Comparative Effectiveness of Dynamic Treatment Strategies for Medication Use and Dosage

Emulating a Target Trial Using Observational Data

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Background: Availability of detailed data from electronic health records (EHRs) has increased the potential to examine the comparative effectiveness of dynamic treatment strategies using observational data. Inverse probability (IP) weighting of dynamic marginal structural models can control for time-varying confounders. However, IP weights for continuous treatments may be sensitive to model choice.

Methods: We describe a target trial comparing strategies for treating anemia with darbepoetin in hemodialysis patients using EHR data from the UK Renal Registry 2004 to 2016. Patients received a specified dose (microgram/week) or did not receive darbepoetin. We compared 4 methods for modeling time-varying treatment: (A) logistic regression for zero dose, standard linear regression for log dose; (B) logistic regression for zero dose, heteroscedastic linear regression for log dose; (C) logistic regression for zero dose, heteroscedastic linear regression for log dose, multinomial regression for patients who recently received very low or high doses; and (D) ordinal logistic regression.

Results: For this dataset, method (C) was the only approach that provided a robust estimate of the mortality hazard ratio (HR), with less-extreme weights in a fully weighted analysis and no substantial change of the HR point estimate after weight truncation. After truncating IP weights at the 95th percentile, estimates were similar across the methods.

Conclusions: EHR data can be used to emulate target trials estimating the comparative effectiveness of dynamic strategies adjusting treatment to evolving patient characteristics. However, model checking, monitoring of large weights, and adaptation of model strategies to account for these is essential if an aspect of treatment is continuous.

Keywords: Anemia; Continuous treatment; Erythropoiesis stimulating agents; Hemodialysis; Marginal structural model; Observational data; Target trial

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Randomized controlled trials (RCT) are often preferred for establishing and estimating causal effects of health interventions on patient outcomes, but they can be expensive and time-consuming, and the questions of interest are limited by ethical considerations and the need for equipoise. There is increasing interest in using observational data from electronic health records (EHRs) to examine the comparative effectiveness of treatment strategies, but use of this data also poses challenges.[1] In clinical care, treatments received by a patient change over time, based on the disease progression and response to prior treatment. Time-varying treatment can lead to the possibility of time-varying confounding, when a risk factor for the outcome also predicts subsequent treatment; and when past treatment predicts current risk factor levels. When past treatment predicts current risk factors ("treatment-confounder feedback"), effect estimates from conventional methods (e.g., Cox models conditioning on the time-varying confounders) may be biased.[2] Newer methods, including g-methods[3] such as inverse probability (IP) weighting of marginal structural models (MSM)[4] and the g-formula,[5] can attempt to avoid this bias.

Erythropoiesis stimulating agents (ESAs) are used to correct and maintain hemoglobin levels in chronic kidney disease (CKD) patients.[6] In UK clinical practice, ESA dosing decisions are based on the regular (e.g., monthly)

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The data are not available for replication due to privacy restrictions. Sample code is available from https://github.com/123KB/IPW-medication-use-and-dosage.

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hemoglobin measurements. A clinician reviews the hemoglobin test result and decides whether to alter the ESA dose. This is generally done without a written dosing protocol, and may also consider other clinical and laboratory variables, but the optimal hemoglobin target is unknown. Large RCTs in patients with CKD not yet on dialysis found no evidence of benefit of a higher (compared with lower) hemoglobin target for cardiovascular events, or for a composite outcome of death, myocardial infarction, hospitalization for congestive heart failure and stroke, but found increased risk of adverse events.[7–9] Observational studies suggest the best outcomes occur in patients who have high hemoglobin concentrations but require only low doses of ESAs.[10–12] Adverse effects of higher hemoglobin targets seen in RCTs may thus be due to high ESA doses, particularly in patients with ESA resistance due to other underlying health problems. Hence, results of observational data analyses comparing outcomes when there is a cap on the maximum dose of ESAs might aid clinical decision-making.

"Dynamic" treatment strategies that are sustained over time and adapt treatment to the evolving characteristics of patients can be assessed using g-methods to control for time-varying treatment-confounder feedback, allowing for valid effect estimation from EHR data. Inverse probability (IP) weighting methods, in particular, have become popular in pharmacoepidemiology,[13,14] but there is limited information on the use of these methods when treatment is not a binary decision. In many pharmacoepidemiology applications, patients receive or do not receive a specified drug treatment, with drug dose dependent on patient characteristics. When IP weights are based on the models for continuous treatments, estimates of the comparative effectiveness of different treatment strategies may be sensitive to the choice of model.[15] Using a simulation study, Naimi et al.[16] explored different modeling approaches for constructing IP weights for continuous treatments and recommended an ordinal logistic regression approach (with "quantile binning").

In this article, we described a target trial comparing dynamic strategies for treatment of anemia, using the ESA darbepoetin, in hemodialysis patients using EHR data. Patients were untreated or treated with a specified dose (microgram/week) of darbepoetin, depending on hemoglobin target levels. The aim of the article is to describe 4 methods for time-varying treatment and compare their performance. These methods are as follows: (A) logistic regression models for zero dose and standard linear regression for log dose; (B) logistic regression models for zero dose and heteroscedastic linear regression for log dose; (C) logistic regression models for zero dose, heteroscedastic linear regression for log dose, and multinomial regression for patients who recently received very low or very high doses; and (D) ordinal logistic regression. We examined IP weights resulting from each method and compared resulting estimates of the mortality hazard ratio (HR) of strategies with higher versus lower hemoglobin target levels.

METHODS

Data

The UK Renal Registry (UKRR) collects clinical and biochemical EHR data from all patients receiving renal replacement therapy (RRT) in the United Kingdom. Data are extracted quarterly, with the last test result for that quarter recorded.[17] Estimating comparative effectiveness of different treatment strategies in observational studies requires careful measurement and appropriate adjustment for confounding. The dataset analyzed was based on all patients treated in the participating centers during specified periods and contained information about every ESA prescription decision and the hemoglobin values that led to these, which should mitigate selection bias and lead to the findings being generalizable to other patients receiving hemodialysis. The UKRR obtained bespoke data extractions on hemodialysis patients from 10 centers, including the results of every test (hemoglobin, ferritin, white blood count, albumin, C-reactive protein, and urea reduction ratio) along with ESA dose, drug name, and treatment date. All these variables are in the UKRR dataset and therefore covered by the Registry's permissions. Further information on the extracted data is in the eAppendix; http://links.lww.com/EDE/C52.

Data on 8,131 adult (age ≥18 years) hemodialysis patients treated in UK renal centers between 2004 and 2016 were available for analysis. Of these, 6,773 (83.3%) were on darbepoetin at the start of their follow-up and 7,910 (97.3%) were treated with darbepoetin at some time during follow-up. Doses were predominantly in discrete categories (Figure 1, left panel). The likelihood of not receiving darbepoetin increased with patients' measured hemoglobin at the previous visit (Figure 1, middle panel), while for those on darbepoetin, the median dose decreased with increasing values of measured hemoglobin at the previous visit (Figure 1, right panel).

Research Ethics and Informed Consent

The processing of UK Renal Registry data for research has been approved by the NRES Committee North East—Newcastle and North Tyneside 1 Research Ethics Committee, reference 21/NE/0045. A waiver of consent for research purposes has been granted centrally by the Health Research Authority, reference 16/CAG/0064.

Design of the Target Trial

We designed a target trial to compare the effect on all-cause mortality of ESA treatment strategies based on the specified hemoglobin targets (low-target range, 95–115 g/L and high-target range, 105–125 g/L) among hemodialysis patients. For the full target trial definition and emulation, see eTable 1; http://links.lww.com/EDE/C52. Each strategy follows a protocol for dose change decisions based on the current and previous ESA dose and current and previous hemoglobin (Figure 2) and for acceptable dose changes based on these (eTable 2; http://links.lww.com/EDE/C52). Eligible patients were aged ≥18 years on hemodialysis for at least 3 months

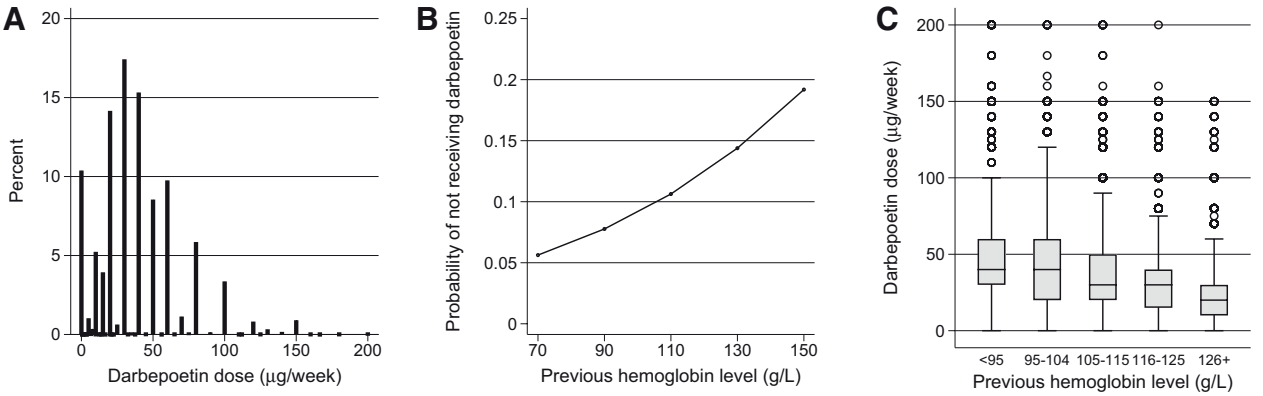

FIGURE 1. Distribution of weekly darbepoetin dose (µg/week) (left, A), probability of zero darbepoetin dose by previous hemoglobin level (g/L) (middle, B), and darbepoetin dose (µg/week) by previous hemoglobin level (g/L) (right, C).

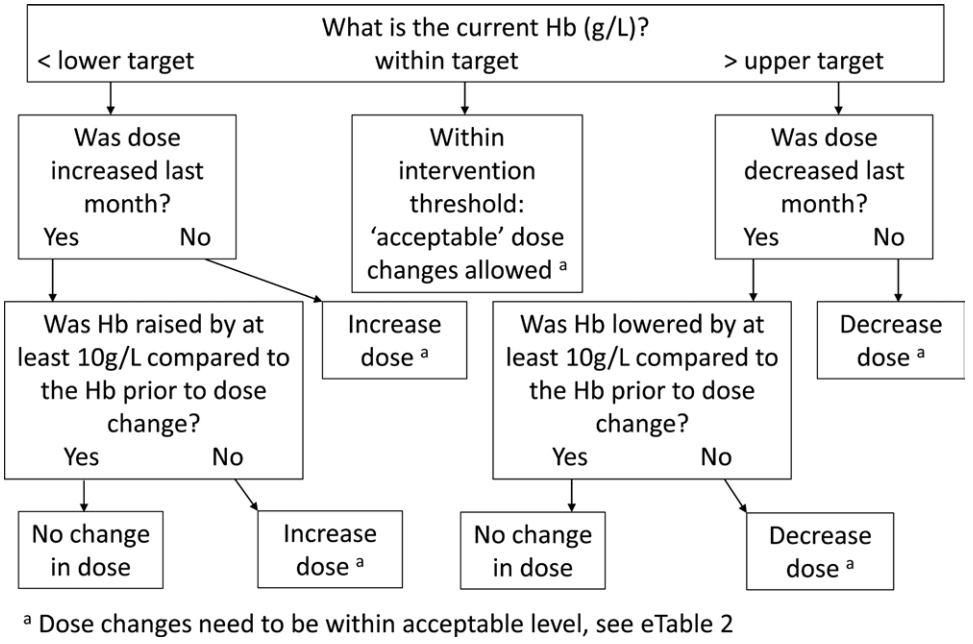

FIGURE 2. Dose change decisions protocol. Hb indicates hemoglobin.

at one of the 10 renal centers and either on darbepoetin or not on darbepoetin with a hemoglobin <110 g/L. Those who had a high darbepoetin dose (≥120 darbepoetin µg/week) and low hemoglobin (<80 g/L) at the time of first eligibility were excluded. Each strategy followed dosing rules based on the current hemoglobin, whether darbepoetin dose was changed in the previous month, and whether hemoglobin changed in response to previous dosing (Figure 2). Cessation of darbepoetin was permitted while a patient's hemoglobin was greater than the upper target for the assigned strategy (eTable 2; http://links.lww.com/EDE/C52). We allowed a grace period of up to 1 month for dose changes to be implemented, when the dosing rule indicated needed changes.[1] Use of grace periods aligns with observed lags in dosing data, makes the strategies more realistic, and minimizes censoring due to departures from assigned strategies. Randomization of treatment assignment is emulated via a cloning procedure. Follow-up started after patients completed 3 months of hemodialysis at a contributing renal center and ended 8 months after baseline, death, or loss to follow-up, whichever happens first. The outcome was all-cause mortality, and the causal contrast of interest was the per-protocol effect.

IP Weighting of a Dynamic Marginal Structural Model

Unlike RCTs, treatment strategies are not explicitly assigned in observational studies, and comparisons rely on treatment received. Inappropriate analysis of observational data, when patient characteristics that vary after the start of follow are used to identify an individual's treatment strategy, can lead to immortal time bias. The "clone, censor, and weight" approach proposed by Hernán[18,19] attempts to avoid this bias and was used in this study. Briefly, we copied

("cloned") all data for each patient and assigned 1 clone to each strategy (high vs. low hemoglobin target). Clones were censored when the patient's data became inconsistent with the clone's assigned strategy: (1) darbepoetin dose was changed but should have stayed constant; (2) darbepoetin dose stayed constant but should have changed; or (3) the darbepoetin dose was changed beyond the range of doses specified by the treatment strategy. The probability of a clone remaining uncensored at each time equals the probability of adhering to the assigned treatment strategy based on the past covariate and treatment history. Therefore, models for treatment were used to derive the probability of being censored at each time point and this probability was used to derive IP weights.

Organizing Darbepoetin Data and Test Results

We included new and established hemodialysis patients during any period between 2004 and 2016 when their treatment center reported at least 60% of hemodialysis patients being treated with ESAs (to minimize misclassification). Patients entered the study at the latest of the dates when their center became eligible and when they first met the target trial eligibility criteria, at which point their follow-up time was set to 0. Data were formatted into discrete time intervals,[20] with 1 observation per person per 28-day ("month") period for the duration that they remained in the study. This structure allowed lagged variables (e.g., darbepoetin dose during the previous months) to predict subsequent values and ensured lagged values are comparable between patients. Further details of how the daily data for an individual patient was converted to monthly data is in the eAppendix; http://links.lww.com/EDE/C52.

Notation

Let T_i denote the observed outcome time in months for patient i and let $A_i(t)$ denote treatment (darbepoetin dose, microgram/week) received by patient i in month t with $A_i(t)$=0 if patient i was not receiving darbepoetin in month t, and where nonzero doses were log-transformed to ensure the distribution was symmetrical. For lagged values of treatment from previous months, we used categories of darbepoetin dose (0, 0.1–20, 20.1–50, and 50.1+ μg/week), to allow zero doses in the lagged variable. The vector $L_i(t)$ represents the covariates in month t for patient i, including cubic splines for hemoglobin (g/L) and lagged hemoglobin from previous month. Further information on covariates is provided in the eAppendix; http://links.lww.com/EDE/C52. $\bar{A}_i(t)$ denotes treatment history (the vector of darbepoetin dose values from baseline to month t) and the matrix $\bar{L}_i(t)$ denotes the history of time-varying covariates for patient i. We often suppress the i subscript denoting individual patient in the notation because we assume that the random vector for each subject is drawn independently from a distribution common to all subjects.

Models for Treatment Received

To construct the IP weights, the following models for treatment received were fit to the original data, and then used to estimate treatment censoring weights for the cloned data. At each month, patients not currently treated with darbepoetin could remain off treatment or start darbepoetin, while those receiving treatment could stop treatment, or remain treated with the same or different dose.

For each method (A)–(D), we used parameter estimates from models to calculate the probability of adhering to the assigned treatment strategy in each month, among patients (clones) who remained uncensored from treatment strategies. The cumulative probability of adhering to strategy j to the end of month t is the product of the probabilities of adhering to strategy j during each month from 1 to t. The IP weights [W(t)] were calculated as 1/probability of adhering to strategy j to the end of month t.

Method (A): Logistic Regression for Zero Dose and Normal Linear Regression for Log-transformed Dose

Method (A) used a 2-step modeling process with the following:

1. Logistic regression for the probability of not receiving darbepoetin each month, fit separately by darbepoetin treatment status in the previous month: $Pr(A(t)=0|\bar{L}(t),\bar{A}(t-2),A(t-1)=0)$ among those not receiving darbepoetin at *t-1*, and $Pr\left(A(t)=0\left|\bar{L}(t),\bar{A}(t-1),A(t-1)\right\rangle 0\right)$ among those receiving darbepoetin at *t-1*, with $A(t)$ coded as 1 during months on darbepoetin. We used cubic splines for months because baseline to model changes in the probability of not receiving darbepoetin since start of follow up. The models also included current values of covariates at month t, and lagged values of hemoglobin (at t-1), and treatment (at months t-2 and t-3).
2. Linear regression model assuming normally distributed (Gaussian) error terms for the probability density of the log of darbepoetin dose each month, among those receiving darbepoetin at month *t-1*: $f\left(A(t)\left|\bar{L}(t),\bar{A}(t-1),A(t-1)\right\rangle 0\right)$.

To estimate the IP weights, we defined $R_l(j,t)$ and $R_u(j,t)$ to be the lower and upper limits of the range of acceptable nonzero doses, for strategy j=1 or 2 and month t, according to the dosing rules (Figure 2 and eTable 2; http://links.lww.com/EDE/C52). For example, if a patient was on a dose of 40 μg/week and the protocol recommended an increase, the acceptable dose range would be 40.1–80 μg/week. If the protocol specified no change, we extended the acceptable range around the current dose to avoid arbitrarily small probabilities. For example, for a dose of 40 μg/week, we calculated the probability of having a dose between 35 and 45 μg/week. The probabilities of zero and nonzero dose were calculated from logistic regression models in step 1 and the probability of prescribed dose being within an acceptable dose range was obtained from the linear model in step 2. We estimated the mean $\mu_{\bar{L}(t),\,\bar{A}(t-1)}=E[A|\bar{L}(t),\,\bar{A}(t-1)]$ and estimated the

constant variance σ^2 as the root mean square error. The overall probability of adhering to the assigned treatment strategy in the current month was the combined probability of nonzero dose (from step 1) and the probability of dose being in the acceptable range (from step 2); i.e., the probability of adhering to strategy *j* is as follows:

$$\Pr(A(t)=0|\bar{L}(t),\bar{A}(t-1)) + \Pr(A(t)>0|\bar{L}(t),\bar{A}(t-1)) \int_{R^l(t,j)}^{R^u(t,j)} f(A(t) \mid \bar{L}(t),\bar{A}(t-1)),$$

if a zero dose is acceptable, and

$$\Pr(A(t)>0|\bar{L}(t),\bar{A}(t-1)) \int_{R^l(t,j)}^{R^u(t,j)} f(A(t) \mid \bar{L}(t),\bar{A}(t-1)),$$

if a zero dose is not acceptable.

Method (B): Logistic Regression for Zero Dose and Heteroscedastic Linear Regression for Log Dose

Method (B) used the logistic regression models from method (A), but replaced the linear model with a multiplicative heteroscedastic linear regression of log-dose, modeling variance as an exponential function of selected covariates and previous darbepoetin dose. We estimated the mean $\mu_{\bar{L}(t),\,\bar{A}(t-1)} = E[A|\bar{L}(t),\,\bar{A}(t-1)]$ and variance $\sigma^2_{\bar{L}(t),\,\bar{A}(t-1)}$ for all combinations of $\bar{L}(t)$, $\bar{A}(t-1)$. Probabilities were calculated using these predicted mean and SD estimates as per method (A).

Method (C): Logistics Regression for Zero Dose, Heteroscedastic Linear Regression for Log Dose, and Multinomial Regression for Coming from Very Low and Very High Doses

Method (C) combined the probabilities estimated from the logistic regression models from method (A) and heteroscedastic linear regression model of log-dose from method (B) with a multinomial logistic regression model for the change in dose, stratified by extreme dose levels (2.5, 5, 120, and 150 μg/week). We coded 8 mutually exclusive groups *G* for an individual's dose change: (1) go off darbepoetin (i.e., move to zero dose); (2) unacceptable decrease in dose for both strategies (i.e., the patient's darbepoetin dose was lowered when the protocol for both strategies said the dose should be constant or increased); (3) acceptable decrease for low hemoglobin strategy only (for when the protocol would only say to lower the darbepoetin dose for the low hemoglobin strategy); (4) acceptable decrease both strategies; (5) keep the darbepoetin dose constant; (6) acceptable increase for both strategies; (7) acceptable increase for high hemoglobin strategy only; and (8) unacceptable increase for both strategies. Further details are shown in eTable 3; http://links.lww.com/EDE/C52.

We used multinomial logistic regression to model the probability of a suitable dose for each stratum of nonzero dose at month *t-1*, and calculated the probability of adhering to each treatment strategy in the current month by summing the predicted probabilities of the appropriate acceptable dose changes: $\sum_{S}^{S} \Pr(A(t)=g|\bar{L}(t),\ A(t-1)=D)$ where D = 2.5, 5, 120,[1] or 150 and S is the vector of suitable dose changes (1,... S) for a given individual in month *t*. For example, from a dose of 2.5 μg/week, if protocol said a patient on the low hemoglobin strategy should increase their dose, we used the probability of "acceptable increase for both strategies." For a patient following the high hemoglobin strategy, if the protocol recommended dose increase, we summed the probabilities of "acceptable increase for both strategies" and "accept increase for high hemoglobin strategy only." The most frequently occurring category, "keep the darbepoetin dose the same," was used as the reference group. Because some groups had small numbers, hemoglobin and month (cubic splines) were the only covariates included in the multinomial models.

Method (D): Ordinal Logistic Regression for all Dose Levels

Finally, in method (D), we transformed dose into an ordinal variable *V*, with 17 levels (coded 0–16) to represent the dosing ladder: 0, 2.5, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 100, 120, 150, and 180 μg/week. Doses between ladder rungs were coded as the higher rung, e.g., a dose of 35 was coded as 40 μg/week. We used an ordinal logistic regression model to estimate the probability of each rung, given prior dose and covariates. For each strategy *j* = 1 or 2 and month *t*, we defined $O_l(j,t)$ and $O_u(j,t)$ to be the lower and upper limits of the range of acceptable doses from the dosing ladder, including zero dose, according to the dosing rules (Figure 2 and eTable 4; http://links.lww.com/EDE/C52). To obtain the probability of prescribed dose being within an acceptable dose range in the current month, we combined the probabilities of each dose within the range:

$$\sum_{O_l}^{O_u} \Pr(A(t)=v|\bar{L}(t),\ A(t-1).$$

Comparative Effectiveness Estimation

We created IP censoring weights for withdrawal from the target trial if a patient (1) changed from hemodialysis to peritoneal dialysis, (2) had a kidney transplant, or (3) was lost to follow-up (eAppendix; http://links.lww.com/EDE/C52). For all methods above, we multiplied treatment and withdrawal weights together to give a final model weight. We also truncated final weights truncated at the 90th, 95th, and 99th percentile of the weight distribution to mitigate the impact of large weights.

We fit a pooled logistic regression model to the cloned data to estimate the HR for all-cause mortality comparing high versus low hemoglobin targets (reference group). The outcome model included cubic splines for month and used robust standard errors for clustering by patient. We also conducted an unadjusted analysis by fitting an unweighted pooled logistic regression model for mortality after censoring, using only the terms for treatment strategy and time, and sensitivity analyses omitting withdrawal weights.

RESULTS

A total of 8,131 patients met the eligibility criteria and were included in the analyses. There were 355 deaths from 38,337 patient months in the lower hemoglobin strategy and 303 deaths from 37,422 months in the higher hemoglobin strategy. In an unweighted analysis, the estimated mortality HR comparing the higher to the lower hemoglobin strategy was 0.87 (95% CI, 0.81, 0.94).

The linear regression model for log-dose in method (A) showed evidence of heteroscedasticity: the variance of the residuals varied with predicted dose (eFigure 1; http://links.lww.com/EDE/C52; Breusch-Pagan test $P < 0.001$). Method (A) also resulted in some very large IP weights (>9999) due to high (>50) monthly treatment weights (Table). Large weights were most common when patients' prior darbepoetin dose was at an extreme of the dose distribution (Figure 3A), suggesting the model did not predict well for patients with very small or very large prior darbepoetin doses. The 99th, 95th, and 90th percentile of the final weights were as follows: 113.2, 13.0, and 6.7, respectively (Table 1). The fully weighted model was influenced by extreme weights, giving an estimate of the HR of 0.09 (95% CI, 0.01, 0.56). After truncating weights at the 99th percentile (113.2), the estimate HR was 0.96 (95% CI, 0.81, 1.13).

Method (B) accounted for heteroscedasticity, and compared with method (A), the 99th, 95th, and 90th percentile of the final weights were reduced slightly: 87.1, 11.0, and 5.9, respectively (Table 1). However, final model weights still showed extreme values (>9999) stemming from months with very low or very high prior doses (Figure 3B). The estimated of HR for method (B) from the weighted analysis was as follows: 0.05 (95% CI, 0.01, 0.37). After truncating weights at the 99th percentile (87.1), the HR was 0.96 (95% CI, 0.81, 1.13).

Method (C) adapted method (B) to deal with large weights by using multinomial models for extreme dosages (Figure 3C). The 99th, 95th, and 90th percentile of the overall (cumulative) weights from method (C) were as follows: 23.8, 8.6, and 5.3, respectively, and the estimated HR for the weighted analysis was 0.94 (95% CI, 0.76, 1.15). This estimated HR was relatively similar after truncating the weights at the 99th percentile (23.8), although CIs were a little narrower: 0.91 (95% CI, 0.80, 1.04). The sensitivity analysis, fitting method (C) without withdrawal weights found a very similar estimated HR: HR 0.94 (95% CI, 0.76, 1.16).

Finally, method (D) used an ordinal logistic approach across the levels of dose, but the proportional odds assumption

TABLE. Results from the Different Modelling Approaches Estimating the Hazard Ratio for All-cause Mortality Comparing High versus Low Hemoglobin Strategies

				Distribution of Weights					
Method	Description	Truncation of Weights	Median (IQR)	90th pct	95th pct	99th pct	Max	Hazard Ratio	95% CI
A	Logistic regression models for zero dose and normal linear regression for log dose	Full	1.6 (1.7)	6.7	13.0	113.2	>9999	0.09	(0.01, 0.56)
		99th pct	1.6 (1.7)	6.7	13.0	113.2	113.2	0.96	(0.81, 1.13)
		95th pct	1.6 (1.7)	6.7	13.0	13.0	13.0	0.92	(0.83, 1.03)
		90th pct	1.6 (1.7)	6.7	6.7	6.7	6.7	0.90	(0.82, 0.99)
B	Logistic regression models for zero dose and heteroscedastic linear regression for log dose	Full	1.5 (1.6)	5.9	11.0	87.1	>9999	0.05	(0.01, 0.37)
		99th pct	1.5 (1.6)	5.9	11.0	87.1	87.1	0.96	(0.81, 1.13)
		95th pct	1.5 (1.6)	5.9	11.0	11.0	11.0	0.93	(0.84, 1.04)
		90th pct	1.5 (1.6)	5.9	5.9	5.9	5.9	0.91	(0.83, 1.00)
C	Logistic regression models for zero dose, heteroscedastic linear regression for log dose, and multinomial regression for coming from very low and very high doses	Full	1.5 (1.5)	5.3	8.6	23.8	793.7	0.94	(0.76, 1.15)
		99th pct	1.5 (1.5)	5.3	8.6	23.8	23.8	0.91	(0.80, 1.04)
		95th pct	1.5 (1.5)	5.3	8.6	8.6	8.6	0.91	(0.82, 1.01)
		90th pct	1.5 (1.5)	5.3	5.3	5.3	5.3	0.90	(0.82, 0.99)
D	Ordinal regression model for all levels of dose	Full	1.8 (3.7)	14.4	33.5	387.7	>9999	0.22	(0.05, 0.94)
		99th pct	1.8 (3.7)	14.4	33.5	387.7	387.7	1.07	(0.83, 1.37)
		95th pct	1.8 (3.7)	14.4	33.5	33.5	33.5	0.99	(0.87, 1.13)
		90th pct	1.8 (3.7)	14.4	14.4	14.4	14.4	0.93	(0.83, 1.03)

Full weights means that no truncation has taken place. 99th pct means the weights have been truncated at the 99th percentile. A pooled logistic regression model was fitted to the cloned data to estimate the hazard ratio for all-cause mortality comparing high versus low hemoglobin strategy (reference group).

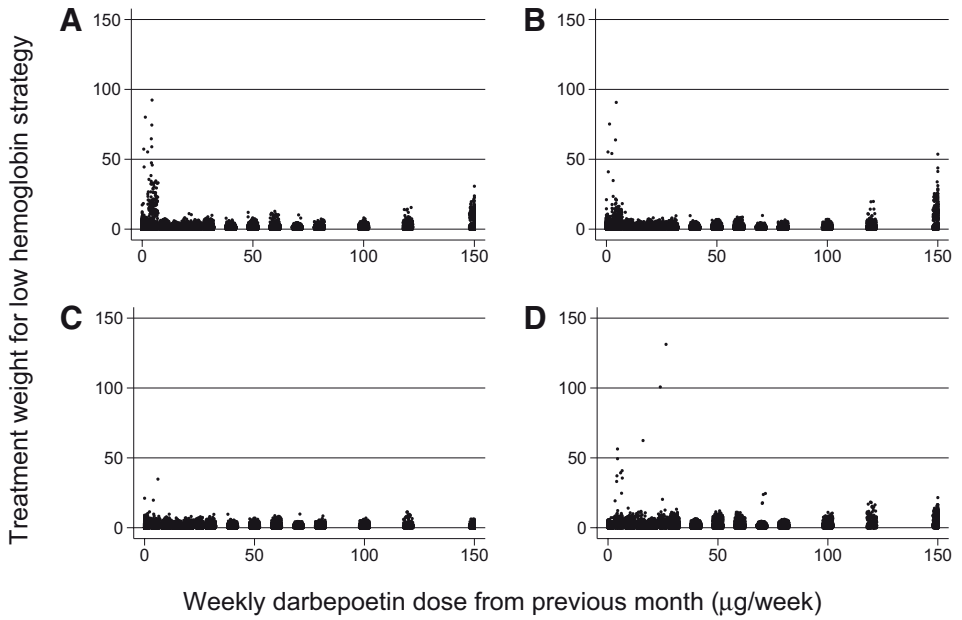

FIGURE 3. Monthly treatment weight for the low hemoglobin strategy by previous darbepoetin dose (µg/week), for methods (A)–(D).

was not met (Brant[21] test $P < 0.001$). The 99th, 95th, and 90th percentile of the overall (cumulative) weights using method (D) were as follows: 387.7, 33.5, and 14.4, respectively, and the fully weighted analysis appeared influenced by extreme weights (>9999): HR 0.22 (95% CI, 0.05, 0.94).

After truncating the model weights at the 95th percentile, estimated HRs were similar across all methods (Table 1). The estimated weighted survival curves for the 4 methods are presented in eFigure 2; http://links.lww.com/EDE/C52. After truncating weights at the 95th percentile, curves were similar across all methods. For completeness, the estimated unweighted survival curve is presented in eFigure 3; http://links.lww.com/EDE/C52. Based on the improved model fit and distribution of weights, we concluded that method (C) was the best IP weighting strategy for this dataset and treatment setting.

DISCUSSION

We used observational EHR data obtained from the UKRR to emulate a target trial estimating the effects of higher versus lower target hemoglobin strategies on all-cause mortality in hemodialysis patients, taking account of time-varying confounding by hemoglobin levels. We compared different modeling approaches for deriving IP treatment weights for medication use and dosage (ESA dose, if prescribed) and determined that a flexible modeling approach provided the most robust results in this dataset. Method (C) had less-extreme weights in a fully weighted analysis and was the only approach where there was no substantial change of the HR point estimate after weight truncation. The goal of weight truncation is to improve the variance at the cost of potentially introducing a small amount of residual confounding.[22] Ideally, we expect to see truncation narrow the confidence interval without affecting the point estimate substantially; this was the case for method (C). For the other methods, there was a large difference in the HR point estimates between the untruncated and truncated results, and this suggests that the weights were not performing well. Our final weights modeling approach combined logistic regression models for zero dose, heteroscedastic linear regression for log-dose, and multinomial models for extreme doses. However, after we truncated the model weights at the 95th percentile, estimates of HRs were similar regardless of method.

Emulating a target trial with detailed observational data has several strengths. Explicitly specifying the protocol of the target trial and describing how to emulate it with observational data ensures synchronization of eligibility and treatment assignment with time zero. This can prevent[23] prevalent user bias,[24] which could occur if prior successful treatment reduces the risk of adverse events following future treatment and immortal time bias,[18] which can occur if treatment categorization depends on survival time. The UKRR is a large and highly representative database allowing trends in clinical practice patterns to be captured.[12] The bespoke extract for this project allowed us to carry out an in-depth analysis of observational data. Together, the data and study design allow the estimation of the causal effect of higher versus lower hemoglobin targets outside of an RCT.

Our study also has several limitations. First, some renal centers do not routinely record computerized data on

darbepoetin dose or drug type, limiting the number of centers we could include. To minimize inaccurate dose information, we restricted to centers reporting at least 60% of hemodialysis patients being treated with ESAs. Second, the use of a dynamic treatment strategy, while more realistic, meant that we could not use stabilized IP weights that are commonly used for static regimes. Alternative numerators for the weights for dynamic regimes are not guaranteed to produce estimates that are less variable than those obtained using unstabilized weights.[25] As a result we had some large IP weights in all methods and our variance was high. Confidence intervals were narrower with truncated weights, but truncation can reintroduce some residual confounding. Finally, although we used statistical methods that appropriately control for measured time updated confounders, no observational study can exclude the possibility of unmeasured confounding. However, because hemoglobin results are the main clinical decision factor in ESA dosing, we anticipate that our dataset captured the most important source of confounding. High blood pressure may have led to some ESA doses being delayed or omitted. Because only prescribed doses were recorded in the electronic health record and we did not have data on blood pressure, we were unable to adjust for this.

We encountered some novel methodologic challenges when attempting to design a clinically relevant and computationally feasible target trial for emulation with the observational data. The main steps we followed in our analysis are shown in Figure 4. Our first attempt at a target trial design aimed to compare restrictive with liberal dosing strategy to achieve a standard hemoglobin target with darbepoetin doses decreased or increased according to a strict dosing ladder, but this resulted in patients being rapidly censored due to treatments inconsistent with assigned strategies. While an RCT comparing these strategies might be feasible, observational emulation requires that patients actually followed the 2 dosing strategies being assessed in clinical practice. Our final target trial design reflected more closely treatment policies used by clinicians during the follow-up period. A second challenge was the requirement to model a continuous treatment. Most prior implementations of IP weighting of MSMs have relied on dichotomous treatment strategies, with little guidance available on modeling more complex treatment strategies. Positivity is an important assumption when carrying out IP weighting; if the treatment of interest is binary, e.g., medicine use, the assumption is that there are both treated and untreated individuals at each level of the combination of covariates. When treatment is continuous, e.g., dose of a medicine, it must be possible to receive every level of the dose at each level of the combination of covariates. Near violations of this assumption can lead to extreme IP weights. An alternative analytic approach would be to use the g-formula, which is more robust to sparse data and could reduce the difficulties in estimating continuous treatments, but which is less widely known in pharmacoepidemiology. We advise that others who wish to use these methods for similar applications and future directions use large, rich datasets that include detailed information about the treatment and covariates at baseline and throughout follow-up. Careful checking of model assumptions, and examination of the distribution of inverse probability weights, is essential when making causal inferences about the comparative effectiveness of dynamic treatment strategies based on the observational data.

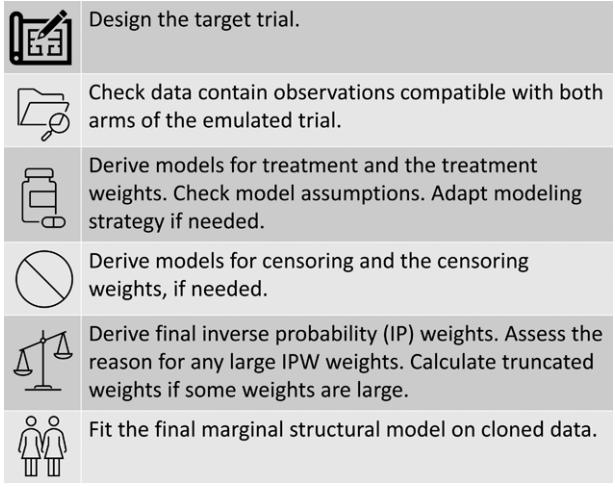

FIGURE 4. The process followed to arrive at the final estimate of the causal effect of the treatment strategies compared.

Our study demonstrates the emulation of a target trial with data from EHRs to estimate comparative effectiveness of dynamic strategies that are sustained over time and adjust treatment to evolving characteristics of patients. However, careful model checking, monitoring of large model weights, and adaptation of modeling strategies to account for these is essential whenever treatment is continuous.

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