However, even though no event of PRCA was observed in our study, this information is of value in that it can contribute to a meta-analysis of studies that collected similar data at an individual-patient level.

Given the observational nature of the study, no indication was provided to the participating centers about the use of different epoetin alpha products; since almost all the biosimilar prescriptions referred to one biosimilar epoetin, the observed findings cannot be extended to the other marketed products. Moreover, our findings do not extend to the comparative safety of all marketed epoetins. Since the main objective of the study was to establish whether any clinically relevant difference could be highlighted between biosimilar and originator epoetin alfa products in current practice, we excluded from the analysis patients receiving other originator epoetins.

5 Conclusion

In conclusion, the study did not show any differences in the safety outcomes of originator and biosimilar epoetins. Even though relevant to the clinical setting of dialysis, our findings provide further reassurance about the use of biosimilars in clinical practice.

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Compliance with Ethical Standards

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Conflicts of interest Giovanna Stoppa, Carmen D'Amore, Anita Conforti, Giuseppe Traversa, Mauro Venegoni, Maurizio Taglialatela, and Roberto Leone declared that they have no conflicts of interest.

Ethical approval The study protocol was approved by the Ethics Committees of the participating hospitals. Written informed consent was obtained from all individual participants included in the study.

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