SUPPLEMENTAL MATERIAL

"Safety of Dynamic Intravenous Iron Administration Strategies in Hemodialysis Patients"

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Data sources

We constructed our study cohort using a limited data set derived from the electronic health records of a large dialysis organization in the United States, linked with the United States Renal Data System (USRDS) (2009-2012). With over 2,042 dialysis centers located throughout the country, this dialysis provider manages services to approximately one third of all Americans with ESRD receiving dialysis (1). The limited data set was statistically deidentified to make sure the re-identification risks for the data are very small. We obtained detailed clinical information regarding patients' dialysis treatments, vascular access, laboratory test data, intravenous (IV) medications, and anemia management using this clinical database from the dialysis organization. We obtained information regarding their demographic characteristics, comorbidities, healthcare system encounters, and outcomes of interest including death from the USRDS. The study was approved by the University of North Carolina at Chapel Hill Institutional Review Board (IRB #15-1991).

Study design and study population

We used a retrospective cohort design with the index date for IV iron administration strategy defined as the first time a TSAT test result became available within 90-136 days after dialysis initiation. The range of 90-136 days was chosen to ensure patients were receiving chronic anemia management after surviving the first 3 months of dialysis. We anchored the index date on the date of a TSAT measurement result because in clinical practice: (1) recommendations for subsequent IV iron dosing approach typically occur upon the availability of iron indices tests; (2) TSAT is updated more frequently than ferritin (approximately monthly versus quarterly); and (3)

when no current ferritin is available, the last available ferritin is used with the updated TSAT to make treatment recommendations. The TSAT measurement on the index date was defined as the index TSAT. We defined treatment intervals as the period between two consecutive TSAT measurements. The treatment interval between the index TSAT and its subsequent TSAT measurement was defined as the index treatment interval.

We used the 14-day window following the index TSAT to assess the index IV iron administration strategy a patient was initiated on in the index treatment interval. We defined the baseline period as the period starting 90 days prior to dialysis initiation and ending on the day before the index date. Eligible patients were followed for outcomes of interest in a 4-month follow-up period starting on day 15, the day following the index strategy assessment window (Figure 1).

Our study population comprised outpatients who initiated in-center hemodialysis between 1 January, 2009 and 16 September, 2012 and survived up to 90 days after dialysis initiation (Supplemental Figure 1). We excluded patients who (1) aged <65 years at initiation (to get their comprehensive clinical history for confounding control), (2) who did not have Medicare as primary insurer, (3) did not continue hemodialysis for ≥90 days, (4) had incomplete information on baseline covariates (2), or (5) had <9 dialysis sessions in the baseline month prior to the index date to ensure patients were receiving regular hemodialysis and anemia management. We also excluded patients who had polycystic kidney disease because their iron administration strategies could differ due to their heterogeneity of need for erythropoiesis stimulating agents.

IV iron administration strategies

We considered five dynamic IV iron administration strategies that were adapted from existing protocols used by several dialysis organizations in contemporary routine practice, but that have never been compared in randomized trials. Each strategy consisted of a set of decision rules that specified a range of acceptable iron therapy values (including dose and frequency) during a treatment course given a patient's current iron status values (Table 1).

We identified the IV iron administration strategies initiated by eligible patients in the index treatment interval using an approach outlined in Li et al (3, 4). This identification approach matched a patient's treatment pattern in the 14-day assessment window and current iron status test values with candidate strategies by concordance. The length of assessment window was chosen to maximize the representativeness of treatment experience during the assessment window for the treatment experience in the entire treatment course while minimizing the days required for assessment to maximize follow-up time for outcomes (Supplemental Figure 2). Each candidate strategy consisted of a set of decision rules that specified a range of acceptable iron therapy values (including dose and frequency) during a treatment course given a patient's current iron status test values (Table 1). These candidate strategies were adapted from existing protocols used by dialysis clinics of several dialysis organizations in contemporary routine practice; we incorporated expert opinion in the development of candidate strategies. We assessed the levels of ferritin and hemoglobin on the same day of TSAT measurement. If ferritin and hemoglobin values were not available on the index date, values were obtained from their previous measurements. Patients were excluded from the main analyses if their treatment patterns in the 14-day assessment window were incompatible with any of the candidate strategies.

Effect measure of interest

We estimated the 120-day cumulative risks of two safety outcomes, all-cause mortality and infection-related events, under continuous treatment with each IV iron administration strategy. We focused on this per-protocol effect of these administration strategies—the effect that would have been observed if patients had adhered to their assigned administration strategy throughout the 120-day follow-up—because the typical intention-to-treat effect may be suboptimal for assessment of comparative effectiveness or safety, particularly in the presence of non-adherence to the strategy (5, 6).

Outcomes

Two safety outcomes were examined: all-cause mortality and a composite outcome of infection-related hospitalization (sepsis, vascular access infection, or pneumonia) or death in the four months following initiation of IV iron administration strategy. These events were identified using Medicare inpatient and outpatient claims and death notification data with definitions listed in Supplemental Table 1. Other potential IV iron-induced safety outcomes, including cardiovascular events, would occur over a much longer timeframe and were beyond the scope of this study.

Patients were censored by death attributed to reasons other than infection (for the infection-related events outcome), receipt of kidney transplantation, time of switching modality, loss to follow-up, disenrollment from the dialysis provider, loss of Medicare coverage, or the administrative end of follow-up (December 31, 2012).

For both analyses, patients were also censored by deviation from index strategy during follow-up to evaluate the effect of fully following these strategies. A patient was considered as having deviated from index strategy when they received treatment in a way that was inconsistent

with their index strategy during follow-up. To assess deviation, we first discretized the observation of an individual patient into treatment intervals anchored by dates of TSAT laboratory tests (Supplemental Figure 3). At each measurement of TSAT (i.e., the start of a treatment interval), we then evaluated the treatment pattern in the 14-day assessment window (starting on the day of TSAT measurement) and updated iron status laboratory test values against the index strategy for consistency and censored patients for deviation if they were not consistent. The date of deviation was the end of the 14-day assessment window when the individual first deviated from the index strategy. Patients were not censored for deviation if insufficient information was available for exposure assessment in the window (e.g., the gap between two consecutive TSAT tests was shorter than 14 days, or the patient was hospitalized or had active infection in the assessment period, during which the anemia management strategy was unknown). Potential selection bias introduced by this censoring was adjusted for by inverse-probability censoring weighting (IPCW) as described in the statistical analysis section below.

Covariates

We evaluated both baseline and time-varying covariates. Baseline covariates included demographic characteristics (e.g. age, sex, race, region of residence, year of strategy initiation), clinical characteristics (e.g. cause of end-stage kidney disease (ESKD), body mass index), facility-related factors (geographical region of dialysis, vascular access type), and a list of comorbidities. Time-varying covariates included laboratory values (e.g. TSAT, ferritin, hemoglobin, albumin, creatinine), clinical characteristics (e.g. vascular access type, number of dialysis sessions, median post-treatment systolic blood pressure), and comorbidity measures (e.g. days of hospitalization, receipt of blood transfusion). Comorbidities were assessed using

definitions consisting of International Classification of Disease, Ninth Revision diagnosis codes (Supplemental Table 2).

Statistical analysis

We compared IV iron administration strategies with respect to risks of all-cause mortality and infection-related events using inverse probability weighted estimation of Cox marginal structural models (7, 8). We chose the frequently used strategy 1 as the reference (Table 1).

Four main analyses were carried out. We first estimated an unadjusted analysis. Similar to an intention-to-treat analysis, this estimate ignored any treatment changes occurred during the follow-up and estimated the effect of initiating one strategy versus the referent strategy on outcomes of interest. No adjustment was done for baseline confounding between strategy initiation and outcome risks.

The second analysis estimated the effect of continuous treatment by artificially censoring patients for strategy deviation during the follow-up. No adjustment was done to adjust for potential selection bias arising from such censoring. No adjustment was done to control for baseline confounding either.

The third analysis used standardized mortality ratio weighting (9) to adjust for potential baseline confounding for strategy initiation. As a multivariable standardization method, this weighting method uses the treated study subjects (i.e., the patients who initiated strategy 1 in this analysis) as the standard population and estimates the treatment effect in a population whose distribution of risk factors is equal to that of the treated study subjects only. This analysis used the same structure as the second analysis by censoring patients when they deviated from index

strategy. No adjustment was done to adjust for the potential selection bias introduced by artificial censoring.

The final analysis compared the effect of continuing a strategy on each outcome of interest adjusted for informative censoring due to strategy deviation using a product of SMR weights for baseline confounding control and IPCW (10) for potential selection bias introduced by censoring patients who deviated from index strategies in the follow-up.

During the index strategy assessment window, a patient's treatment experience might be consistent with multiple administration strategies. The methods we used to estimate treatment effect assume that it is unknown which of these strategies the patient was treated under. To accommodate the fact that it may be possible for a patient to be consistent with multiple strategies with our classification approach, we replicated a patient's observation and created k copies of the same patient's complete treatment and covariate history for k strategies she was consistent with initially (7, 11-**Error! Reference source not found.**). Within each strategy group, the copy of the patient was followed up until she deviated from the respective index strategy. As described previously, patients who deviated from index administrations strategies were artificially censored at the end of 14-day assessment window. The remaining patients were weighted by the probability that they stayed on their index strategies to estimate the risks of all-cause mortality and infection-related hospitalization or mortality. These patients were also censored for reasons other than deviation as described previously, but the cohorts were not re-weighted to account for possible dependent censoring related to these additional events.

We fit a censoring model to each strategy group separately to allow for different mechanisms that might have contributed to each strategy group. For each interval anchored by TSAT measurements, we estimated the probability of deviation given potential covariates associated

with both deviation and outcomes using a Cox proportional hazards model. Variables in the model for censoring weights included time-dependent factors for both outcomes and censoring (including length of hospital stay, total epoetin doses received, number of dialysis sessions, type of vascular access, current iron status tests in the treatment course before deviation), and time-independent factors (including gender, cause of ESKD, comorbidities). Patients who experienced outcomes of interest were weighted inversely using the probability that the failure time was observed to account for potential informative censoring due to deviation.

We first estimated the cumulative risk of outcomes in initiators of each administration strategy separately. We then estimated the cumulative risk differences between each strategy and the referent strategy during the follow-up period. The 95% confidence intervals (CI) for cumulative risk differences were estimated using a non-parametric bootstrap procedure with 200 repetitions (0).

We conducted sensitivity analyses using different covariates for censoring weights estimation and various definitions for strategy deviation. All statistical analyses were conducted using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

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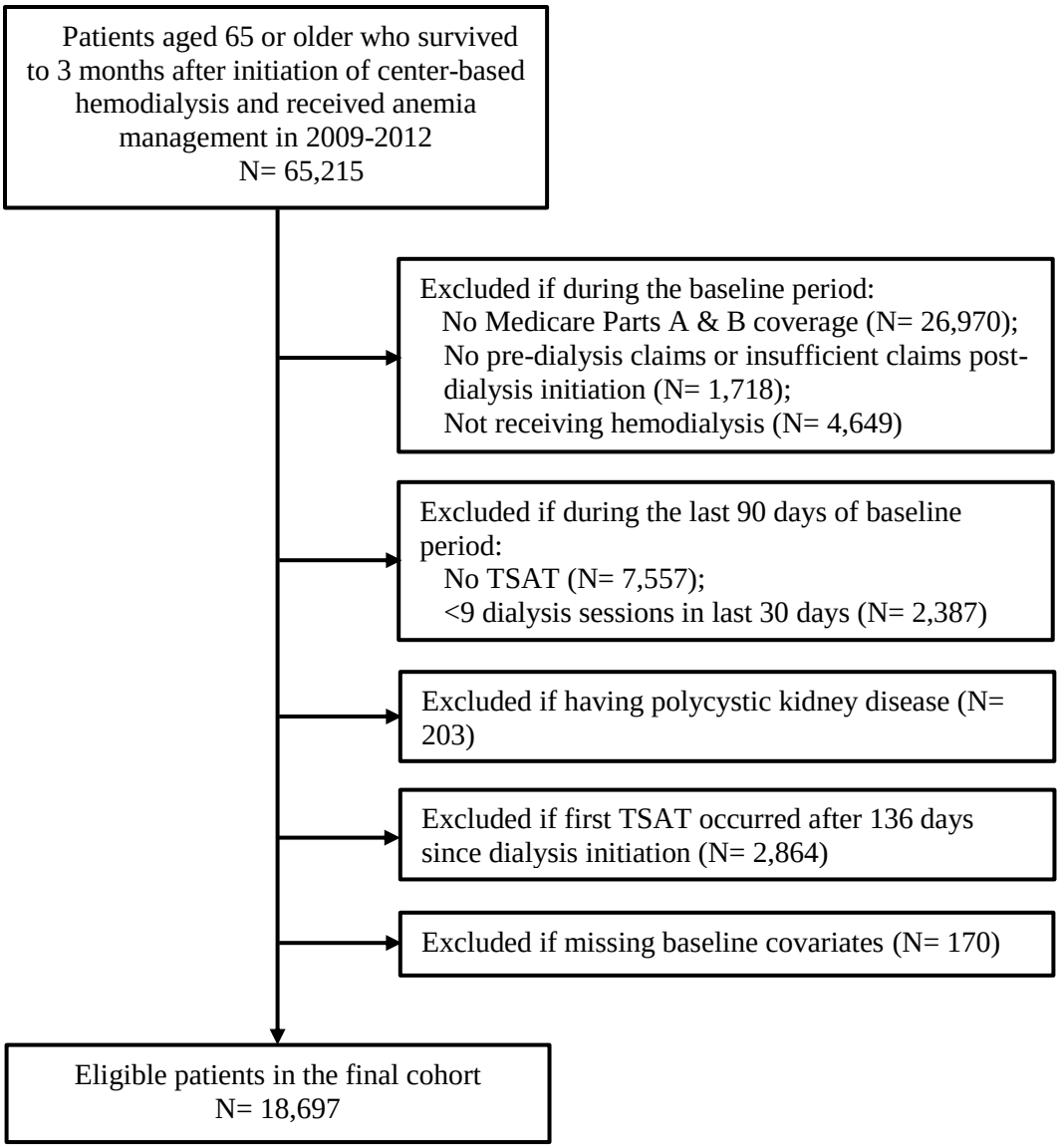
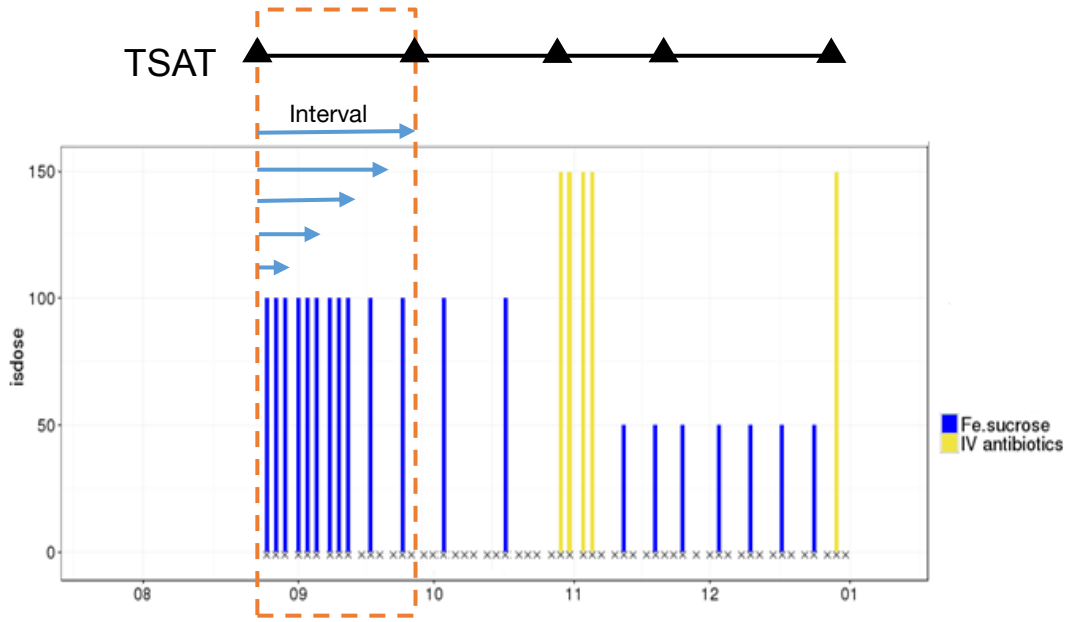


Supplemental Figure 1. Flow chart showing how patients were selected into the cohort.

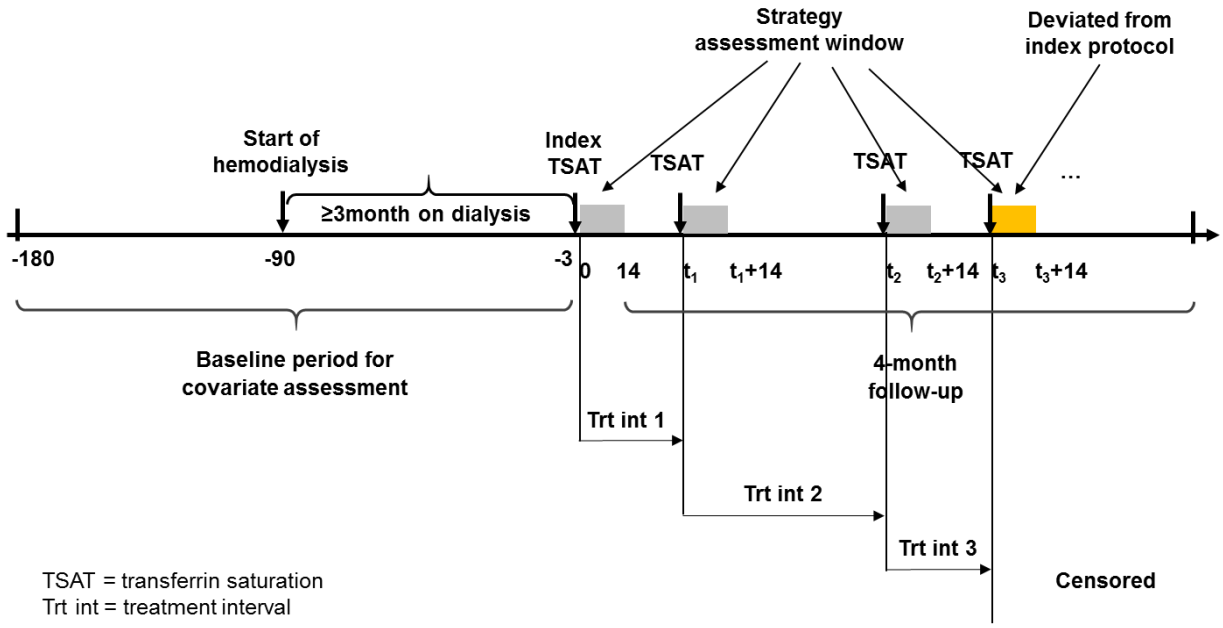
(a)



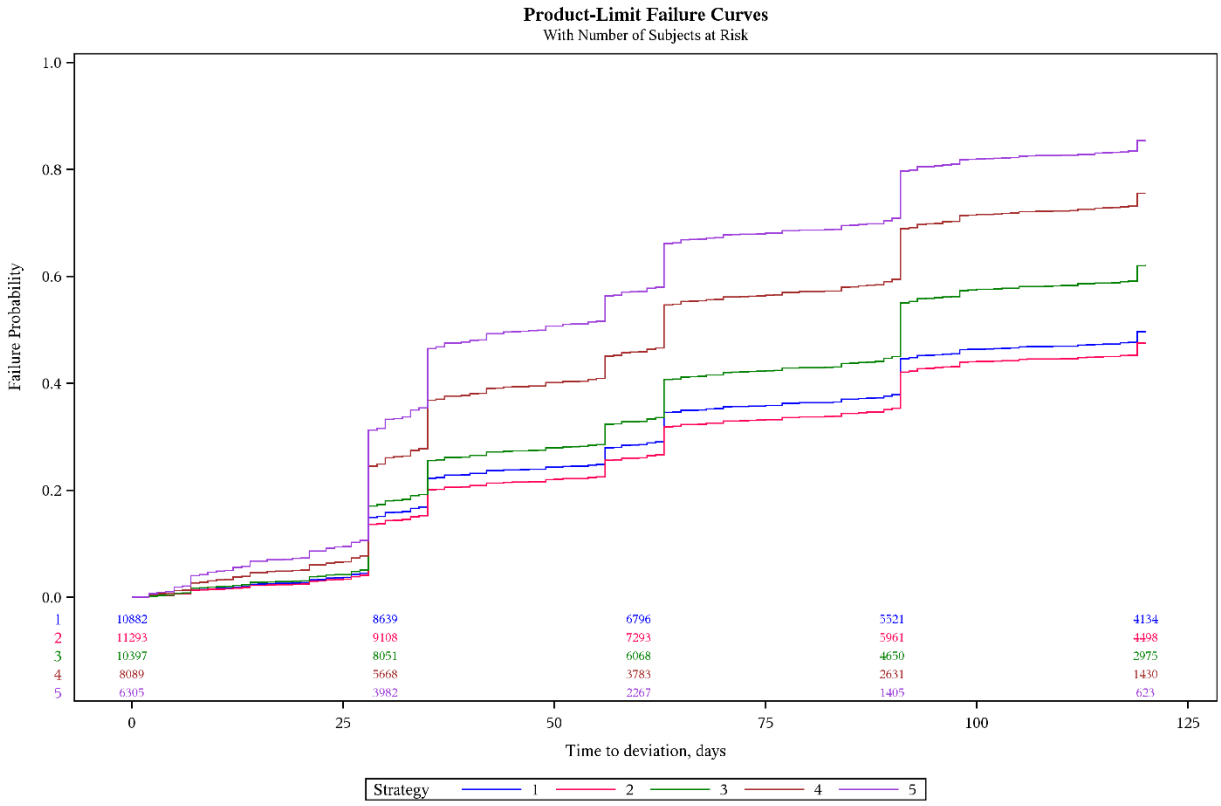
(b)

Assessment window	Dosing pattern classified	Representativeness of treatment experience in treatment interval	Days needed
Full interval	Bolus	Yes	28
4-week	Bolus	Yes	28
3-week	Bolus	Yes	21
2-week	Bolus	Yes	14
1-week	Half-bolus	No	7

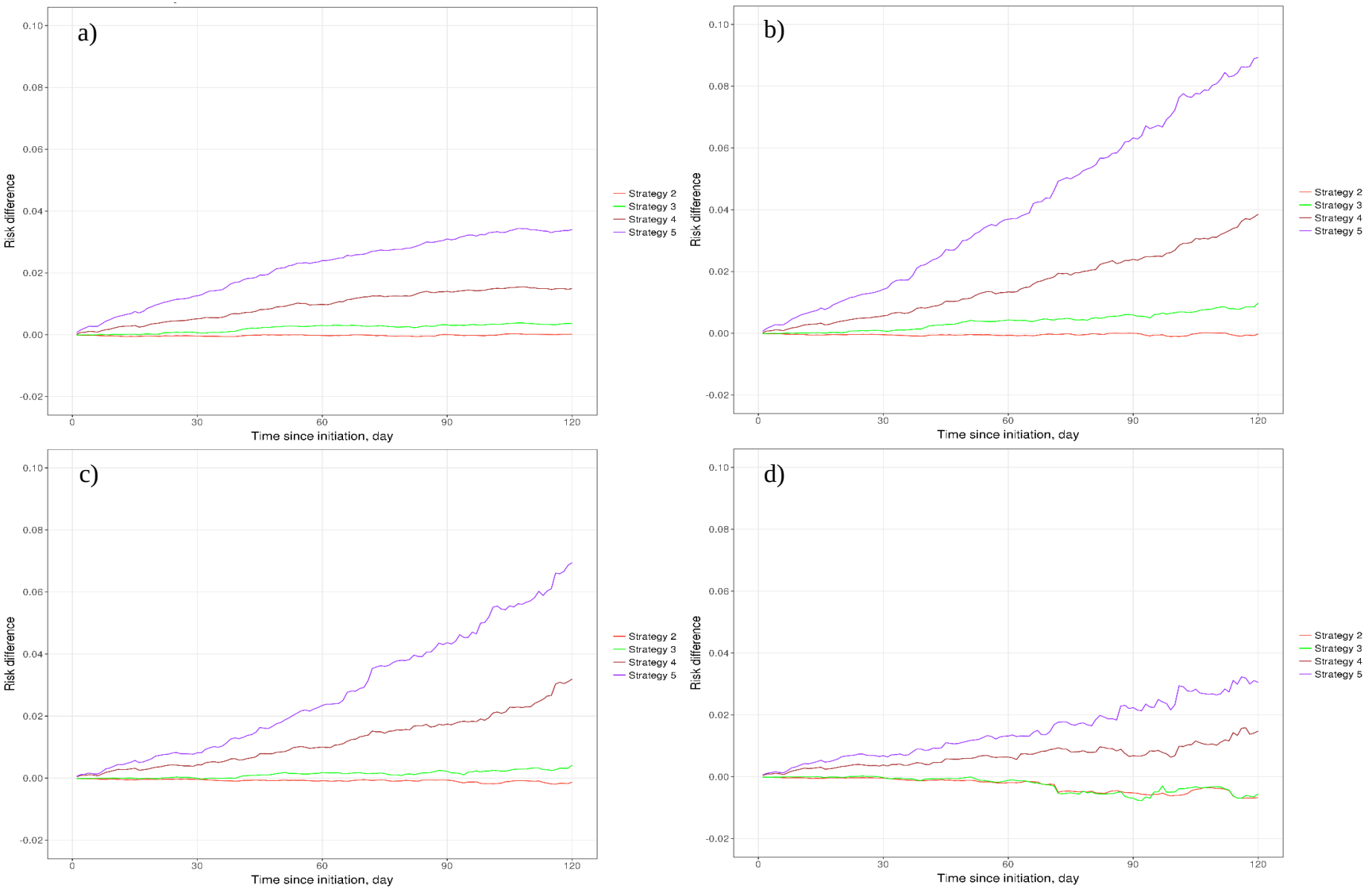
Supplemental Figure 2. Schematic illustration of the process to determine the length of assessment window. (a) a treatment interval was anchored by two consecutive transferrin saturation (TSAT) laboratory results. Five assessment windows with different lengths were considered: full-interval, 4-week, 3-week, 2-week, and 1-week. (b) the 2-week window was shown to be representative of treatment experience in the entire treatment interval but require the least number of days for assessment.



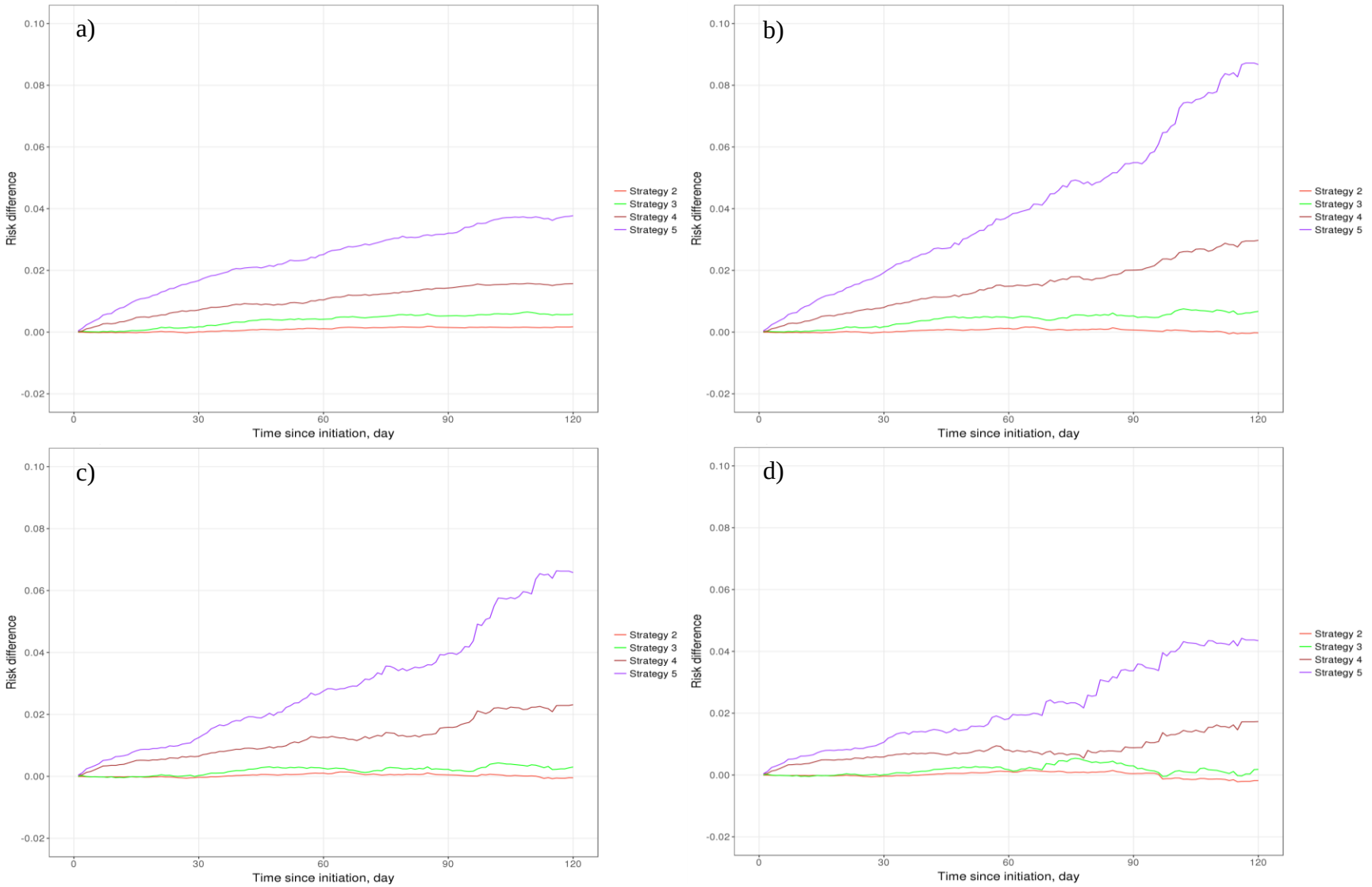
Supplemental Figure 3. Schematic illustration of the process to assess patient adherence to their intravenous iron administration strategy during follow-up. The observation of an individual patient was discretized into treatment intervals anchored by dates of TSAT laboratory test results. At each measurement of TSAT (i.e. the beginning of a treatment interval), we evaluated the treatment pattern in the 14-day assessment window (starting on the TSAT measurement date) and updated iron indices values against the index strategy for consistency. Patients who had treatment pattern inconsistent with their index strategy were considered as non-adherent and censored for deviation. The date of deviation was the end of the 14-day assessment window when the individual first deviated from the index strategy.



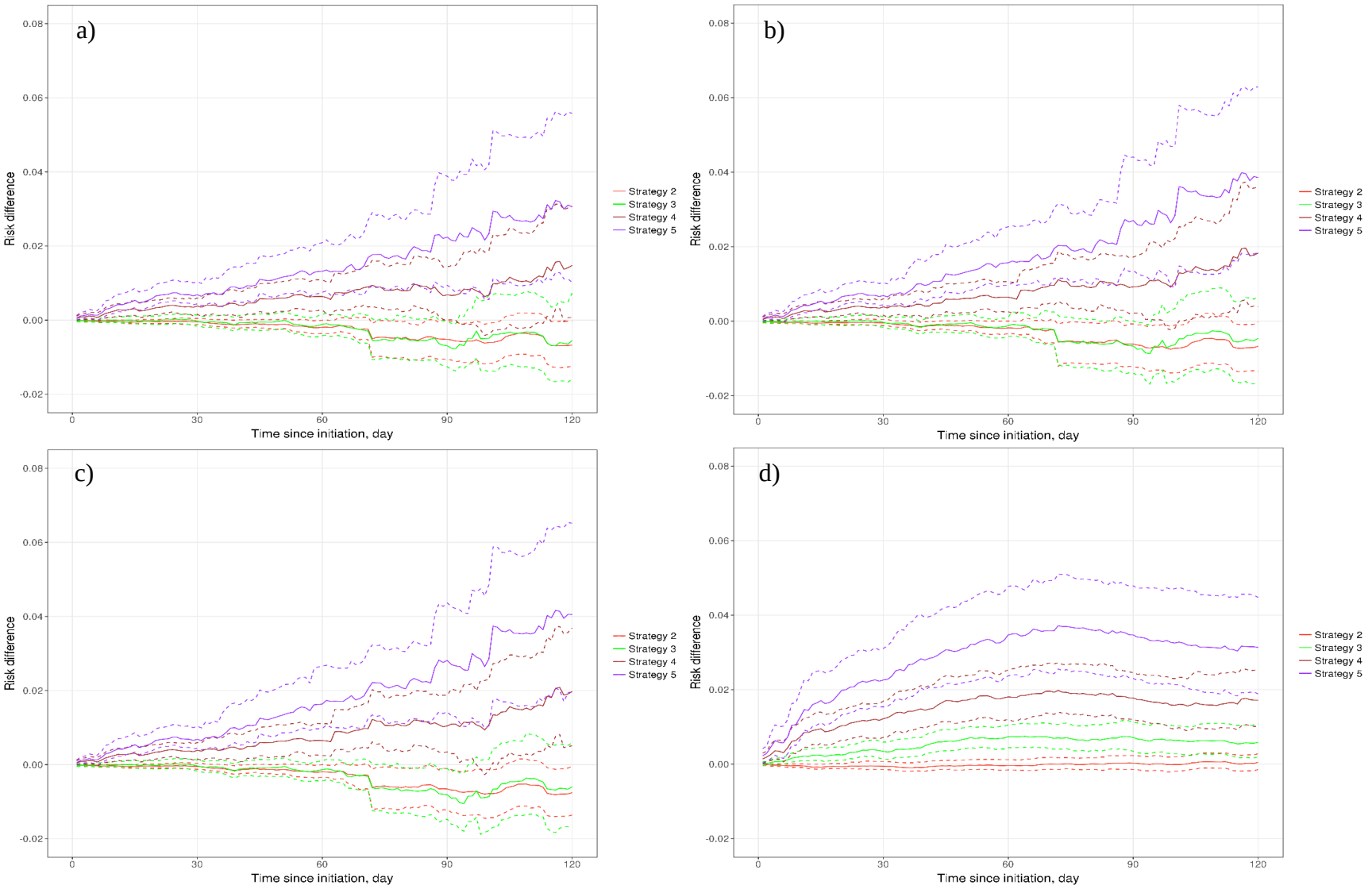
Supplemental Figure 4. Cumulative risk of deviation from their index strategy for initiators of the five dynamic intravenous iron strategies during the 120-day follow-up.



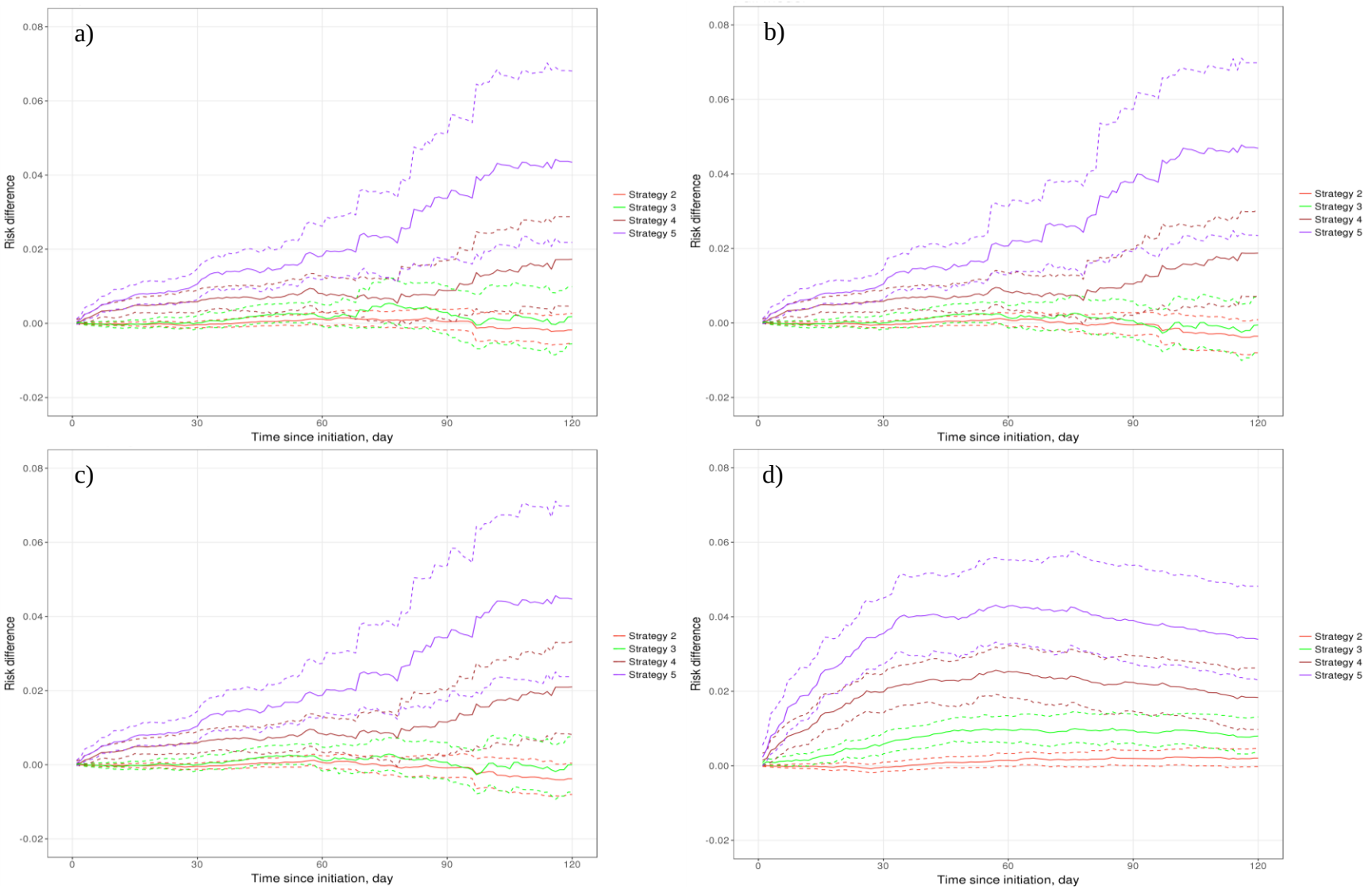
Supplemental Figure 5. Cumulative risk difference curves for all-cause mortality varying models for effect estimation (a) crude-intention-to-treat; (b) crude-as treated; (c) SMRW-as treated; (d) SMRW-IPCW



Supplemental Figure 6. Cumulative risk difference curves for infection-related events varying models for effect estimation (a) crude-intention-to-treat; (b) crude-as treated; (c) SMRW-as treated; (d) SMRW-IPCW



Supplemental Figure 7. Cumulative risk difference curves for all-cause mortality varying models for deviation (a) simplified full model; (b) full model with time-fixed and time-varying covariates; (c) time-varying covariates only model; (d) intercept-only model



Supplemental Figure 8. Cumulative risk difference curves for infection-related event varying models for deviation (a) simplified full model; (b) full model with time-fixed and time-varying covariates; (c) time-varying covariates only model; (d) intercept-only model

Supplemental Table 1. Claims-based definitions for study outcomes

Outcomes	Definition	Data Source
Infection outcomes		
Infection-related hospitalization	Any ICD-9-CM diagnostic codes of 996.62 (vascular access), 481.xx (pneumonia), 038.xx (sepsis)	Medicare Part A
Infection-related death	Primary cause of death: 33, 34, 45-58, 51, 52, 61-63, 70	Death Notification File
All-cause mortality		
All-cause death	Death as indicated in CMS file	Death Notification File

Supplemental Table 2. Claims-based definitions for study covariates

Covariate	Definition	Data Source
Demographic		
Age	Continuous variable	USRDS
Sex	Male or female	USRDS
Race	White, Black, Other (as reported on the Medial Evidence Form (CMS-2728)	USRDS
Medicaid eligibility	Indicator for dual eligibility during any part of the baseline	USRDS
Census region	Based on location of last dialysis center in baseline period: Northeast, South, Midwest, West	USRDS
Year of treatment	2004, 2005, 2006, 2007, 2008	Clinical Database
Clinical		
Vintage	Time since start of renal replacement therapy, categorized as 0; 1-3; 4 or more years	USRDS
Cause of ESRD	Diabetes, Glomerulonephritis, hypertension, other	USRDS
BMI	As reported in the clinical database or the Medical Evidence Form (CMS-2728), categorized as underweight, normal, overweight, obese	Clinical Database & USRDS
Serum creatinine, mg/dL	Most proximal prior to index TSAT date	Clinical Database
IV antibiotics use	Use of IV antibiotics (listed under infection definition)	Clinical Database
Anemia Management		
Access	Most recent vascular access (catheter vs fistula/graft) prior to TSAT index date	Clinical Database
Epoetin dose (baseline)	Total epoetin dose in the last month of baseline	Clinical Database
Epoetin dose (exposure)	Total epoetin dose in the 2-week exposure window	Clinical Database
Index TSAT, %	Last TSAT at baseline	Clinical Database
Iron dose, mg	Total dose at last month of baseline.	Clinical Database
Hemoglobin, g/dL	Most proximal Hb lab prior to index TSAT date	Clinical Database
Ferritin, ng/mL	Most proximal serum ferritin prior to index TSAT date	Clinical Database
Serum albumin, g/dL	Most proximal prior to index TSAT date	Clinical Database
Comorbidities		
Hospital days in last month of baseline	Total hospital days, continuous variable	USRDS, Medicare Part A Claims
Infection in last month	Any hospital admission in the last month with one of the following ICD-9-CM diagnostic codes as the principal diagnostic code: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383.0, 386.33, 386.35, 388.60, 390–393, 421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0, 475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494, 510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3, 540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3, 575–575.12, 590–590.9, 595–595.4, 597–597.89, 598, 599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4, 611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9, 706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8, 996.60–996.69, 997.62, 998.5, and 999.3.	USRDS, Medicare Part A Claims
	Any claims with the following HCPCS codes for antibiotic use in last month of baseline: J3370, J0690, J0713, J0692, J0696, J1580, J3260, J0278, J1840, J1956.	USRDS, Medicare Part A & B Claims
	Any indication of the use of the following drugs: Amikin® (amikacin sulfate); ampicillin; Ancef®, Kefzol® (cefazolin); aztreonam; Cefizox® (ceftizoxime); Cefotan® (cefotetan);	Clinical Database

Covariate	Definition	Data Source
	Fortaz®, Tazicef® (ceftazidime); Claforan® (cefotaxime); clindamycin; Cubicin® (daptomycin); ethambutol; gentamicin; Keflin® (cephalothin); Levaquin® (levofloxacin); Mefoxin® (cefoxitin); Merrem® (meropenem); nafcillin; Nebcin® (tobramycin); oxacillin; Penicillin G; Zosyn® (piperacillin and tazobactam); Primaxin® (imipenem and cilastatin); Rocephin® (ceftriaxone); streptomycin; Timentin® (ticarcillin and clavulanate potassium); Unasyn® (ampicillin and sulbactam); Vancocin® (vancomycin); Vibramycin® (doxycycline); Zinacef® (cefuroxime); Zyvox® (linezolid)	
Pneumonia	Any ICD-9-CM diagnostic code of 481.xx – 486.xx in baseline period	USRDS, Medicare Part A & B Claims
Vascular access infection	Any ICD-9-CM diagnostic code of 996.62 in baseline period	USRDS, Medicare Part A & B Claims
Sepsis	Any ICD diagnostic code 038.xx, 995.90, 995.91, 995.92 in baseline period	USRDS, Medicare Part A & B Claims
Diabetes	Any ICD-9-CM diagnostic code of 250.xx in baseline period	USRDS, Medicare Part A & B Claims
Ischemic stroke	Any ICD-9-CM diagnostic code of 434.01, 434.11, 434.91, 435, 436, 437, 438, V12.54 in baseline period	USRDS, Medicare Part A & B Claims
MI	Any ICD-9-CM diagnostic code of 410.xx in baseline period	USRDS, Medicare Part A & B Claims
COPD	Any ICD-9-CM diagnostic code of 490.xx-496.xx, 505.xx, 506.4 in baseline period	USRDS, Medicare Part A & B Claims
Cancer	Any ICD-9-CM diagnostic code of 173.3, 173.9, 174.0-175.9, 179-195, 196-199, 232.9, 233.0, 233.1, 300.29, 338.3, 789.51, 795.82, 799.4, V67.2, 200, 201, 202.0-202.3, 202.50-203.01,203.8, 238.6, 273.3 in baseline period	USRDS, Medicare Part A & B Claims
GI bleeding	Any ICD-9-CM diagnostic code of 578.xx in baseline period	USRDS, Medicare Part A & B Claims
Time-Varying Covariates		
Iron dose in previous month	Total iron dose in the first month prior to the exposure period	Clinical Database
Iron dose in preceding two months	Total iron dose in the second and third month prior to the exposure period	Clinical Database
Hospitalization for infection	Any hospital admission in the last month with one of the following ICD-9-CM diagnostic codes as the principal diagnostic code: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383.0, 386.33, 386.35, 388.60, 390–393, 421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0, 475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494, 510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3, 540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3, 575–575.12, 590–590.9, 595–595.4, 597–597.89, 598, 599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4, 611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9, 706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8, 996.60–996.69, 997.62, 998.5, and 999.3.	USRDS, Medicare Part A Claims
Vascular access	Indicators representing most recent vascular access in the previous month (catheter, graft, fistula, or other/unknown)	Clinical Database
Hospital days	Total hospital days in the previous month	USRDS, Medicare Part A
IV antibiotics	Use of antibiotics during in last interval	Clinical Database

Covariate	Definition	Data Source
TSAT level, %	Most proximal TSAT level in prior interval	Clinical Database
Ferritin level, ng/mL	Most proximal ferritin level in prior interval	Clinical Database
Hemoglobin level, g/dL	Most proximal hemoglobin level in prior interval	Clinical Database
Epoetin use	Total epoetin use in prior interval	Clinical Database
Serum albumin level, g/dL	Most proximal albumin level in prior interval	Clinical Database
Serum creatinine, mg/dL	Most proximal creatinine level in prior interval	Clinical Database
Pre-dialysis systolic blood pressure	Median value in prior 2 weeks	Clinical Database
Ultrafiltration rate	Median calculated value in prior 2 weeks	Clinical Database
Pre-dialysis weight (kg)	Median value in prior 2 weeks	Clinical Database
Dialysis session length	Median value in prior 2 weeks	Clinical Database
Post-dialysis weight (kg)	Median value in prior 2 weeks	Clinical Database