COMPARATIVE SAFETY OF INTRAVENOUS IRON TREATMENT PROTOCOLS IN HEMODIALYSIS PATIENTS: CAUSAL INFERENCE WITH DYNAMIC TREATMENT REGIMES

Xiaojuan Li

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Approved by:

M. Alan Brookhart

Stephen R. Cole

Abhijit V. Kshirsagar

Til Stürmer

Jason Fine

ABSTRACT

Xiaojuan Li: Comparative Effectiveness of Intravenous Iron Treatment Protocols in Hemodialysis Patients: Causal Inference with Dynamic Treatment Regimes
(Under the direction of M. Alan Brookhart)

Decisions regarding intravenous iron treatment follow dosing protocols for anemia management of hemodialysis patients. These protocols are a type of dynamic treatment regimes, consisted of a set of decision rules with iron status values - transferrin saturation and ferritin - and corresponding iron dosing patterns. Multiple protocols exist in clinical practice, but their comparative safety is unknown.

Using clinical data from a large US dialysis provider linked to healthcare utilization data from United States Renal Data System (2004-2012), our objectives were to (1) develop an approach to identify intravenous iron dosing protocols that were commonly used, and (2) evaluate the comparative safety of continuous exposure to commonly used protocols.

The identification approach classified intravenous iron dosing protocols at measurements of iron status tests, where decisions regarding iron treatment occur in clinical practice. Using current test levels and iron treatment experience in a two-week assessment window, candidate protocols were assigned to a patient if they were consistent with treatment experience in the assessment window. Among 43,166 patients who initiated hemodialysis in 2004-2012, 79.1% of them were matched with candidate protocols. The prevalence of protocol matches increased from

75.0% in 2004 to 90.7% in 2012. Higher prevalence of knowingly implemented protocols confirmed the performance of this identification approach.

In the comparative safety analyses, we estimated the effect of continuous exposure to the five most commonly initiated protocols in 2009-2012 on risks of mortality and infection-related events. Two less commonly initiated protocols were more aggressive, recommending a large amount of iron at higher iron status levels; their initiators were sicker at baseline. Compared with one commonly initiated and less intensive protocol, these two protocols were at elevated mortality risk (120-day risk differences (95% confidence interval): 1.5% (0.1, 3.1%), 3.1% (1.0, 5.6%)). The magnitude of elevated risk increased with the aggressiveness of the protocols. We observed similar trends in elevated risks for infection-related events among more aggressive protocols.

Protocols that recommend less intensive use of iron at high levels of iron status tests may lower risks of mortality and infection-related events, but further exploration is needed to address potential residual confounding and selection bias.

To my parents, who sacrificed hard;
and to my sister, who gave me strength to chase my dreams.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CI	Confidence interval
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CREAT	Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta Trial
CRP	C-reactive protein
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
Hct	Hematocrit
HD	Hemodialysis
HCPCS	Health Care Financing Administration Common Procedural Coding System
HMO	Health maintenance organization
HR	Hazard ratio
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IPTW	Inverse probability of treatment weights
IV	Intravenous iron
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	Clearance expressed as a function of urea or body water volume

MSM	Marginal structural model
NHANES	National Health and Nutrition Examination Survey
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NKF	National Kidney Foundation
PD	Peritoneal dialysis
QOL	Quality of life
RBC	Red blood cell
RCT	Randomized controlled trial
rHuEPO	Recombinant human erythropoietin
RR	Relative risk
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSAT	Transferrin saturation
US	the United States
USRDS	United States Renal Data System

CHAPTER 1: STATEMENT OF SPECIFIC AIMS

Anemia, a common complication of end-stage renal disease (ESRD),[1] is associated with elevated morbidity, mortality, and healthcare costs.[1] A primary cause of anemia in ESRD is iron deficiency, particularly among patients requiring hemodialysis (HD). Iron deficiency can be classified into absolute iron deficiency and functional iron deficiency; their causes are multifactorial.[3] Absolute iron deficiency, or depleted iron stores, is frequently a result of blood loss, reduced intake, and impaired intestinal absorption of dietary iron.[3] Functional iron deficiency, or insufficient iron availability at the site of erythropoiesis despite adequate iron stores, can be caused by chronic inflammation associated with ESRD or elevated hepcidin levels.[3] Overall, HD patients lose an average of 1 to 2 g of iron per year, and some as much as 4 to 5 g per year.[4] Management of iron deficiency to meet the need for erythropoiesis is thus essential for optimal management of anemia in ESRD patients.

Intravenous (IV) iron is an effective way to supplement iron and optimize erythropoiesis. Existing randomized controlled trials (RCTs) showed that supplementing erythropoiesis-stimulating agent (ESA) therapy with IV iron increases hemoglobin production and lowers ESA requirement.[5-6] Consequently, co-administration of ESAs and IV iron has become the primary management strategy for anemia in HD patients.[4] Subsequent to emerging evidence on the cardiovascular (CV) safety of ESAs[7-9] and changes in the reimbursement policies in Medicare's ESRD programs,[10] the reliance on IV iron has increased, leading to reduction in ESA use and in potential risk of ESA-related adverse events.[11-12] International guidelines correspondingly

recommended a wider use of iron.[13-16] Altogether, these events led to significant, albeit transient, changes in clinical practice in recent years. Mean IV iron dose increased sharply from 210 mg per month in 2009-2010 to 280 mg per month in 2011, then back to a stable 200 mg per month in 2012-2013.[17,18] During this time period, about 40% of HD patients had ferritin levels greater than 800 ng/mL.[17] The persistently high levels of ferritin raised concerns about the safety of IV iron administration in HD patients.

In contemporary clinical practice, IV iron is either provided intermittently via large doses over consecutive dialysis sessions (often termed "bolus dosing") or via small doses provided every one to two weeks to maintain iron stores (often termed "maintenance dosing"). Decisions regarding when to use each dosing approach follow certain protocols adopted by dialysis clinics. A variety of dosing protocols exist in clinical practice, and they differ with respect to target levels of iron status parameters and dosing approach recommendations.[19-21]

Several existing studies consistently demonstrated short-term benefits of bolus iron administration on hemoglobin levels and iron status compared to maintenance dosing.[6,22] No difference in CV risks was associated with either dosing approach;[23,24] however, a modestly increased risk of infection was associated with bolus dosing among patients with a history of infection and those with a central venous HD catheter.[24,25] A recent observational study has reported an association between lower mortality risk and maintenance strategy relative to non-maintenance strategies.[26]

Compared to short-term effects, less is known about the long-term safety and effectiveness of different iron treatment protocols. Clinical trials assessing the long-term use of iron administration strategies are lacking; existing large observational studies have focused on the effect of cumulative iron exposure over a long period, which were not large enough to

resolve clinically meaningful effects of iron exposure on infection outcomes.[20,27] The cumulative exposures do not align well with the treatment decisions that a physician needs to make regarding iron use in routine care.[28]

Given the increased use of IV iron and data suggesting some risk, evaluating the long-term safety of different IV iron dosing protocols is the overall goal of this thesis. This dissertation has two primary aims:

1) Characterize IV iron treatment protocols in routine use among ESRD patients undergoing chronic hemodialysis; and
2) Evaluate the comparative safety of continuous exposure to different commonly used IV iron treatment protocols.

CHAPTER 2: REVIEW OF THE LITERATURE

2.1. Overview of ESRD

ESRD is the last stage of chronic kidney disease (CKD) where the renal function falls below 15% of normal. The kidneys can no longer support the body's needs by adequately removing nitrogenous waste or excess fluid from the body. Renal replacement therapy, such as dialysis or kidney transplantation, is necessary for survival. ESRD is a syndrome characterized by hypertension, anemia, renal/metabolic bone disease, nutritional impairment, neuropathy, impaired quality of life, and reduced life expectancy.

As of 2012, 636,905 patients were receiving treatment for ESRD in the US, an increase of 1.3% in prevalence from 2011.[29] Although slowing down, prevalent ESRD population continues to grow, and the counts are expected to reach 774,386 in 2020.[30] The incidence of ESRD cases has been slowly decreasing since 2006 with 359 new cases per million population after adjusting for age, sex, and race. This rate is still 11 cases above the targeted rate of Healthy People 2020.[29] As shown in Table 2.1, the rate of incident ESRD is high among nonwhites, men or older people. The incidence rates are almost as three times among Blacks/Africans and Native Hawaiians/Pacific Islanders compared to Whites and Asians. Hispanics also have higher incidence rate than non-Hispanics. Males have a rate 59% higher than females, and this difference has increased by 17% from 2001. The incidence rate increases with age and varies dramatically by geographic region. The highest rates are in the South and Mississippi River valleys while the lowest rates are in the Northwest, New England, and some Rocky Mountain

states with the largest difference of 170 cases per million/year between ESRD Network 1 (Maine, New Hampshire, and Rhode Island) and Network 14 (Texas).[29]

Four primary causes of ESRD are diabetes, hypertension, glomerulonephritis, and cystic kidney disease. Most cases of ESRD are caused by diabetes or hypertension; their incidences had been increasing rapidly since 1980 but have been decreasing from 2010 to 2012.[29] The number of cases with glomerulonephritis as the primary cause has declined since the 1990s while the number of cases with cystic kidney disease as the primary cause has been stable over the period from 1980 to 2012. New cases with diabetes have the highest rate among these four causes.

Patients with ESRD require renal replacement therapy, either through dialysis or kidney transplantation. Dialysis is the mechanical process by which the blood is filtered to clean out excess water, minerals, and other metabolism products. There are two types of dialysis, hemodialysis (HD) and peritoneal dialysis (PD). HD is the most commonly used method to treat kidney failure and the focus of this thesis. Out of the 114,813 new ESRD patients in 2012, 89% started on HD, and 8% started on PD.[29] In the process of HD, a patient's blood flows through tubes into a dialyzer while a premixed dialysate solution flows into the dialyzer in the opposite direction. In the dialyzer, excess water, minerals, and wastes diffuse across a semi-permeable membrane that separates the blood and dialysate compartments. Cleaned blood then flows out of the dialyzer back into the patient through another tube. This process recurs during a typical dialysis session whereby blood volume several times greater than a patient's innate amount flows through the dialysis circuit. Patients undergoing HD receive dialysis at a dialysis clinic three times a week generally, and each dialysis session lasts about three to four hours.

The morbidity rates in ESRD patients are high. Among HD patients in 2012,[29] the adjusted hospitalization rate was 1.73 admissions per patient year and 11.0 hospital days per

Table 2.1. Summary statistics on cases of ESRD in the US, by age, race, ethnicity, sex, and primary diagnosis

	Incidence			Prevalence		
	Count	**%**	**Adj. rate**	**Count**	**%**	**Adj. rate**
All	114,813	100	353.2	636,905	100	1,942.9
Unadjusted			358.6			1,968.2
Age						
0-19	1,163	1.0	13.1	7,545	1.2	83.1
20-44	13,162	11.5	122.2	101,994	16.0	938.0
45-64	45,069	39.3	570.2	283,021	44.4	3,550.1
65-74	27,933	24.3	1,270.1	140,238	22.0	6,301.8
75+	27,486	23.9	1,618.4	104,107	16.3	6,261.1
Race						
White	76,089	66.3	279.2	383,534	60.2	1,431.8
Black/African American	31,398	27.3	908.0	200,797	31.5	5,670.5
Native American	1,273	1.1	411.5	8,154	1.3	2,599.5
Asian	5,840	5.1	378.9	35,878	5.6	2,271.8
Other	50	0		5,860	0.9	
Unknown	163	0.1		2,682	0.4	
Hispanic	17,024	14.8	501.3	106,308	16.7	2,931.9
Non-Hispanic	97,789	85.2	340.5	530,597	83.3	1,857.8
Gender						
Male	65,842	57.3	446.0	363,497	57.1	2,396.7
Female	48,971	42.7	278.0	273,312	42.9	1,558.4
Unknown gender				96	0	
Cause						
Diabetes	50,534	44.0	154.3	239,837	37.7	731.0
Hypertension	32,610	28.4	101.1	159,049	25.0	489.4
Glomerulonephritis	9,115	7.9	28.3	106,012	16.6	325.8
Cystic kidney disease	2,530	2.2	7.9	29,881	4.7	92.4
Urologic disease	538	0.5	1.6	7,447	1.2	22.9
Other known	12,281	10.7	38.2	59,714	9.4	184.7
Unknown cause	3,506	3.1	10.8	25,977	4.1	78.2
Missing cause	3,699	3.2	10.6	8,988	1.4	18.1

a. Rates are per million population. Rates by age are adjusted for race and sex. Rates by sex are adjusted for race and age. Rates by race are adjusted for age and sex. Rates by disease group and total adjusted rates are adjusted for age, sex, and race. Adjusted rates do not include patients with other or unknown race. b. Statistics shown are for year 2012, adapted from Annual Data Report from the 2014 USRDS Annual Data Report On kidney disease. [29]

year. Although the overall hospitalization rate and average length of stay continued to decline, some cause-specific hospitalizations have been increasing. Among HD patients, hospitalization due to infection has increased by 34% since 1993 while hospitalization for cardiovascular (CV)

events has decreased by 12.7%. Patients aged 20-44 or 75 and older, females, Whites, Blacks/African Americans, and patients who have diabetes as their primary cause of ESRD have a higher risk of hospitalization.[29] For HD patients, the rate of rehospitalization is also high. In 2012, the overall all-cause rehospitalization rate was 35.2% while the CV- and infection-related hospitalization rates were 36.2% and 32.9%, respectively.[29]

Patients with ESRD are very ill, and their mortality rates are high. In 2012, the mortality rate was 137.8 per 1,000 person years for all ESRD patients. Among HD patients, the mortality rate was 168.5 per 1,000 person years. Patients who are older, male, or White have higher rates. Mortality rates also increase with vintages in general, however, high rates also occur early in the first year among HD patients, especially in the second month on dialysis (all-cause mortality: 421 per 1,000 patient years; CV mortality: 163 per 1,000 patient years; infection mortality: 35 per 1,000 patient years).[29] Compared to the general population, patients with ESRD have lower survival probabilities, and adjusted all-cause mortality rates are about 6.1 to 7.8 times higher. After adjusting for age, sex, race, Hispanic ethnicity, and primary diagnosis, only 54.2% of HD patients were alive 3 years after ESRD onset and 40.4% at 5 years after ESRD onset. They are expected to live less than one-third as long as people with similar characteristics but no ESRD (dialysis versus general population, 2010: 6.6 years versus 22.2 years).[29]

The cost of ESRD is substantial. Although the total population of ESRD comprises less than 1% of the total Medicare population, the cost of ESRD accounts for about 6% of Medicare spending.[29] In 2011, spending on HD patients accounts for about 85% of the total cost of ESRD and averaged $88,000 per person per year.[31] In 2012, the second full year under the expanded, bundled Prospective Payment System (PPS), total spending increased by 3.5% from 2011 while inpatient spending was similar to 2011.

2.2. Anemia in the ESRD Population

Patients with advanced kidney diseases such as ESRD often are anemic.[32] The incidence of anemia increases as the GFR, a marker of kidney function, declines. Anemia, as defined by WHO, refers to lower than normal hemoglobin concentrations, with different cut-off values in different populations: below 13.0 g/dL in adult men and non-menstruating women, and below 12.0 g/dL in menstruating women.[33]

Factors contributing to anemia in the dialysis-dependent ESRD patients include (1) insufficient erythropoietin (EPO) production, (2) blood loss and iron deficiency, (3) acute and chronic inflammatory conditions, (4) severe hyperparathyroidism, (5) aluminum toxicity, (6) folate deficiency, and (7) decreased survival of red blood cells (RBCs).[1,34] The kidneys produce about 90% of circulating EPO, an essential stimulus for bone marrow production of RBCs. The loss of EPO production in the setting of kidney failure is the primary mechanism responsible for anemia in these patients.

Anemia has an adverse impact on health-related life as well as quality of life in ESRD patients. Clinical symptoms of anemia include fatigue, shortness of breath, skill pallor, palpitations, angina, decreased cognitive function, loss of libido, and decreased sense of well-being.[2,35-37] The goals of anemia management are to treat its underlying causes and reverse symptoms attributable to decreased hemoglobin.

2.2.1. The Role of EPO and Iron in Erythropoiesis

In the first stage of erythropoiesis process (Figure 2.1), the presence of decreased oxygen delivery due to hypoxemia or anemia leads to delayed spontaneous degradation of hypoxia inducible factor (HIF) produced by the kidneys and other tissues. The continuing presence of

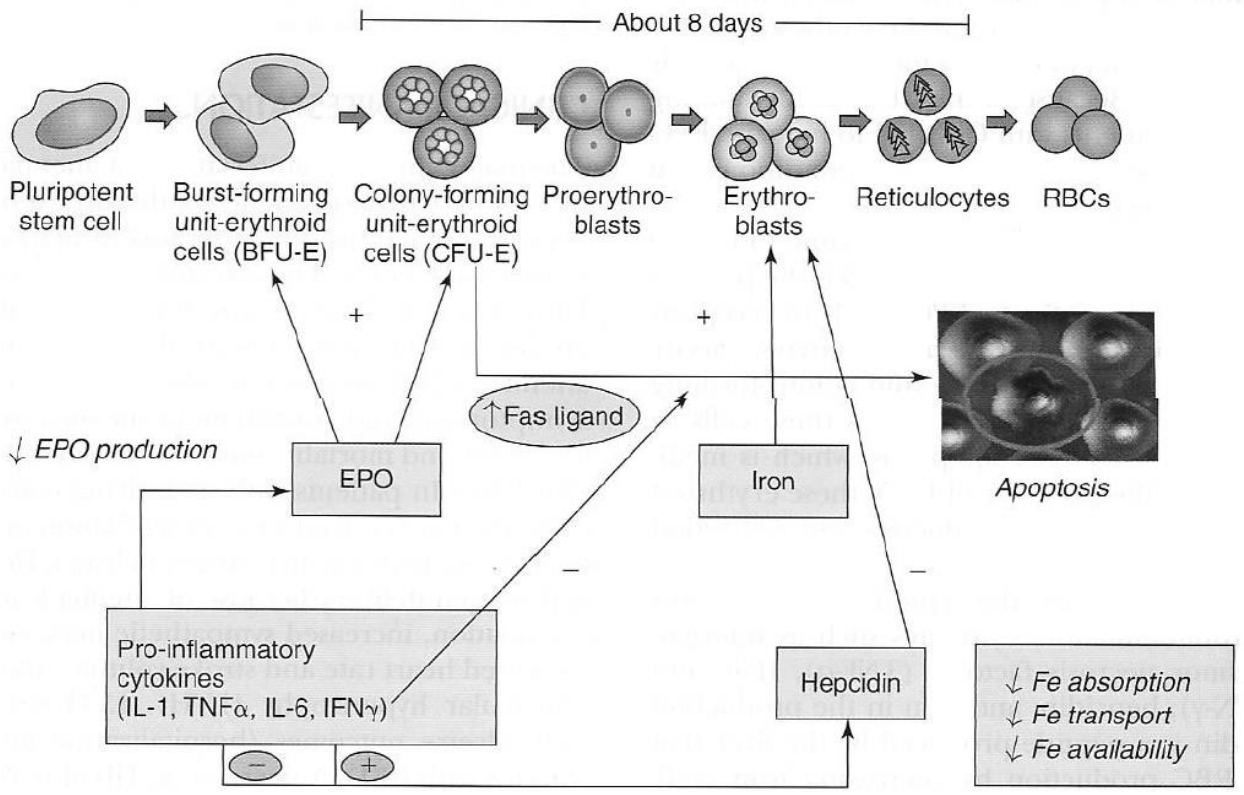

Figure 2.1. Erythropoiesis in chronic kidney disease
Adapted from National Kidney Foundation's Primer on Kidney Diseases[34]

HIF promotes production of hormone EPO in the kidneys. EPO binds to receptors on erythroid progenitor cells, the burst-forming units (BFU-E), and colony-forming units (CFU-E) cells in the bone marrow, which then differentiate into erythroblasts. In the second stage, erythroblasts undergo rapid cell division and iron-dependent hemoglobinization to form reticulocytes that leave the bone marrow to circulation. The EPO-dependent first stage takes about 8 to 13 days and shortens as erythrocyte production increases. The second iron-dependent stage takes about 4 days while iron-acquisition takes about 2 to 3 days. In the absence of EPO, the erythroid progenitor cells will undergo programmed death or apoptosis. In the absence of iron, hemoglobin formation in reticulocytes will stop, resulting in reduction of RBCs. Therefore, it is clear that

sufficient erythroblast production and adequate levels of iron are necessary for optimal RBCs or hemoglobin production in the treatment of anemia in ESRD patients.

As shown in Figure 2.1, some other factors also play important roles in the production of RBCs, including proinflammatory cytokines such as interleukin 1 (IL-1), tumor necrosis factor-α (TNF- α), IL-6, interferon-γ (INF-γ), and hepcidin. They may be the basis for most of the anemia of chronic disease syndromes and contribute to the anemia in ESRD patients when inflammation and infection are present. However, for patients who are anemic without inflammation or infection, EPO deficiency and iron deficiency play a much greater role.

2.2.2. Iron Deficiency

Sufficient iron availability is necessary in erythropoiesis. Iron deficiency occurs in majority of ESRD patients on HD and can be classified into absolute or functional iron deficiency. Absolute iron deficiency reflects little or no iron stores.[38] As defined by Weiss and Gordeuk,[39] absolute iron deficiency refers to a concentration of serum ferritin <15 µg/L for men and <19 µg/L for women in general population. The cut-off values for patients with ESRD, however, are markedly higher. Because high serum ferritin levels may be a result of chronic inflammation, infection, malnutrition or malignancy and not necessarily reflect iron overload,[40] having serum ferritin >500 µg/L does not exclude iron deficiency in these patients. As a result, both serum ferritin levels and transferrin saturation (TSAT) are used for diagnosis, and concurrent low levels are thought to indicate absolute iron deficiency. Current evidence-based guidelines recommend a target serum ferritin level of ≥200 µg/L for dialysis patients,[41] and serum ferritin as a marker for iron stores in the body should be measured every 3 months in patients undergoing ESA therapy and IV iron supplementation. No guidelines are available on the upper limit of serum ferritin at which iron treatment should be withheld.

Functional iron deficiency occurs when there is inadequate release of iron to support erythropoiesis although adequate amounts of iron stores are present.[38] A common occurrence is in the presence of inflammation in patients undergoing ESA maintenance therapy. Functional iron deficiency is generally thought to be present when serum ferritin level is high but TSAT level is low. However, this view has been challenged by results from recent studies.[38] TSAT, the ratio of serum iron to total serum iron binding capacity, is a measure of circulating iron available for delivery to the erythroid marrows. Patients with iron deficiency have TSAT levels <15% while the normal values lie between 16-40%. The level of TSAT fluctuates greatly with varying serum iron level while transferrin level is affected by the nutritional status. In the presence of inflammation, TSAT decreases, and a level <20% with normal or elevated serum ferritin levels indicates functional iron deficiency in patients with CKD. However, a TSAT level >20% and/or a serum ferritin level >100 µg/L does not exclude functional iron deficiency, because the specificity and sensitivity of these measures for iron deficiency are low.[42]

It is hard to differentiate between absolute and functional iron deficiency without histological examination of the bone marrow.[38] Common practice in clinical care has used the response to IV iron supplementation as a guide; it is thought that patients with absolute iron deficiency are generally more likely to respond to this therapy compared to those with functional iron deficiency. However, about 30% of patients with functional iron deficiency also respond to treatment.[38] Nevertheless, both deficiencies contribute to iron-restricted erythropoiesis. It is recommended to use a trial of IV iron therapy to identify patients who need IV iron supplementation to optimize ESA therapy when hemoglobin (Hb) is below target levels or high ESA doses are used but iron status target levels are indefinite. A response to IV therapy with a 1 to 2 g/dL increase in hemoglobin confirms iron deficiency.[43]

The cause of iron deficiency in ESRD patients on HD is also multifactorial.[44] Absolute iron deficiency, or depleted iron stores, is frequently a result of blood loss, reduced intake, and impaired intestinal absorption of dietary iron. These patients undergo HD 3 times a week. Blood loss occurs due to clotted dialysis membranes and in the process of running through dialyzer, as well as frequent blood sampling. On average, a patient loses about 2-5 L of blood per year, which includes about 0.5-1.5 g of iron.[45,46] Absorption of iron from food seems to vary inversely with ferritin levels, however, the amount absorbed from food is not sufficient enough to meet the need for erythropoiesis in these patients.[44,47,48] Acquired gastrointestinal diseases such as autoimmune atrophic gastritis and *Helicobacter pylori* infection affect about 90% of HD patients, and the resulting use of gastric proton pump inhibitors and H_2-antagonists contributes to the malabsorptive mechanism of iron deficiency anemia.[49,50] Functional iron deficiency, caused by insufficient iron availability at the site of erythropoiesis despite adequate iron stores, can be a result of chronic inflammation associated with ESRD or elevated hepcidin levels.[38,44] Hepcidin, a peptide hormone, regulates absorption of dietary iron and recycled iron from senescent RBCs in splenic and hepatic macrophages, and the release of iron from storage in hepatocytes. Hepcidin is cleared by the kidneys and therefore elevated in ESRD patients. Abnormal hepcidin synthesis thus results in increased hepcidin levels that lead to decrease in iron absorption, availability of recycled iron from macrophages, and then functional iron deficiency.[34,44]

Iron deficiency has been linked with elevated risk for thromboembolic events and mortality in CKD patients on ESA treatment.[44] It is also a cause of hyporesponsiveness to ESA therapy, which is potentially correctable with iron supplementation.[41,44,47] Achieving adequate iron stores and availability is thus essential for optimal management of anemia in ESRD patients.

2.2.3. Consequence of Anemia

The consequences of anemia are severe. Anemia in ESRD patients is associated with elevated morbidity, mortality, and healthcare costs.[2,35-37] Left untreated, anemia can affect major organs such as heart and brain and contribute to CV morbidity and mortality outcomes, including an exacerbation of angina and left ventricular hypertrophy.[36] While the incidence of ESRD is on the rise, affecting nearly 637,000 patients in the US as of December 31, 2012,[29] anemia in ESRD patients remains an important public health problem. To minimize the potentially severe consequences of anemia in ESRD patients, adequate management of anemia is of great importance, and identifying optimal management strategies is essential.

2.3. Management of Anemia in ESRD patients on HD

Anemia, among the physiologic complications of advanced kidney disease, is probably the most responsive to treatment. Management of anemia in these patients has been evolving through time. Prior to 1990s, it was mainly through transfusions and IV iron supplementation, accompanying risk of transfusion reactions, immune sensitization, iron overload, and infection. The introduction of ESAs has decreased the use of transfusions.[51] Treatment with concurrent use of ESAs and IV iron has become the standard therapy due to relative health benefits[52-54] and cost-effectiveness[11] compared to ESA alone. Recent studies[7,8,55] showed evidence of harm associated with normalizing Hb with ESAs, contributing to a "black box" warning for ESAs and label change.[56,57] Together with changes in CMS's reimbursement program, the use of ESAs has been decreasing whereas reliance on IV iron has increased.[58,59]

2.3.1. RBC Transfusions in HD Patients

Before 1990s, anemia in HD patients required frequent RBC transfusions with an average of 6 times a year.[45] During a RBC transfusion, a needle is used to insert an IV line into one of the

patient's blood vessels, and healthy blood is given to the patient through this line. Transfusions raise the percentage of RBCs in the patient's blood, increasing the amount of oxygen available to the body. Prior to the introduction of recombinant human erythropoietin (rHuEPO) in 1989, low hemoglobin levels of 5-7 g/dL were prevalent in HD patients.[60] When iron and anabolic steroid treatments failed to improve the clinical symptoms of anemia, frequent blood transfusions were required.

For ESRD patients, RBC transfusions are almost universally successful in increasing a patient's blood volume and raising the hemoglobin level, and thus can help improve the patient's symptoms and quality of life. They, however, do come with risks. Risks associated with RBC transfusions include both infectious and non-infectious reactions. Due to the advancements in viral and bacterial testing methodologies and extensive donor interviewing process, the incidence of transfusion-transmitted infections has reduced greatly.[61] At the same time, reporting of non-infectious complications of transfusion has increased, which will likely remain the leading cause of transfusion-related morbidity and mortality.

The risk of transfusion-transmitted viral infections including HIV (risk 1 in 2.3 million), HBV (1 in 350,000) and HCV (1 in 1.8 million) infections is now greatly reduced, due to improved methods of donor history screening and laboratory testing.[61] Bacterial and parasitic infections, in comparison, are rising concerns. Sepsis secondary to gram-negative bacteria carries a mortality rate as high as 60%;[62] *Babesia* accounts for 30% of reported deaths due to RBC microbial infections with no currently available FDA-approved test to detect *Babesia*.[61]

RBC transfusions can also cause a variety of non-infectious reactions, and the risks of their occurrence vary greatly as well as their impact on mortality. As reported to the FDA between 2005 and 2010, the top 3 causes of transfusion-related deaths were transfusion-related

acute lung injury (incidence 1 in 1,200-190,000 transfusions), hemolytic transfusion reactions, and transfusion-associated circulatory overload (<1 in 100 transfusions), accounting for 50%, 25%, and 12% of the total events respectively. Serious allergic reactions, anaphylactic reactions (1 in 20,000-50,000 transfusions), accounted for 4% of total transfusion-related deaths, whereas mild allergic reactions such as mild urticarial reactions (incidence 1-3%) were less fatal.[61]

Iron overload, another non-infectious risk of transfusion, was a common and potentially serious complication during the pre-EPO era.[63] Because the amount of iron being released (~1 mg iron per mL of RBCs) during transfusion dramatically exceeds what can be excreted (~1 mg per day), transferrin becomes saturated quickly after 10-15 units of RBCs. Excess iron accumulates in essential vital organs (reticuloendothelial system, liver, heart, spleen and endocrine organs), which may lead to liver failure and heart failure.

Another common non-infectious reaction is alloimmunization, which can occur against RBC (incidence 6-10%) or Human Leukocyte antigens (HLA, incidence 2-25%).[61] The incidences are much higher among patients receiving multiple transfusions. HLA alloimmunization is undesirable in ESRD patients because it is considered as a contraindication to transplantation.

With the introduction of EPO, the hemoglobin levels of patients on HD greatly improved, and the need for RBC transfusions dramatically decreased. However, RBC transfusions are still necessary for patients who need an immediate increase in oxygen carrying capacity.

2.3.2. ESA Use in HD Patients

The availability of rHuEPO in 1989 has revolutionized anemia management in patients with ESRD. The initial phase III trial showed elimination of the need for transfusions within 2 months of initiation of ESA therapy, compared with 1,030 transfusions within the 6 months prior

to initiation.[64] Because they dramatically reduced the need for frequent RBC transfusions and androgen as well as their associated adverse effects, ESA therapy became very appealing and widely used for anemia management in ESRD patients on HD.

Exogenous ESAs are structurally and biologically similar to endogenous hormone EPO. They stimulate erythropoiesis via the same mechanism,[34] inducing the body to create more RBCs and raise the hemoglobin level. ESAs also help mobilize iron stores, which is particularly helpful in ESRD patients with iron overload due to previous frequent transfusions.[34,65,66]

ESAs in the US

Two ESA agents are available for the treatment of anemia of CKD in the US: epoetin alfa (Epogen®/Procrit®) and darbepoetin alfa (Aranesp®). Approved by the FDA in 1989, epoetin alfa is the first agent in the ESA family and has been prescribed to 1.5 million Medicare patients on dialysis as of 2012.[67,68] In 2001, the second-generation ESA darbepoetin alfa was approved.[69] Darbepoetin alfa differs from epoetin alfa in that it contains two more N-linked oligosaccharide chains, resulting in longer half-life than epoetin alfa. In November 2007, the third generation ESA methoxy polyethylene glycol-epoetin beta (Mircera®) was approved for the treatment of anemia associated with CKD in both patients on dialysis and not on dialysis.[70] It is the only FDA-approved ESA to maintain stable hemoglobin levels with once-monthly or one-every-two-week dosing in all CKD patients. Compared to the other ESAs, Mircera® has the longest half-life, up to six times longer than darbepoetin alfa and up to 20 times longer than epoetin alfa. Mircera® has been available in Europe but not launched in the US due to a patent case.

Indications and contraindications in HD patients

Both epoetin alfa and darbepoetin alfa are indicated for the treatment of anemia due to CKD in most patients on HD who have a hemoglobin level of <10 g/dL.[68,69] They are not

indicated to use in HD patients who have a history of stroke or malignancy, or active malignancy receiving treatments, unless also receiving concomitant myelosuppressive chemotherapy. ESAs cannot substitute for RBC transfusions in patients requiring immediate correction of anemia.[68,69] They are also contraindicated in patients with uncontrolled hypertension, pure red cell aplasia, and serious allergic reactions to ESA therapy.[68,69]

ESA administration

ESAs can be administered both intravenously and subcutaneously. Studies have shown that subcutaneous administration is 20% to 30% more efficient than a comparable intravenously administered dose.[71] Nonetheless, ESAs are mostly administered intravenously for patients on HD in the US due to the convenience of IV administration and the potential risk of pure red cell aplasia subcutaneous administration carries. Initially, subcutaneous administration was more common in other countries.[72] However, due to the association between cases of pure red cell aplasia and subcutaneous administration of epoetin alfa in Europe, IV administration of ESAs becomes more common. Recent guidelines suggest either administration route for HD patients.[13]

Compared to long-acting darbepoetin alfa that requires injections once every one or two weeks, administration of epoetin alfa is more burdensome by requiring two or three injections per week.[68] The difference of administration frequencies is due to the relatively shorter circulating half-time in plasma.[74,75] In the US, epoetin alfa is the most frequently used ESAs.[76]

Frequent monitoring, at least monthly, is recommended for patients who are receiving an ESA. Hemoglobin monitoring is performed prior to a mid-week HD session, aiming to minimize hemoglobin variability due to the longer inter-dialytic interval between the last treatment of one week and the first of the next. Hemoglobin testing should also be performed whenever clinically indicated, such as after a major surgical procedure, hospitalization, or bleeding episode.[13]

Efficacy and benefits of ESAs

Data consistently demonstrated the ability of ESAs to raise the hemoglobin level in patients on HD. Ever since ESAs became the standard of care for anemia management in patients with advanced CKD, mean levels of hemoglobin and hematocrit (Hct) rose consistently.[77] As of 2006, the mean hemoglobin level was 12.0 g/dL while two thirds of them have a level between 11.0-13.0 g/dL.[72,78] The need for regular transfusions dropped by about 50% between 1999-2000 and remained low since then, resulting in great reduction in complications including iron overload.[30] Thanks to the ESA therapy, severe anemia is no longer a major cause of morbidity in HD patients. Improvements have been shown on the CV and hemodynamic abnormalities[79,80] and non-hematologic symptomatic conditions[81,82] with partial correction of severe anemia. Epoetin alfa and darbepoetin alfa are similarly effective in achieving and maintaining target hemoglobin levels; the main difference is that darbepoetin alfa is relatively long-acting.[83-85]

Side effects of ESAs

Since the introduction of ESAs, clinical practice guidelines for managing anemia in HD patients changed from transfusions to normalizing hemoglobin using ESAs. Despite the alleviation of anemia, emerging data suggested that ESAs are associated with increased mortality and morbidity starting 2003. Consequently, the FDA responded with package insert changes and a "black box" warning. Over the same period, Medicare underwent multiple changes to its reimbursement policy for ESAs, and anemia management guidelines were revised.

Epidemiologic studies based upon data from the USRDS or Health Care Financing Administration (HCFA) database suggested that hemoglobin levels between 11-13 g/dL are associated with better outcomes compared to lower values.[86-98] However, results from multiple RCTs, meta-analyses, and systematic reviews suggested that full correction of anemia with

hemoglobin approaching the normal range does not result in significant clinical benefit but is rather associated with elevated risk of adverse outcomes, compared with partial correction.[99-104]

The pivotal RCTs (Table 2.2) raised concerns about ESAs, such as increased risks of arterial thrombotic events including stroke, venous thromboembolism, and exacerbation of cancer.[7-9,55] The majority of meta-analyses performed showed similar results. In one recent meta-analyses with 27 trials,[104] compared with lower targets or placebo, higher hemoglobin targets were associated with an elevated risk for hypertension (risk ratio (RR) 1.67, 95% confidence interval (Cl), 1.31-2.12), stroke (RR 1.51, 1.03-2.21), and vascular thrombosis (RR 1.33, 1.16-1.53). Although not statistically significant, higher risks were observed for mortality (RR 1.09, 0.99-1.20) and serious CV events (RR 1.15, 0.98-1.33). The underlying mechanisms of these adverse effects are still unclear, which could be a direct effect of the higher hemoglobin level mediated by hemodynamic or rheological effects or indirect effects due to higher ESA doses.

Examination of the effects of ESAs on quality of life returned inconsistent results. Some studies showed improvements,[55,105-107] while others showed either no difference or not sustained effects.[7-9] As evidence accumulates, they attracted the attention of the Congress, the FDA, the CMS, and the National Kidney Foundation (NKF) (Figure 2.2). The FDA responded by issuing a "black box" warning for ESAs that first recommended the minimum dose required to avoid the need for transfusion, and later changed to recommending a hemoglobin target of 10-12 g/dL.[56,57] The CMS responded by changing ESA reimbursement policy multiple times to a bundled composite pay rate system that includes services provided for dialysis including ESAs, iron, antibiotics, and laboratory tests related to the treatment of ESRD.[10] The NKF followed with revisions to their KDOQI anemia guidelines in 2007 to recommend a target hemoglobin of 11-12 g/dL in ESA-treated patients and to avoid hemoglobin >13 g/dL.[109]

Table 2.2. Large randomized studies of ESA in CKD patients with anemia

	NHS	CHOIR	CREATE	TREAT
Year Published	1998	2006	2006	2009
Location	US, 51 sites	US, 130 sites	Europe, 22 nations 94 sites	International, 24 nations 623 sites
ESA	Epoetin alfa	Epoetin alfa	Epoetin beta	Darbepoetin alfa
CKD Stage and Comorbidity	Hd with cardiac disease	Nondialysis	Nondialysis	Nondialysis with type 2 diabetes
Sample Size	1,233	1,432	603	4,038
Duration (year)	3+ (planned)	Max 3	Max 4.25; Mean 3	Max 4; mean 2.42
High Hb Target (g/dL)	14 (Hct 42)	13.5	13 to 15	13
Low Hb Target (g/dL)	10 (Hct 30)	11.3	10.5 to 11.5	9
CV Endpoints	RR 1.3 (0.9 to 1.9)	High in high Hb group	No difference	No difference except higher stroke in high Hb group
Progression of CKD	Not applicable	No difference	More in high Hb group	No difference
Cancer Deaths	Not noted	Not noted	Not noted	Higher in high Hb group among patients with previous cancer
Quality of Life	Better physical function in high Hb group	No difference	Better in high Hb group in the first year	No difference except less fatigue in high Hb group

Note: CKD=Chronic kidney disease, Hb= hemoglobin, Hct=Hematocrit, CV=Cardiovascular. Adapted from National Kidney Foundation's Primer on Kidney Diseases[34], and publication of these studies[7-9]

Overall, evidence suggest that ESAs may increase risks of morbidity and mortality although they are effective at raising hemoglobin levels. The use of ESAs has gradually decreased, accompanying with gradually fallen target hemoglobin level for patients receiving ESAs and the lowest hemoglobin level for ESA initiation.[110] Between 2009 and 2011, the mean hemoglobin level fell to 10.96 g/dL, ESA doses dropped by 19.2%, while the use of IV iron has increased by 3.4% in the US. A slight increase in use of transfusions was noted.[111,112]

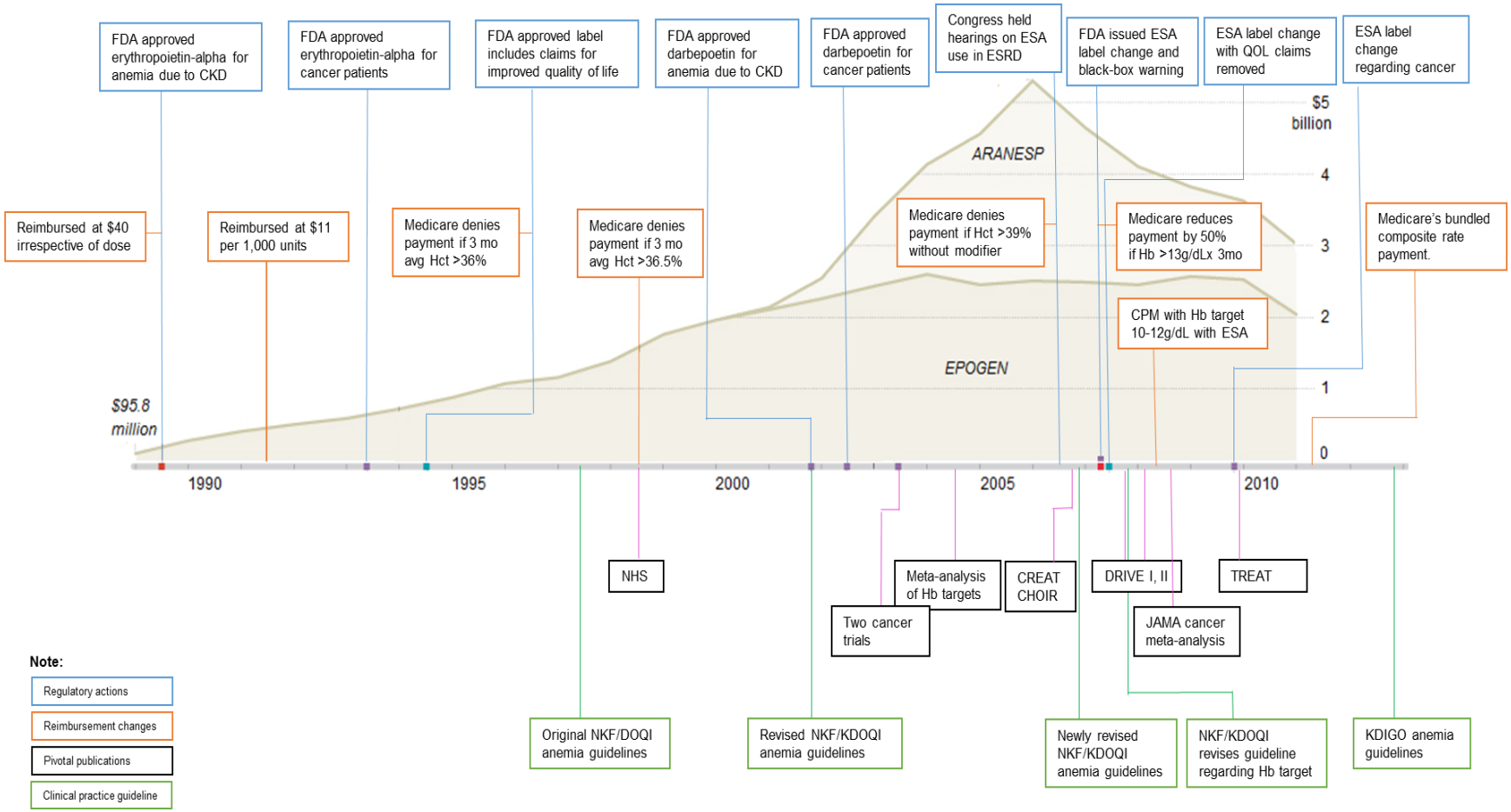

Figure 2.2. A timeline of the major events related to ESAs in the US that occurred between 1998 and 2012

Regulatory actions and reimbursement changes are presented above the time line, and pivotal publications and clinical practice guidelines for anemia management in ESRD patients are presented below the time line. The adapted background graphs represent Amgen's sales of Epogen® and Aranesp® from 1989 to 2010.[108] Complete sales data for Procrit® were not available.

2.3.3. IV Iron Use in HD Patients[1]

A primary cause of anemia in ESRD is iron deficiency, particularly among patients requiring hemodialysis (HD). Iron deficiency can be classified into absolute iron deficiency and functional iron deficiency, each with multifactorial causes.[3] Absolute iron deficiency, or depleted iron stores, is frequently a result of blood loss, reduced intake, and impaired intestinal absorption of dietary iron.[3] Functional iron deficiency, or insufficient iron availability at the site of erythropoiesis despite adequate iron stores, can be caused by chronic inflammation associated with ESRD or elevated hepcidin levels.[3] Overall, HD patients lose an average of 1-2 g of iron per year, and some as much as 4-5 g per year.[4] Management of iron deficiency to meet the need for erythropoiesis is thus essential for optimal management of anemia in ESRD patients.

Intravenous (IV) iron is an effective way to supplement iron and optimize erythropoiesis. Existing randomized controlled trials (RCTs) showed that supplementing erythropoiesis-stimulating agent (ESA) therapy with IV iron increases hemoglobin production and lowers ESA requirement.[5-10] Consequently, co-administration of ESAs and IV iron has become the primary management strategy for anemia in HD patients.[4] Subsequent to emerging evidence on the cardiovascular (CV) safety of ESAs[7-9] and changes in the reimbursement policies in Medicare's ESRD programs,[10] hemoglobin targets have decreased, allowing providers to reduce ESA dosing, decreasing potential risks associated with ESAs.[11-12] However, despite steadily falling hemoglobin levels, doses of IV iron rose from 210 mg per month in 2009-2010 to 280 mg per month in 2011, then back to a stable 200 mg per month in 2012-2013.[17,18] Consequently, ferritin levels in dialysis patients have generally been elevated, with many greater than 800 ng/mL.[17] The persistently high levels of ferritin raised concerns about appropriate use of iron.

[1] This section was submitted to *Hemodialysis International*.

Despite its established effectiveness, there have been concerns about safety of IV iron supplementation. Unlike oral iron supplements, IV iron bypasses various homeostatic mechanisms that keep iron tightly regulated. Due to the association between labile iron and both induced oxidative stress and bacterial growth, elevated risks of CV events[114-116] and infection[117] have been a concern related to IV iron use in HD patients. Hypersensitivity reactions have also been linked to the use of some iron formulations.[113] Unfortunately, the existing RCTs of IV iron are small and short-duration and therefore do not provide evidence on safety and long-term effects. Recent observational studies, primarily relying on cumulative iron exposure rather than clinical dosing patterns, have showed differing results.

Five forms of IV iron preparations have been approved for use in the United States (Table 2.3). These iron products are formulated with an iron oxyhydroxide core surrounded by a carbohydrate shell.[118] The sizes of the core and its surrounding carbohydrate shell differ among iron formulations, leading to different amount of labile iron being released. In contemporary clinical practice, IV iron is either provided intermittently via large doses over consecutive dialysis sessions (often termed "bolus dosing") or via small doses provided every one to two weeks to maintain iron stores (often termed "maintenance dosing"). Decisions regarding when to use each dosing approach typically follow protocols established by dialysis clinics. These protocols provide treatment recommendations based on target levels of hemoglobin and observed iron status parameters - ferritin and transferrin saturation (TSAT).[13,15] A variety of dosing protocols exist in clinical practice, and they differ with respect to target levels of iron status parameters and dosing approach recommendations.[19,20] Optimal management strategies to administer IV iron have not been identified.

IV Iron and Hypersensitivity Reactions

Hypersensitivity reactions have been a concerning complication of IV iron administration. First, and foremost, an anaphylactic reaction can be life-threatening if not addressed with urgency. Second, the immediacy of the reaction that is experienced by the patient receiving the agent is traumatic for both patients and staff. However, it appears that the absolute incidence of adverse hypersensitivity reactions is low, especially with the use of newer agents.

Mechanism of Harm

All IV iron preparations can lead to hypersensitivity reactions, including anaphylaxis. Historically, occurrences of anaphylaxis were observed with high-molecular-weight iron dextran,[120] raising concerns regarding the safety of IV iron treatment. This product was in turn replaced by low-molecular-weight iron dextran and other non-dextran products and is no longer commercially available. Overall, anaphylactic reactions are rare in IV iron formulations other than high-molecular-weight iron dextran. Using data from the US FDA MedWatch programme (2001-2003), Chertow et al examined the frequency of adverse drug events related to the four older preparations. Compared to high-molecular-weight iron dextran, the rate of severe adverse reactions was much lower in low-molecular-weight iron dextran (3.3 versus 11.3 per million patients), or other non-dextran products (ferric gluconate: 0.9 per million patients; iron sucrose: 0.6 per million patients).[4] These rates were remarkably lower than those observed after their first release.

The mechanism of anaphylaxis associated with IV iron administration remains unknown. Immunological IgE- and IgG-mediated responses associated with the dextran component may explain the relative higher occurrence of anaphylactic reactions associated with high-molecule-weight iron dextran compared to other non-dextran preparations.[4,121] Among the other

preparations, the activation of the complement system triggered by iron nanoparticles is likely to be involved.[121] As a consequence of complement activation, activation of mast cells and basophils increases, resulting in secretion products that potentially lead to hypersensitivity reactions.

Although the precise mechanism of hypersensitivity reactions to IV iron is unknown, the potential risk factors include asthma, mastocytosis, atopic status, and concurrent medications including beta blockers and angiotension-converting enzyme inhibitors.[4] Given the inability to predict hypersensitivity in patients using a serological evaluation, careful monitoring is needed when administering any IV iron product.

Epidemiologic Evidence

Due to the rarity of occurrence, evaluation of the hypersensitivity risk associated with iron formulations is challenging in RCTs and prospective observational studies; impractically large sample size would be needed to reach adequate statistical power. It is even more challenging to compare the risks among different iron formulations using these designs. Consequently, existing evidence base on IV iron and hypersensitivity reactions largely comprised of data from spontaneous reporting.[122-126] Excluding high-molecular-weight iron dextran, the highest risk of anaphylaxis was observed in iron dextran, and no significant difference in risk was observed among other iron formulations including ferric gluconate, iron sucrose, and ferumoxytol. However, caution needs to be exercised when interpreting these results because data from voluntary reporting is prone to reporting bias.[127] Substantial under- or over-reporting and lack of verification makes them unfit for accurate estimation of incidence for a given adverse event.

Large observational studies can be used to examine the risk of such rare events. In a large cohort of 688,183 Medicare beneficiaries from 2003-2010, Wang et al reported higher incidence rate of anaphylaxis associated with incident exposure to iron dextran compared to other iron products combined (68 versus 24 per 0.1 million patients).[128] Following total iron repletion of 1 g administered within a 12-week period, the cumulative anaphylaxis risk was highest with iron dextran (82 per 0.1 million patients) and lowest with iron sucrose (21 per 0.1 million patients).

Despite the rarity of hypersensitivity events, physicians are required to inform patients about these risks before treatment,[129] and management tips have been provided for these adverse reactions.[4] A test dose is recommended for iron dextran. For other non-dextran formations, administration with a relatively small dose and slower rate of infusion has been advised.[130]

IV Iron and CV-related Risk

Cardiovascular (CV) disease is the leading cause of death among HD patients. There have been theoretical concerns that IV iron may increase the risk of CV-related outcomes through inducing increased oxidative stress.[114-116]

Mechanism of Harm

With IV administration, iron is directly released into plasma, resulting in transient concentrations of labile plasma iron and formation of highly reactive free radicals, damaging reactive oxygen species that attack membrane lipids and are associated with atherosclerosis.[131] Excess free radicals could change the redox balance state to increase oxidative stress or at least exacerbate the level of oxidative stress present in HD patients.[131] Iron has been identified in atherosclerotic plaques, suggesting that IV iron may increase atherogenesis leading to CV deaths in HD patients.[132] Cell culture models and animal models have shown IV iron formulations

induce oxidative stress and tissue inflammation.[133-135] However, no definite link has been established between iron treatment, oxidative stress, and CV risk.

Hepcidin, the important regulatory protein for iron, has also been hypothesized to mediate the effect of iron on CV-related risk by promoting iron accumulation in macrophages and subsequently atherosclerosis.[136] However, animal studies have shown conflicting results regarding the association of hepcidin level and the atherosclerosis process.[137-139] Recent clinical studies in HD patients found positive association between increased level of hepcidin and arterial stiffness[140] and risk of CV events.[141]

Epidemiologic Evidence

Evidence from epidemiologic studies on IV iron and CV-related risk is inconclusive although early clinical studies indicated iron use with elevated risks of CV diseases[139] and mortality[142] in HD patients. Susantitaphong et al reviewed and meta-analyzed 24 single-armed studies and 10 parallel-arm RCTs and found no association between high IV iron doses and CV mortality (Table 2.4).[143] The completed studies were largely underpowered and generally evaluated outcomes that were not hard clinical end-points. They also had relatively short duration for follow-up.

A limited number of observational studies have evaluated the effect of IV iron on CV-related events and mortality in HD patients (Table 2.4), and the results are inconsistent. Iron doses greater than 400 mg/month[144] and 300 mg/month[145] were associated with higher CV mortality risk in two large cohort studies. Higher cumulative iron doses were also linked with higher CV events in a Japanese prospective cohort study, which examined a product not currently used in the United States.[146] Conversely, two recent retrospective studies of HD patients showed no association between large doses and short-term CV morbidity and

mortality.[20,23] Similarly, no clear association has been established between IV iron and all-cause mortality. Higher doses were associated with increased risk of death in some studies,[144-146] but no association was found in others,[145,146] with a few demonstrated reduced risks at certain levels of dosing.[20,144,147] The conflicting data is partly due to the difficulty to separate the effect of iron overload from systemic inflammation on CV-related outcomes because serum ferritin level can be a marker for both conditions. Residual confounding by indication is likely another factor contributing to the inconsistency, as patients receiving larger amounts of iron may be at higher underlying CV risk.

Overall, despite theoretical concerns, it is unclear whether IV iron administration exacerbates atherosclerosis and leads to increased risk of CV diseases, the leading cause of death in the ESRD patients. Further research is needed to evaluate hard clinical end pints, including myocardial infarction, stroke, and mortality. The potential mediating role of level of hepcidin and ferritin needs more thorough examination.

IV Iron and Infection Risk

Patients on HD frequently experience infectious complications leading to hospitalization and death. There are concerns that IV iron may increase infection risk because of its effect on bacterial growth, host immunity, and clinical infection risk.

Mechanism of Harm

Iron is essential for bacterial growth. In iron-rich environment, bacteria can acquire iron from the blood stream by producing iron chelating siderophores or obtain iron from transferrin directly via transferrin receptor and use it to grow. Iron is also essential for proper host defense against infection. Iron overload has been linked with impaired neutrophil and T-cell functions, and subsequent immune dysfunction and increased Gram-positive bacteria growth in vitro.[148-150]

Epidemiological Evidence

As with CV risk, the few RCTs of IV iron were not large enough to evaluate infection risk. The Dialysis Patients' Response to Intravenous Iron with Elevated Ferritin (DRIVE) study randomized HD patients with TSAT ≤25% and ferritin 1,124-2,696 pmol/mL receiving high doses of epoetin alfa (>30,000 U per week) to ferric gluconate or no iron. In these patients, 1 g of IV iron did not increase the risk of infection and actually reduced number of serious adverse events compared with patients who received no iron over the 3-month period.[6] Another placebo-controlled trial in patients with heart failure (but not on dialysis) found no elevated risks of infection, hospitalization or mortality in patients who received IV iron therapy.[151]

Compared to oral iron supplements, IV iron showed increased risk of infection and CV events in a recent trial in non-dialysis patients with chronic kidney disease that had to be terminated early.[152] The results were considerably different from that of the Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease (FIND-CKD) study that found no difference in infection risk across all three arms.[153] The discrepancy in the results may be partially caused by the single-center setting and greater loss to follow-up in the first study.

Several systematic reviews and meta-analyses performed to date are inconclusive. Early reviews published in 1999 found no evidence of an effect of iron and infection.[154-156] As more data accumulated, an updated review conducted by Ishida and Johansen suggested a potential link between iron and elevated infection risk.[157] Out of the 24 studies (published in and prior to 2013) included in the review, 12 studies showed an association of usage, dose-dependent risk or frequency-dependent risk between iron and infection or infection-related mortality, whereas the rest showed no association. Most of the 24 studies had small sample size and short follow-up

duration. Many studies did not take into account of iron status parameters such as serum TSAT and ferritin levels, offering little information about the comparability of the patient groups across study groups. More than half of the studies (15/24) were carried out in other countries or in older cohorts in the United States, limiting generalizability of these results.

Two recent meta-analyses of RCTs also reported conflicting results. With both HD patients and non-HD patients with CKD, Litton et al showed increased risk of infection comparing IV iron with either oral iron or no iron supplementation.[158] The other meta-analysis evaluated the safety of IV iron in HD patients with functional iron deficiency reported no association of iron use with infection risk, but only two studies were included in the analyses for this outcome.[143]

Cumulative Iron Exposure and Infection Risk

To date, a number of observational studies examined the effect of IV iron administration and risk of infection; most of them focused on cumulative iron exposures over a long period. Current data, however, give mixed signals. In the last five years, several observational studies with large population of HD patients have been published (Table 2.5). In a cohort of 14,078 dialysis patients in the United States, Miskulin et al examined the accumulated IV iron dose over 1-, 3-, and 6-month rolling windows and found large associations between cumulative dose and infection-related outcomes, but these associations were very imprecise and included the null effect in all case.[20] Another study with 32,435 HD patients from 12 countries also reported non-statistically significant difference across dosage groups. However, infection-related mortality was elevated among patients receiving higher doses of IV iron over 4 months compared to 100-199 mg/month.[145] In another cohort of 9,544 incident HD patients, higher cumulative IV iron doses were not associated with infection-related hospitalizations.[27] Inadequate statistical power

due to small sample sizes might have contributed to the inability to detect the difference in some of these studies.

To identify patient subgroups at higher risk, the effect of IV iron on risk of infection has also been evaluated in several studies. Catheters were found to be the leading risk factor of bacteremia in chronic HD patients.[159] Higher iron dose was also associated in patients with catheter-related sepsis than in patient without.[25] In recent work by our group comparing bolus dosing with maintenance dosing strategy in a large cohort of HD patients, highest risk of infection-related hospitalization was observed among patients with a catheter or history of recent infection.[25]

Safety of Iron Protocols: Towards More Clinically-relevant Effects

Much of the existing research on iron has studied long-term cumulative exposure or shorter-term dose effects – exposures that do not align with treatment decisions made by clinicians. In contemporary clinical practice, IV iron is administered according to protocols, which recommend courses of treatment aimed at achieving target levels of hemoglobin and iron status parameters (ferritin and TSAT). Following availability of levels of these parameters, physicians make decisions about the iron administration approach (e.g., bolus dosing or maintenance dosing) for the next treatment course. A variety of dosing protocols exist in clinical practice, and they differ with respect to target levels of iron status parameters and administration approach recommendations.[19-21]

Little evidence is available regarding the long-term safety and effectiveness of these dosing protocols in the literature. Clinical trials assessing the use of IV iron dosing protocols are lacking; existing large observational studies have focused on the effect of cumulative iron

exposure over a long period, which do not align with the treatment decisions that physicians need to make regarding iron use.[28]

Existing studies have compared the safety of exposure to different administration approaches. Several studies consistently demonstrated short-term benefits of bolus iron administration on hemoglobin levels and iron status compared to more conservative maintenance dosing[22] or no iron.[6] No difference in CV risks was associated with either administration approach.[23,24] Elevated risk of infection was associated with bolus dosing approach. In a large cohort of 117,050 HD patients in the United States, our group compared bolus iron administration with maintenance dosing and found increased short-term risks of infection-related hospitalization or mortality (hazard ratio and 95% confidence interval: 1.08, 1.05-1.11).[25] In another study of 12,969 HD patients in the United States, Michels et al reported lower mortality risk associated with maintenance dosing strategies compared with non-maintenance strategies.[26] It is worth noting that different definitions were used for administration strategies across these studies.

Altogether, the evidence concerning IV iron dosing protocols is inconclusive. The examination of cumulative exposures over a long time period offered little clinically meaningful information to physicians with regard to treatment decisions, which concern more about the dosage, frequency, and timing of IV iron. Evaluation of different dosing protocols are needed to identify optimal strategies for iron treatment in HD patients.

Summary

Data have consistently demonstrated the effectiveness of IV iron treatment in management of anemia in the ESRD patients on HD. However, there remains considerable uncertainty about the best strategy for IV iron treatment of anemia management iron in ESRD

patients. In particular, the dosage, frequency, and timing of IV iron use in HD patients are unknown. Given the increasing utilization of IV iron and data suggesting risk for some dosing practices in some patients, further research is needed to identify optimal dosing strategies that maximize the benefits of IV iron, while avoiding its potential risks.

Table 2.3. IV iron preparations available in the United States

Generic Name	Brand Name (Manufacturer)	Approval Year	Test Dose Needed	Labeled Dosage for Iron Deficiency	IV administration time	Notes
High-molecule-weight iron dextran	DexFerrum (American Regent)	1954	Yes	1000 mg in 10 divided doses or total dose as a single IV infusion	Undiluted at an infusion rate not to exceed 50 mg (1mL)/min	Anaphylactic-type reactions and fatalities reported; resuscitation equipment and trained personnel necessary
Low-molecule-weight iron dextran	InFed (Watson)	1992	Yes	1000 mg in 10 divided doses or total dose as a single IV infusion	Undiluted at an infusion rate not to exceed 50 mg (1mL)/min	Anaphylactic-type reactions and fatalities reported; resuscitation equipment and trained personnel necessary
Ferric gluconate	Ferrlecit (Sanofi-Aventis); Nulecit (Watson)	1999	No	1000 mg in 8 divided doses (HD only)	60 minutes diluted in saline; undiluted IV push at 12.5 mg/min	Reactions to benzyl alcohol ingredient
Iron sucrose	Venofer (American Regent)	2000	No	1000 mg in 10 divided doses (HD); 1000 mg in 5 divided doses (NDD); 1000 mg in 2 doses of 300 mg and 1 dose of 400 mg (PD)	2-5 minutes undiluted or 15 minutes if diluted in saline (HD, NDD); 300 mg infused over 1.5 hours, 400 mg over 2.5 hours 14 days later, 400 mg infused over 2.5 hours 14 days later (PD)	7-day stability; anaphylactoid reactions
Ferumoxytol	Feraheme (AMAG)	2009	No	510 mg × 2 doses separated by 3 or 8 days	IV infusion diluted in saline or Dextrose Injection over 15+ minutes	MRI interaction for up to 3 mo; resuscitation equipment and trained personnel necessary. Anaphylactic-type reactions presenting with cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness
Ferric carboxymaltose	Injectafer (American Reagent)	2013	No	750 mg × 2 doses separated by at least 7 days (weighing ≥110 lb); 15 mg/kg body weight separated by at least 7 days (weighing <110 lb)	Undiluted IV push at 100 (2mL) per minute, or diluted infusion over at least 15 minutes	Anaphylactic-type reactions presenting with shock, clinically significant hypotension, loss of consciousness, and/or collapse

Note: IV= intravenous; HD=hemodialysis; NDD=Non-hemodialysis dependent; PD=peritoneal dialysis

Table 2.4. Characteristics of epidemiological studies on IV iron and CV-related events among HD patients

First Author	Study Year	Country	Databases	N	Iron formulation	Exposures	Follow-up	HR (95% CI)	CV risk[e]
Kalantar-Zedeh 2005[144]	2001-2003	US	USRDS and DaVita	58,058	ferric gluconate, iron sucrose, iron dextran	<400 vs 0 mg/month	2 years	200-399: btw 0.5-0.6[e]	–
						≥400 vs 0 mg/month		≥400: btw 1.1-1.3	+
Kuo 2014[146]	2004-2005	Taiwan	Prospective study at Excelsior Renal Service Co	1,239	ferric chloride hexahydrate	40-800 vs 0 mg/6 months	12 months	1.7 (1.0-2.7)	+
						840-1600 vs 0 mg/6 months		3.5 (1.9-6.1)	+
						1640-2400 vs 0 mg/6 months		5.1 (3.0-9.7)	+
Kshirsagar 2013[23]	2004-2008	US	USRDS and DaVita	117,050	ferric gluconate, iron sucrose, iron dextran	bolus vs maintenance [a]	3 months	1.03 (0.99-1.07)	*
						high vs low (> 200 vs ≤ 200 mg/1 month)		0.99 (0.96-1.03)	*
Miskulin 2014[20]	2003-2008	US	USRDS and Dialysis Clinic Inc	14,078	all formulations[b]	vs >0-150/1 month vs >0-450/3 months vs >0-900/6 months	up to 4 years	>350: 0.95 (0.70-1.29) >1050: 1.02 (0.74-1.41) >2100: 1.17 (0.76-1.79)	*
Susantitaphong 2014[143]	through Dec 2012	multi-country	24 single-arm studies and 10 parallel-arm RCTs	2,658	Multiple formulations[c]	NA	NA	NA	*
Bailie 2015[145]	2002-2011	12 countries	DOPPS	32,435	Multiple formulations[d]	average dose over 4 months (mg/month): 0, 1-99, 100-199 (reference), 200-299, 300-399, 400+	Median (IQR): 1.7 (1.0-2.4) years	increased risks with ≥300; ≥6 vs 1-2 mg/kg per month: 1.35 (1.12-1.62)	+

Note: IV=intravenous; CV=cardiovascular; HD=hemodialysis; US=the United States; USRDS=the United States Renal Data System; IQR=interquartile range; CI=confidence interval; HR=hazard ratio; DOPPS=the Dialysis Outcomes and Practice Patterns Study

[a]Bolus dosing: consecutive doses ≥ 100 mg exceeding 600 mg during one month; maintenance: all other iron doses during the month;

[b]No further explanation provided in the article;

[c]Iron sucrose, ferric gluconate, iron dextran, iron saccharate, iron polymaltose, iron oxide, ferrous colloid, ferumoxytol;

[d]Iron sucrose, ferric gluconate, iron dextran, iron saccharate, iron polymaltose, chondroitin sulfate iron complex, cideferron;

[e]Obtained from a figure in the article, the exact estimates were not available;

[f]Symbol representation: + = increased risk; – = decreased risk; * = no difference

Table 2.5. Characteristics of recent epidemiological studies on IV iron and infection among HD patients (2013-2016)

Author/Year	Study Year	Country	Databases	N	Population	Exposures	HR (95% CI)	Infection risk[d]
Brookhart 2013[25]	2004-2008	US	USRDS and DaVita	117,050	HD patients	bolus vs maintenance[a]; high vs low (> 200 vs ≤ 200 mg/1 month)	1.08 (1.05–1.11) 1.05 (1.02–1.08)	+
Miskulin 2014[20]	2003-2008	US	USRDS and Dialysis Clinic Inc.	14,078	HD patients	vs >0-150/1 month vs >0-450/3 months vs >0-900/6 months	>350: 1.26 (0.75-2.12) >1050: 1.69 (0.87-3.28) >2100: 1.59 (0.73-3.46)	*
Kuragano 2014[161]	2007-2009	Japan	multicenter-prospective	1,086	HD patients	cumulative weekly dose (vs no iron)	High: 5.22 (2.25–12.14); low: 1.78 (1.04–3.05)	+
Zitt 2014[162]	2000-2007	Austria	prospective	235	incident HD patients	yes vs no	0.31 (0.09-1.04)[b]	–
Bailie 2015[145]	2002-2011	12 countries	DOPPS	32,435	HD patients	average dose over 4 months (mg/month): 0, 1-99, 100-199 (reference), 200-299, 300-399, 400+	≥300: between 0.9-1.4[c]	*
Tangri 2015[27]	2003-2008	US	USRDS and Dialysis Clinic Inc.	9,544	incident HD patients	vs >0-150/1 month vs >0-450/3 months vs >0-900/6 months	>350: 0.91 (0.77-1.09) >1050: 1.08 (0.86-1.36) >2100: 1.26 (0.94-1.69)	*

Note: IV=intravenous; HD=hemodialysis; US=the United States; USRDS=the United States Renal Data System; HR=hazard ratio; CI=confidence interval; DOPPS=the Dialysis Outcomes and Practice Patterns Study

[a]Bolus dosing: consecutive doses ≥ 100 mg exceeding 600 mg during one month; maintenance: all other iron doses during the month;

[b]Outcome includes CV-related or sepsis-related mortality;

[c]Obtained from a figure in the article, the exact estimates were not available;

[d]Symbol representation: + = increased risk; – = decreased risk; * = no difference

2.4. Comparing IV Iron Dosing Protocols

IV iron dosing protocols are a type of dynamic treatment regimes. These protocols provide treatment recommendations based on patients' evolving clinical history aimed at achieving target levels of hemoglobin and iron status parameters. To identify the best IV iron dosing protocols among a set of protocols in routine use, we need methods appropriate for estimating effect of dynamic treatment regimes.

2.4.1. IV Iron Dosing Protocols as Dynamic Treatment Regimes

Dynamic treatment regimes refer to treatment strategies involving decision rules to make treatment recommendations based on evolving clinical history.[163] For patients with ESRD maintained on chronic HD, IV iron dosing protocols for anemia management are a type of dynamic treatment regimes. Patients receiving IV iron have laboratory tests evaluated on a regular basis to inform treatment titration. The current levels of hemoglobin and iron status parameters—TSAT and ferritin—inform the dosage level and frequency of IV iron administration for the next treatment course.[13,15,109] Other examples of dynamic regimes include treatment of HIV/AIDs,[164-166] management of type 2 diabetes,[167] and cholesterol control.[168] Increasingly, clinical guidelines present recommendations in this dynamic format.[164-168]

With a dynamic IV iron dosing protocol, levels of time-varying iron status parameters ($\boldsymbol{L}_m$) determine which dosing approach (A_m) to use for the next treatment course; these levels are also affected by treatment (A_{m-1}) in the previous course and associated with future survival (Y_{m+1}) (Figure 2.3). In this situation, current iron status tests are not only confounders for dosing approach and survival but also mediators for effect of previous treatment on survival. Thus, traditional regression-based statistical methods are not appropriate for evaluation of IV dosing protocols.

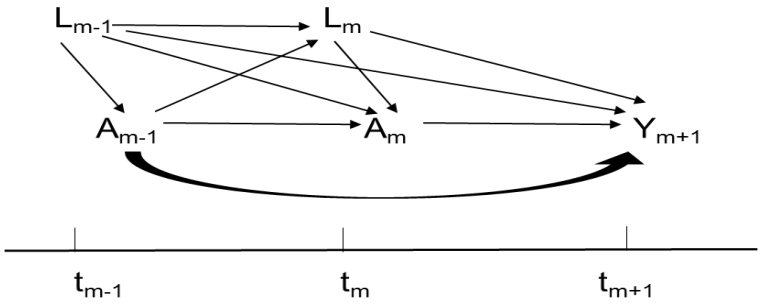

Figure 2.3. A schematic for an observational study involving dynamic treatment regimes
The schematic represents a screenshot of two observational intervals during the follow-up: A_m=treatment, $\boldsymbol{L}_m$=time-dependent covariates, t_m=time of visit, Y_{m+1}=outcome.

2.4.2. Causal Inference with Dynamic Treatment Regimes

Currently, a limited number of methods are available to directly estimate the effect of dynamic treatment regimes in observational studies. One approach is inverse probability weighted (IPW) estimation of Cox marginal structural models (MSMs). It was introduced by Robins to adjust for measured time-varying confounding and selection bias in observational studies.[169-172] Hernán et al employed this method in comparison of two dynamic treatment regimes for the initiation of highly active antiretroviral therapy in HIV-infected patients.[173] They described it as an approach to emulate RCTs with two dynamic treatment regimes using observational data. Using this approach, observation for subjects during follow-up are retrospectively examined to see if individual treatment was consistent with a particular regime of interest and are artificially censored at the first occurrence of a treatment that is not consistent with the regime initiated at baseline. Analyses are then carried out in uncensored individuals under regimes of interest by fitting an IPW Cox model with weights to adjust for potential selection bias introduced by this artificial informative censoring. The estimated effect from comparing two dynamic regimes can be interpreted as the difference in the outcome of interest if all the subjects always adhered to regime 1 versus regime 2.

Further studies generalized this method to compare multiple treatment regimes simultaneously.[174-177] Orellana et al[176] and Cain et al[177,178] created an artificial data set in which each subject contributes observations for each regime they followed. Cotton and Heagerty proposed a data augmentation estimation approach[179] and a weighted log-rank method[180] to test for differences in survival among multiple dynamic regimes. Shortreed and Moodie used bootstrap method for inference.[181] Under appropriate assumptions, IPW can appropriately adjust for measured time-varying confounding and selection bias in observational studies as well as in RCTs with imperfect compliance and loss to follow-up.

The parametric g-formula is an alternative to IPW of MSMs to adjust for time-varying confounding when comparing dynamic treatment regimes. It was first introduced by Robins[182] to estimate the causal effect of arsenic on heart disease and has been applied to compare the effectiveness of dynamic regimes involving lifestyle interventions.[183,184] Young et al used this approach to estimate all-cause mortality risks of several dynamic regimes for combined antiretroviral therapy initiation.[185] A g-estimation approach modeling the effect of the time-varying treatment was also considered to find the optimal regime.[174]

Under appropriate assumptions, these estimation methods can all provide consistent estimates of the counterfactual population parameters of interest. The identifying assumptions are the same, but each approach requires parametric assumptions on different components of the observed data.[185] The parametric g-formula estimator is based on parametric maximum likelihood estimation while the IPW estimator is a semi-parametric estimator. Thus, under correct parametric assumptions, the parametric g-formula and g-estimation produce more efficient estimators (with smaller variance) than the IPW estimators but require more parametric modelling assumptions. The parametric g-formula and g-estimation estimators are generally

more stable than the IPW estimators in the presence of near violations of the positivity assumption. However, due to the reliance on parametric assumptions, parametric g-formula and g-estimation estimators are more vulnerable to bias when the assumptions are violated. Correct specification is needed for the conditional probability of the outcome, the treatment, and the time-varying covariates in all follow-up intervals. In contrast, the validity of the IPW estimators requires correct specification of the treatment, the censoring indicator, and the MSM for the relation between a regime and the outcome of interest had all subjects followed this regime for all follow-up intervals. Parametric g-formula estimators are also subject to the "g-null paradox", which will reject the causal null even when it is true in sufficiently large samples because it is impossible to correctly specify parametric models under the causal null hypothesis.

For this thesis work, we used IPW estimation of Cox MSMs to compare the effect of different IV iron dosing protocols.

CHAPTER 3: ANALYTICAL APPROACH

3.1. Overall Study Design and Methods

This thesis used an observational retrospective cohort study to address the two aims. First, I identified frequently used IV iron dosing protocols for anemia management among end-stage renal disease (ESRD) patients undergoing chronic hemodialysis (HD). I then compared the effect of commonly used dosing protocols on all-cause mortality and infection-related outcomes. As a type of dynamic treatment regimes, the effect of long-term exposure to IV iron dosing protocols were compared using an inverse probability weighted (IPW) Cox marginal structural model (MSM). Under a set of assumptions, the results from Aim 2 allow for a causal interpretation of effect measure estimates. Aim 1 & 2 also demonstrated how to identify and evaluate dynamic treatment regimes in research studies for ESRD patients.

3.1.1. Study Population

This study used a cohort constructed using data derived from the clinical research database of a large dialysis provider in the United States (US), linked with the United States Renal Data System (USRDS). 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.[186]

I used the clinical research database to assess clinical detailed information relevant to dialysis and anemia management for HD patients, including IV iron and ESA use at each dialysis session, clinical laboratory values, current vascular access, and recent IV antibiotics use. As

usual clinical practice, such information is detailed into a patient's record in clinical database. Due to ethics of clinical practice and financial reasons that the dialysis facilities are reimbursed for drugs administrated, the dialysis clinics must maintain accurate drug records and subject them to institutional quality control systems. The quality of the data was not a major concern. A study examined the medication records documenting medications administrated at the clinic including IV iron and erythropoiesis-stimulating agents (ESAs) and showed high accuracy,[187] minimizing the potential for error in exposure measurement and clinical covariate assessment for this study.

I used the USRDS to assess demographic characteristics, comorbidities, healthcare system encounters, and specific outcomes of interest including death. Funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the USRDS is a national data system that collects, analyzes and distributes information about the treatment of ESRD.[188] The data system includes data from the Medicare Enrollment database, the Medical Evidence Report Form, the ESRD Death Notification Form, and the standard analytic files containing final action claims data. Thus, the USRDS contains detailed data on all patients in the Medicare's ESRD system, including information collected at dialysis initiation detailing the primary cause of ESRD, clinical data, and certain laboratory measurements. The USRDS also contains Medicare Parts A and B claims that include information on diagnoses and procedures recorded for all outpatient office visits and hospitalizations. The quality and validity of the USRDS data have been evaluated by studies conducted by the USRDS. An average concordance rate of 90.6% was found for fifty variables under examination when comparing a sample of the USRDS data with patients' medical chart.[189,190]

3.1.2. Cohort Identification

The study population consisted of ESRD patients who were at least 65 years old and receiving center-based, outpatient HD in the US between January 1, 2004 and September 16, 2012 and who had Medicare as their primary insurer.

Patients were included in the cohort if they met the following criteria:

1) started HD between January 1, 2004 and September 16, 2012 (so they had at least 3 months of HD and two-weeks of chronic anemia management);
2) continued HD for at least 3 months after the start of HD;
3) at least 65 years of age at the start of HD (to receive regular Medicare coverage because most HD patients who are younger than 65 do not have complete Medicare data until 3 months after the start of HD);
4) had continuous Medicare Part A and B coverage during the 3-month baseline period;
5) had at least one claim before the first service date and at least 60 days covered by claims during the first 90 days of dialysis;
6) had at least 9 dialysis sessions in the last month of baseline period (suggesting the individual was receiving regular center-based HD).

Patients were excluded if they met the following criteria:

1) had polycystic kidney disease (since many of these patients do not require ESAs and therefore may have different IV iron requirements);
2) had missing values on baseline covariates or IV iron exposure.

Study period

The study period was from January 1, 2004 through December 31, 2012.

Baseline period

The baseline period was the time period starting on 90 days before dialysis initiation and ending on the first TSAT laboratory test date (index TSAT) (Figure 3.4 & Figure 3.5).

3.1.3. Study Variables

Exposure

The exposure of interest was IV iron dosing protocols for anemia management in ESRD patients on HD. Details for exposure assessment are listed separately for each aim under the **Statistical Analysis** section.

Outcomes

The outcomes for Aim 2 were the risks of all-cause mortality and infection-related hospitalization or mortality if all patients were persistent to the index IV iron dosing protocols. These endpoints were examined separately.

Infection-related hospitalization outcomes included hospitalization due to sepsis, vascular access, and pneumonia. They were identified using Medicare Part A inpatient claims and definitions consisted of International Classification of Disease, Ninth Revision (ICD-9-CM) diagnosis codes. Infection-related death all-cause mortality outcomes were identified using the ESRD Death Notification File of the Medicare's ESRD program and the specific cause of death. The detailed definitions were listed in Table 3.6.

Follow-up period

The follow-up period in Aim 2 started at the end of the first two-week exposure window (index exposure window) following index TSAT. Patients were followed up until occurrence of an event of interest, receipt of kidney transplantation, the time of switching modality (from center-based HD to peritoneal dialysis or home HD), loss to follow-up, disenrollment from this

dialysis provider, loss of Medicare coverage, 120 days since start of follow-up or administrative end of follow-up (which was December 31, 2012).

Table 3.6. Definitions for study outcomes

Outcomes	Definition	Data Source
Infection outcomes		
Hospitalized for infection	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

3.1.4. Covariate Assessment

I collected covariates deemed important to the specific aims of this thesis by existing literature and the clinical expertise of the research team. They included demographic and clinical characteristics of the patients and dialysis facility. I evaluated both baseline covariates and time-varying covariates. Baseline covariates were evaluated in the baseline period prior to the index date for first iron dosing protocol. Time-varying covariates were evaluated at fixed intervals following the start of follow-up.

The clinical database, the USRDS, and Medicare Part A and B files were used for covariate assessment. Comorbidities were assessed using definitions consisting of ICD-9-CM diagnosis codes. Table 3.7 lists the detailed definitions for each condition and the data source of assessment.

Table 3.7. Definition for 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

Covariate	Definition	Data Source
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
EPO dose (baseline)	Total EPO dose in the last month of baseline	Clinical Database
EPO dose (exposure)	Total EPO 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); 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);	Clinical Database

Covariate	Definition	Data Source
	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
TSAT level, %	Most proximal TSAT level in prior interval	Clinical Database

Covariate	Definition	Data Source
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
EPO use	Total EPO 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

3.2. Statistical Analysis

3.2.1. Aim 1 Protocol Identification

Study population

The study population for Aim 1 were ESRD patients who were at least 65 years old and who initiated center-based HD in the US between January 1, 2004 and September 16, 2012 and had Medicare as the primary insurer.

Index interval

The index interval was the interval anchored by the index TSAT and the subsequent TSAT.

Dosing protocols

IV iron dosing protocols specify a range of acceptable iron therapy values during an interval given a subject's current time-varying laboratory test values for anemia management parameters. For example, one dosing protocol set a target range of ≤50% for TSAT, ≤1200 ng/mL for ferritin, and 13.0 g/dL for hemoglobin. The strategy recommended bolus dosing (100 mg of iron sucrose for 10 consecutive dialysis sessions) if TSAT fell below 20% and ferritin was below 200 ng/mL. The strategy recommended maintenance dosing (50 mg of iron sucrose

weekly) if TSAT was between 20-50% and ferritin was between 200-800 ng/mL. If any of the parameters were to be above the target range or if the patient was receiving IV antibiotics, the strategy recommended iron be withheld.

Classification of dosing protocols was carried out in the index interval following index TSAT (Figure 3.4). The choice of anchoring on a TSAT measurement was because evaluation of IV iron administration typically occurs following the availability of iron status tests (TSAT and ferritin) in clinical practice.

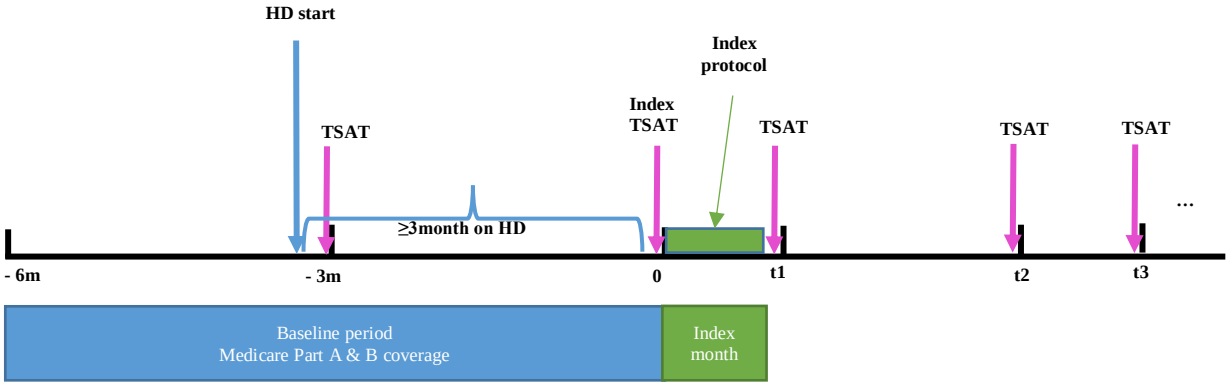

Figure 3.4. Schematic of study design for aim 1

Methods

The initiated dosing protocols $D(\delta, \rho)|\ \theta, \gamma, \lambda$ were characterized by a set of parameters $(\theta, \gamma, \lambda, \delta, \rho)$, where θ= TSAT level, γ= ferritin level, λ= having diagnoses of infection or use of IV antibiotics, hospitalization or blood transfusion, δ= iron dosage, and ρ= iron treatment frequency. Each protocol specified a range of acceptable treatment values for iron use depending on the value of iron status test level and status of infection or IV antibiotic use. I developed an identification approach for dosing protocols using an assessment window following the index TSAT. For each patient, the iron treatment experience in the assessment window was examined to see with which protocol(s) it was consistent.

The initiated protocols were summarized in a figure depicting how IV iron dosage, administration frequency, and iron status parameters relate in individual protocols. Characteristics of patients initiating different dosing protocols were described. The trend of protocol initiation was examined over the calendar years and region of residence during the study period.

Logistic regression was used to estimate for each patient the probability of receiving a particular IV iron dosing protocol given observed characteristics and identify the most important baseline factors that contribute to the initiation of a particular protocol. Potential factors included demographic characteristics, comorbidities, medications, and healthcare use in the baseline period.

Strengths

- The detailed information on dialysis procedures, IV medication, and laboratory test values in the clinical research database offered a great opportunity to examine how IV iron is used for anemia management in HD patients. These patients receive dialysis treatment three times a week, and the clinical research database captured the amount of IV iron use, IV iron formulation, and EPO dose administered, as well as clinical values and laboratory values from each visit. The granularity of the clinical data helped us understand how IV iron was used and classify dosing protocols in everyday clinical practice.
- The size and diversity of the population derived from the linked databases merging the USRDS and a clinical research database from a large dialysis provider allowed for examination of IV iron use for anemia management among general HD patients in the US.

Challenges

- No data were available on IV medications administered during hospitalization. It was unclear if a patient was continuing the dosing protocol from the outpatient dialysis facility or using a different protocol when staying in the hospital. All candidate protocols were assigned to patients if they were hospitalized during the assessment window.
- The prescribed dosing protocols were not available, thus it was challenging to evaluate the performance of the identification approach. I used knowingly previously implemented dosing protocols as a positive control. Their high prevalence of initiation speaks to the validity of the performance of the identification approach.

3.2.2. Aim 2 Comparative Safety of Protocols

I compared a set of commonly used IV iron dosing protocols with respect to the risks of all-cause mortality and infection-related hospitalization and mortality using inverse probability of censoring weighted estimation of MSMs.[172,173]

Study population

The study population included incident HD patients who initiated one of the commonly used IV iron dosing protocols for anemia management between January 1, 2009 and September 16, 2012. This cohort was a subset of the cohort in Aim 1 by restricting to patients who initiated the commonly used dosing protocols between 2009 and 2012.

Exposure

The exposure of interest was commonly used IV iron dosing protocols identified in Aim 1. One of the most frequently initiated protocols was used as the reference protocol. Assessment of index dosing protocols were carried out in the first two weeks following the index TSAT. Although brief, the two-week window was representative of treatment experience in the interval.

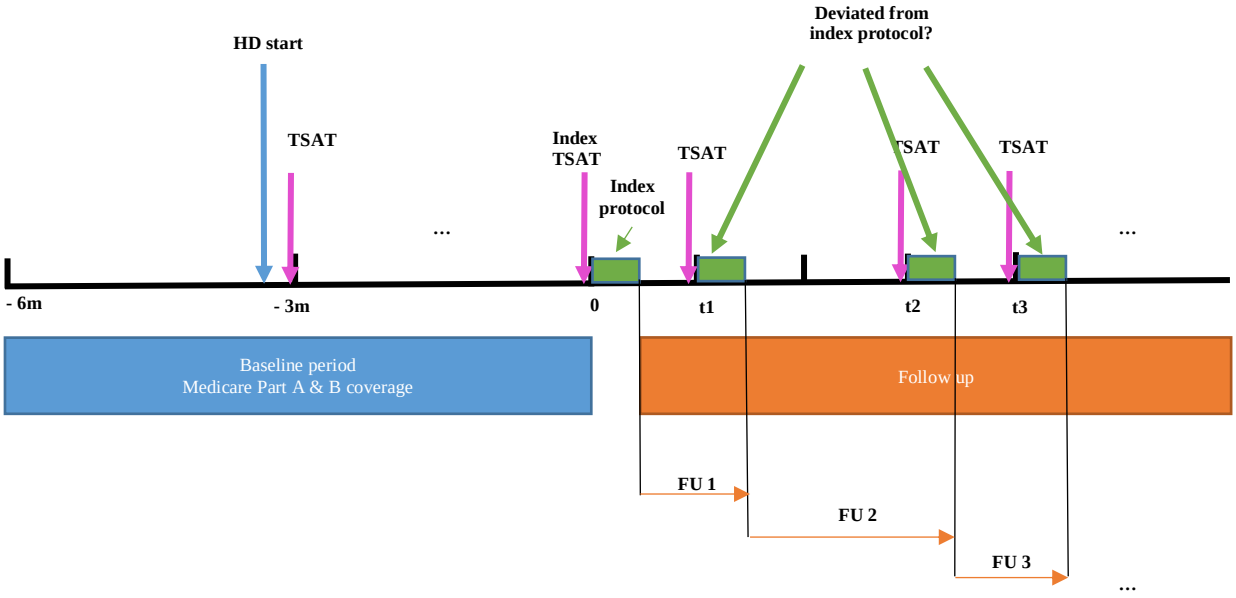

Figure 3.5. Schematic of study design for aim 2

Deviation

During follow-up, the observation of an individual was discretized into intervals anchored by TSAT measurements. The two-week window following each TSAT lab was used to classify what dosing protocol this individual was following. An individual was classified as deviating from the index dosing protocol if the dosing protocol within the current interval was different from the index protocol. The date of deviation was the end of the two-week exposure window when the individual first deviated from the index protocol. Patients who deviated from their index protocols were artificially censored. Potential selection bias introduced by this informative censoring was adjusted for by inverse-probability weighting as described below.

Outcome

The outcomes were all-cause mortality and the composite outcome of infection-related hospitalization or mortality. Table 3.6 lists the detailed definitions for outcomes.

Methods

Descriptive analyses described the characteristics of the subjects and their baseline comorbidities using percentages or medians and quartiles as appropriate.

Survival time was measured from the IV iron dosing protocol initiation to outcome event of interest. Patients were administratively censored at December 31, 2012, or occurrence of one of the following: event of interest, 120 days since index date, receipt of kidney transplantation, the time of switching dialysis modality, loss to follow-up, disenrollment from this dialysis provider or loss of Medicare coverage. Patients who deviated from the index dosing protocols during follow-up were artificially censored. Deviation from initial dosing protocol was assessed to identify important predictors for treatment deviation. Survival plots for compliance of index dosing protocols were created using Kaplan-Meier survival curves.[191]

I estimated the cumulative risk of each outcome of interest using the complement of the Kaplan-Meier survival function[191] for each dosing protocol and calculate cumulative incidence differences between each dosing protocol and the reference protocol during the follow-up period. One of the most frequently used dosing protocols was used as the reference protocol. The 95% confidence intervals for the cumulative incidence differences were estimated using a non-parametric bootstrap procedure. I performed four different analyses.

1) Crude intention-to-treat effect of treatment

This approach summarized the effect of initiating one dosing protocol versus the reference protocol on each outcome of interest. Protocol deviation in the follow up was ignored. No adjustment was done to control for baseline confounding.

2) Crude effect of continuous compliance not adjusted for informative censoring

Individual observation during follow-up was discretized into intervals anchored by TSAT laboratory tests. Patients who deviated from the index protocol were artificially censored. Once censored for deviation, patients could not reenter the study population. No adjustment was done for potential selection bias arising from such censoring or for baseline confounding control.

3) Effect of continuous compliance not adjusted for informative censoring

With the same setup as the second analysis, patients who deviated from their index protocol were artificially censored. I compared the effect of initiating and continuing each treatment protocol versus the reference group on each outcome of interests. Standardized mortality ratio weights (SW_i^T) were estimated at the index date to adjust for baseline confounding by weighting initiators of each comparator protocol using the reference protocol initiator group as the standard.[192,193] Weights were estimated using a logistic regression model that included baseline risk factors for outcome event of interest which also predicted protocol initiation. I used basic splines to flexibly model continuous variables. Potential selection bias introduced by artificial censoring due to protocol non-adherence was ignored.

4) Effect of continuous compliance adjusted for informative censoring

This approach used the same data structure in Analysis 3) described above. This analysis estimated the effect of continuing each dosing protocol versus the reference protocol on each outcome of interest adjusting for informative censoring due to protocol non-adherence using a product of standardized mortality ratio weights (SW_i^T)[192,193] for baseline confounding control and inverse probability of censoring weights for deviation (SW_{ij}^D) for selection bias.[173,177,179]

We fitted censoring model to each protocol group separately to allow for different mechanisms that might have contributed to each 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. These covariates included baseline covariates and the most recent time-varying covariates in the interval prior to the 14-day assessment window in which deviation was thought to have occurred. 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 incidence of adverse outcomes in initiators of each dosing protocol separately. We then estimated the cumulative incidence differences between each protocol and the reference protocol during the follow-up period. The 95% confidence intervals (CI) for cumulative incidence differences were estimated using a non-parametric bootstrap procedure with 200 repetitions. We conducted sensitivity analyses by using different covariates for censoring weighting estimation.

Assuming no unmeasured covariates that contributed to deviation from the index protocols and also to the outcomes of interest, this weighting approach adjusted for the time-varying selection bias due to artificial censoring. This approach estimated the effect of continued compliance with initiated dosing protocols on the outcomes of interest.

During the index assessment window, a patient's treatment experience might be consistent with multiple administration strategies. I created k copies of the same patient for k strategies she was consistent with initially. 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 strategy were artificially censored at the end of 14-day assessment window. The remaining patients were weighted by the probability that they stayed on the index strategy 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 reweighted to account for possible dependent censoring related to these additional events.

Strengths

- Most previous observational studies on IV iron evaluated cumulative iron doses over a period of time, which could classify two different dosing protocols, one with smaller doses and more frequent treatments and another with larger doses and infrequent treatments, into the same category based solely on the aggregated dose. This made it difficult to understand the safety of IV iron use in HD patients without differentiating the effectiveness and safety of different IV iron dosing strategies. To my knowledge, this thesis is the first to compare different dosing protocols and examine their safety profile of longer-term effects, providing evidence to help identify optimal treatment protocols for anemia management in HD patients.
- The weighted survival curves provide an easy presentation of the outcome risks over the entire follow-up period and estimation of cumulative incidence risks that are clinically relevant and interpretable.

Challenges

- As the study population were patients on HD from a single dialysis managing company, results from this study may not be completely generalizable to patients who receive HD from other dialysis providers. However, this company is one of the largest dialysis providers in the US and provides services to approximately one third of all Americans with ESRD receiving dialysis. Selected from their large clinical database with few exclusion criteria, the study population had characteristics similar to a general ESRD patients receiving dialysis in the US.

- There is potential for unknown confounders not included in the model for protocol initiation or model for protocol non-adherence and hence the effect estimates are subject to residual confounding and selection bias. However, the clinical research database and the USRDS database contain rich, frequently measured clinical, laboratory, treatment, and demographic variables that reduce the chance of strong residual confounding. Additional investigation is needed to explore the extent of residual confounding.
- It is possible but unlikely that patients excluded from the study had a different distribution of factors associated with deviation compared to patients included in the study, so the amount of selection bias was small.
- The outcomes based on claims-based algorithms are subject to some measurement error. However, the potential for measurement error of mortality outcome was low as the ESRD Death Notification form identifies more than 99% of HD patient deaths.[188]

3.3. Human Subjects

This research project used de-identified data from existing databases and involved no direct contact with the patients in this study or access to personal identifying information, incurring no direct physical or psychological risks to these patients. The full database as well as all interim and analytic datasets were stored on a secure Pharmacoepidemiology server located at the Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, North Carolina. Access to the data on the server was via password-protected secure remote connections and was limited to project personnel. Copies of the data were not made or transmitted outside of these guidelines. This study was approved by the Non-Biomedical Institutional Review Board (IRB) at University of North Carolina at Chapel Hill.

CHAPTER 4: IDENTIFICATION OF DYNAMIC TREATMENT REGIMES IN COMPLEX LONGITUDINAL DATA[1]

4.1. Introduction

Clinical management of patients with chronic disease frequently involves sequences of treatment decisions regarding treatment, dose adjustments, testing, and use of add-on therapies. For example, almost all end-stage renal disease (ESRD) patients maintained on chronic hemodialysis receive intravenous (IV) iron therapy to help manage anemia by correcting iron deficiency. Patients receiving IV iron for anemia management have laboratory tests evaluated on a regular basis. The levels of hemoglobin and iron status parameters—transferrin saturation (TSAT) and ferritin—inform the dosage level and frequency of IV iron administration for the next treatment course.[13,15,109] Treatment strategies involving decision rules to make treatment recommendations based on evolving clinical history are termed "dynamic treatment regimes".[163] Other examples of dynamic treatment regimes include treatment of HIV/AIDs,[164-166] management of type 2 diabetes,[167] and cholesterol control.[168] Increasingly clinical guidelines present recommendations in this dynamic format.[164-168]

Dynamic treatment regimes can be evaluated directly in randomized controlled trials in which patients are randomized to one of a set of different regimes that specify how treatments and tests are to be used given a patient's evolving clinical history. Additionally, designs such as sequential, multiple assignment, randomized trial (SMART) allow construction and comparison of dynamic treatment regimes to identify the optimal regime.[195,196] However, in the settings of

[1] This section was submitted to *Epidemiology*.

multiple candidate regimes with differing therapy options and management goals, trials would likely be prohibitively expensive and impractical. Consequently, in practice, trials of dynamic treatment regimes tend to compare a few limited options. For example, currently completed trials for IV iron in hemodialysis patients have only evaluated static regimes such as "125 mg ferric gluconate with eight consecutive dialysis sessions".[6] Static regimes, in contrast to dynamic regimes, specify a fixed treatment strategy at the start of treatment and stay unchanged during the course of treatment, making them suboptimal for patients with changing response to treatment and evolving clinical needs. Consequently, despite the completion of several randomized trials, there still remains considerable uncertainty in the best practice for IV iron administration for anemia management in hemodialysis patients.[11,22,23,25,197] As anemia affects almost all hemodialysis patients with ESRD, comparative effectiveness research of different iron administration strategies is needed to identify the optimal treatment approaches to iron treatment.

Currently, epidemiologic and statistical methods exist that can be used to estimate the effect of dynamic treatment regimes using observational data.[173-185,198]. However, these methods require accurate assessment of the treatment decisions being made by the physician as well as the clinical and laboratory variables that guide such treatment decisions. Increasingly available large healthcare databases containing rich, granular patient-level information may make such approaches more feasible. For example, for ESRD patients on chronic hemodialysis, linked clinical and administrative research databases exist that contain detailed longitudinal information on patients, including medication treatment, routine laboratory tests, and healthcare encounters. These data arguably provide all relevant information needed to assess the effectiveness of different IV iron administration strategies in hemodialysis patients. Yet even with suitable data, one can only estimate the effectiveness of treatments and treatment regimes that actually occur in

practice. In other words, if certain sequences of treatment decisions are never made, the data will not be informative about the effects of protocols that would dictate such treatment decisions.

In this study, we aimed to develop a process to identify treatment regimes that could be evaluated given a particular data source. We considered regimes that prescribe a range of treatment values based on multiple time-varying covariates by using IV iron administration strategies for anemia management in hemodialysis patients as an example.

4.2. Methods

Data source, study design, and study population

We constructed our study cohort using data derived from the clinical research database of a large dialysis provider in the United States, linked with the United States Renal Data System (USRDS) (2004-2012).[188,199] With over 2,042 dialysis centers located throughout the country, this company provides services to approximately one third of all Americans with ESRD receiving dialysis.[186] We obtained detailed clinical information regarding patients' dialysis treatments, vascular access, routine laboratory tests, IV medications, and anemia management using the clinical research database. We obtained patient information regarding their demographic characteristics, comorbidities, and healthcare system encounters from the USRDS. The study was approved by the University of North Carolina at Chapel Hill Institutional Review Board, Chapel Hill, NC, USA.

We used a 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 choice of anchoring on a TSAT measurement was because evaluation of IV iron administration strategy typically occurs following the availability of iron status tests (TSAT and

ferritin) in clinical practice. Results of iron status tests are typically interpreted together with hemoglobin levels and ESA doses to guide iron therapy including the dose and duration.[13,15,109] We defined the TSAT measurement on the index date as the index TSAT. We assessed the levels of ferritin and hemoglobin on the same day. If ferritin and hemoglobin values were not available on the index date, values were obtained from their previous measurements in the baseline period. The baseline period was defined as the period starting 90 days prior to dialysis initiation and ending on the day before the index date. We defined the interval between index TSAT and its subsequent TSAT measurement as the index interval, where the strategy that guided IV iron administration was the focus of this article (Figure 4.6).

Our study population comprised outpatient hemodialysis patients who initiated in-center hemodialysis between 1 January, 2004 and 16 September, 2012. Patients included were aged 65 and older and who had Medicare as their primary insurer, continued hemodialysis for at least 90 days, and had complete information on baseline covariates and IV iron exposure. To ensure patients were receiving regular in-center hemodialysis and anemia management, we excluded patients who had fewer than nine dialysis sessions in the last month of baseline period or no TSAT measurement during the 120 days following dialysis initiation. We also excluded patients if they had polycystic kidney disease because their management strategies of IV iron could differ (see Appendix A).

Strategy identification process

The identification was an iterative process that consists of four major steps: 1. Development of candidate administration strategies; 2. Determination of assessment window; 3. Identification of administration strategies; 4. Fine-tuning of identification process.

We defined an administration strategy as a dosing protocol or dosing strategy that a clinician uses to make treatment decisions. A strategy consisted of a set of decision rules with laboratory test values and corresponding dosage patterns. In this IV iron example, dosage patterns referred to the iron therapy patients received, including the dosage level for each session and therapy frequency in a period of treatment.

Step 1- Development of candidate administration strategies

We considered IV iron administration strategies that specified a range of acceptable iron therapy values during an interval given a subject's current time-varying laboratory test values for anemia management parameters. For example, this example administration strategy (see Appendix B) set a target range of ≤50% for TSAT, ≤1200 ng/mL for ferritin, and 13.0 g/dL for hemoglobin. The strategy recommended bolus dosing (100 mg of iron sucrose for 10 consecutive dialysis sessions) if TSAT fell below 20% and ferritin was below 200 ng/mL. The strategy recommended maintenance dosing (50 mg of iron sucrose weekly) if TSAT was between 20-50% and ferritin was between 200-800 ng/mL. If any of the parameters were to be above the target range or if the patient was receiving IV antibiotics, the strategy recommended iron be withheld.

We developed administration strategies from existing dosing protocols in routine clinical use and modified them through consultations with experts. Two sets of administration strategies were considered, one set with hemoglobin as a deciding factor, and another set without hemoglobin restriction. Definitions of the strategies are listed in Appendix C. The strategies varied in terms of cut-off laboratory test levels and corresponding iron dosage pattern choices. The strategy definitions were updated by incorporating the choice of assessment window and the distribution of dosage levels in the data in Step 2. We examined the influence of three laboratory

tests on the decision for iron therapy by assessing the distribution of a particular laboratory test across different iron dosage patterns. The results presented in this article focused on the set of administration strategies with influential laboratory tests.

Step 2- Determination of assessment window

We developed a data visualization tool using ggplot2 package in the R statistical package to examine patient-level data, including laboratory test values, clinical data, treatment information, and healthcare system encounters.[200] The visualization tool depicted the patient journey with treatment and her clinical condition evolution across time using two panels (Appendix D). The top panel illustrated the changes in anemia management parameters, while the bottom panel presents the IV iron dosage level received at each dialysis session, occurrence of hospitalization, skilled nursing facility stay, hospice use, and IV antibiotic use (a marker for active infection).

To inform the length of assessment window and classification of iron dosage patterns, we examined the patient journey of a random sample of eligible patients in the cohort using this data visualization tool. The length of assessment window was chosen so that it maximized the representativeness of treatment experience in the window for the treatment experience in the interval while minimizing the days required for the assessment window to maximize follow-up time for subsequent studies evaluating effect of strategies on health outcomes. The dosage patterns in the assessment window were classified into groups by prorating iron dosage levels for different dosage patterns specified in the candidate strategies over the chosen assessment window. These dosage patterns were then incorporated into the candidate administration strategies.

Step 3- Identification of administration strategies

We identified IV iron administration strategies that were consistent with treatment patterns in the assessment window for index interval. For each patient, we compared three laboratory test levels (TSAT, ferritin, and hemoglobin) on the index date together with the dosage pattern in the assessment window with the candidate administration strategies to identify consistent strategies. The consistent strategies were then assigned as the index administration strategy for that patient. Because considered strategies contained overlapping target ranges for anemia management parameters and same treatment patterns for some ranges of laboratory value, multiple strategies could be consistent with a patient's treatment history and be assigned for that patient.

Step 4- Fine-tuning the identification process

Strategy identification drew information from a patient's treatment history in the assessment window. Insufficient information could have been resulted from hospitalization, use of IV antibiotics during active infection, or use of blood transfusion during the strategy assessment window. For patients with insufficient information in the assessment window, all candidate administration strategies were assigned to their index intervals.

Evaluation of strategy initiation

We examined the distribution of initiated administration strategies in the study period 2004-2012. Important predictors for strategy initiation were identified by assessing their standardized mean differences between patients who initiated a strategy and those who initiated other strategies. Potential predictors included patient demographic characteristics, clinical characteristics, and comorbidities. We also examined the trend of initiation across calendar year

and region of residence. All analyses were performed in R, version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) or SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

For dosage patterns that could not be matched with the candidate strategies, we detected interaction using classification and regression trees (CART).[201] The objective was to identify baseline predictors for the use of different dosage patterns in the assessment window and summarize these unique practice patterns. Potential predictors included measures of demographics (race/ethnicity, age, gender), infection, transfusion, days in the hospital, type of access, iron status tests, and hemoglobin). Trees were built by recursive portioning, and cross-validation was used to prune the tree. The importance of factors for initiation of these unique practice patterns was evaluated using random forest.[202]

4.3. Results

Identification process

We focused on administration strategies initiated in the index interval defined by the first two consecutive TSAT laboratory tests after the baseline period. As informed by explorative analysis with the data visualization tool (Appendix D), treatment patterns in the two-week window following the index TSAT measurement was representative of the treatment experience in the interval. We used the two-week window starting from the index date as assessment window for identification of IV iron administration strategies in the index interval.

Between 2004 and 2012, 43,166 patients met the eligibility criteria for study entry and were included in the cohort (Appendix A). Table 4.8 presents their baseline demographic and clinical characteristics. Overall, about half of the cohort were female, and a quarter of them were black. The mean age was 75.8 years. The length of index interval has a median of 28 days

(interquartile range [IQR]: 28-35 days), with 995 (2.3%) shorter than 14 days and 429 (1.0%) longer than 120 days.

The IV iron dosage pattern in the two-week assessment window was categorized into five levels: bolus dosing (> 500 mg), half bolus dosing (201-500 mg), maintenance dosing (101-200 mg), low maintenance dosing (1-100 mg), and none (0 mg) (Appendix E). More than half of the patients initiated dosage patterns with lower doses or no iron in the index interval. The most frequently initiated pattern was low maintenance dosing (32.9%, median (IQR) of iron dose: 100 (50-100) mg). About 7.5% of patients were treated with bolus dosing (median (IQR): 600 (600-600) mg). The distribution of the iron status tests on the index date, TSAT and ferritin, were different among patients initiated with different dosage patterns (Appendix E and Figure 4.7). The levels of these tests were inversely associated with the dosage pattern initiated. In comparison, the distribution of hemoglobin levels was similar among these dosage patterns, and the proportion of dosage patterns did not change much across hemoglobin levels (results not shown), suggesting that hemoglobin was not playing a huge role in the decision for administration strategies during this study period.

Figure 4.8 shows how dosage pattern initiation was related to levels of TSAT and ferritin simultaneously. For patients with TSAT greater than approximately 50% or ferritin greater than 800 ng/mL, no IV iron was given. For intervals with TSAT levels below 50% and ferritin levels below 800 ng/mL, there was considerable heterogeneity in dosage patterns, suggesting different strategies were guiding treatment decisions and we could exploit this variation to compare effect of various IV iron dosing strategies.

Results of administration strategies

Explorative analyses showed little influence of hemoglobin levels on initiation of dosage patterns, so we focused on the strategies without hemoglobin restrictions in the following sections. Appendix C listed definition of all candidate strategies.

Between 2004 and 2012, 79.1% of 43,166 patients had treatment experience consistent with one or more candidate administration strategies, and 20.9% of them were not matched to considered strategies. Among the eight strategies without hemoglobin restriction, the three most frequently initiated were strategy 2 (54.8%), strategy 3 (52.3%), and strategy 1 (52.2%) (Table 4.9); the least frequently initiated strategy was strategy 5 (34.2%).

Year and regional trend of protocol initiation

Figure 4.9 shows the trend of strategy initiation persisted across calendar years, with the first three strategies more frequently initiated. However, the proportion of patients initiating these three strategies increased sharply in 2011 and 2012, whereas the proportion of patients initiating other strategies stayed constant. Consequently, the prevalence of treatment patterns that could not be matched dropped dramatically from 25.0% in 2004 to 11.6% in 2011 and to 9.3% in 2012. There was not much variation in the initiation of strategies across regions (Appendix F).

Characteristics of patients initiating different protocols

Baseline characteristics of patients initiating candidate strategies were similar, suggesting little confounding by indication at baseline (Figure 4.10). The distribution of initiation throughout calendar year was different for strategy 1, strategy 2, and treatment patterns not matched. Compared to patients who were matched with candidate strategies, patients who could not be matched had different laboratory test values (lower TSAT and ferritin levels and higher hemoglobin level) and prevalence of comorbidities, specifically lower infection risks in the last

month of the baseline period. They also spent fewer days in the hospital and received fewer transfusions in the baseline period.

Characteristics of treatment patterns that could not be matched

These practices were collapsed into 10 different exception rules (Figure 4.11). The important factors that predicted which pattern to initiate were TSAT, ferritin, total Epoetin received, post-dialysis weight in the last two weeks, creatinine, pre-treatment systolic blood pressure in the last two weeks, hemoglobin, age, and albumin level.

4.4. Discussion

We developed an identification process for dynamic treatment regimes in complex longitudinal, observational data when it is not known what regimes may be in use in a given population. We aimed to systematically construct cohorts of patients initiating treatment strategies under consideration for comparative effectiveness research studies. This identification approach matches treatment pattern and current laboratory test values with candidate strategies by consistency; whereas candidate strategies are constructed using expert's knowledge and examination of patient-level data using visualization techniques. This approach allows pragmatic classification of dynamic treatment regimes for causal inference using rich observational data.

We applied this identification process in an empirical example of IV iron administration strategies for anemia management in ESRD patients undergoing chronic hemodialysis. Between 2004 and 2012, 79% of patients were matched with one or more strategies under consideration. The prevalence of match increased sharply starting in 2010 to 91% in 2012. The increasing trend of matches across calendar years was consistent with the fact that the installation of administration strategies occurred in recent years in dialysis clinics.[20,21,180] The baseline characteristics of patients initiating different strategies were very similar, indicating little

confounding by indication at baseline, which improves our ability to compare these strategies with respect to their effects on outcomes.

The identification process fits well with the need for estimation of the effect of dynamic treatment regimes in non-experimental settings. Time-varying confounding is a pertinent problem in evaluating complex medical decisions that change with patients' evolving clinical needs, but has not been sufficiently investigated. Cumulative exposures are often examined in the literature using marginal structure models. However, our data visualization tool revealed that aggregated cumulative exposures over a long period could mask the substantial heterogeneity among patients' experience. Moreover, studies of cumulative exposures do not align with decisions made by clinicians. For example, clinicians treating dialysis patients do not make decision about how much cumulative iron to provide a patient over an extended time period, although contemporary dosing schedules have an upper limit of cumulative dose over 3 or 6 months. Instead, they want to know when to provide a course of iron and how to provide it. Comparative effectiveness research of dynamic treatment regimes is clearly needed in many contexts.

Without the information on the exact regime a patient was treated under, there was no direct way to evaluate the performance of this identification process. However, positive controls such as knowingly implemented strategies in routine clinical care could help gauge the performance of classification. In this empirical example, we considered three strategies that were adapted from known pre-existing dosing protocols. These strategies were more highly initiated and adhered to relative to the other strategies, and the trend of the rapid uptake in recent years was also consistent with their installation in clinical practice around 2010, confirming the performance of the identification approach.

This identification approach could assign multiple strategies to a single patient at a point of time, if the strategies under consideration are not entirely distinct, which is common in practice. When two strategies prescribe same treatment in certain ranges of laboratory test values, the treatment experience of a patient receiving that treatment would be consistent with both strategies. Well-developed statistical methods exist to help us make valid inference on the effect of these regimes on outcome of interest.[173,176-180]

This identification process can be easily adapted for other dynamic treatment regimes, but adaptation needs to be evaluated on a study-by-study basis. It can also be extended for more complex strategies. In addition to hemoglobin, iron status tests, and infection status, some guidelines recommended incorporation of erythropoiesis-stimulating agent (ESA) doses and trend of iron status tests.[13-15,109] Although we did not consider ESA doses and the trend of iron status because the knowingly implemented strategies did not consider these factors, the role of these additional factors on IV iron administration could be explored in future studies.

Data visualization was a helpful tool that provided insight into the data structure and informed strategy identification. Extensive examination of patient-level data with complex data visualization revealed that aggregated cumulative iron exposure over a long time period would mask heterogeneity across patients. Patients with same total or average iron doses over a fixed time period could have different treatment and clinical experience with respect to iron treatment frequency, treatment intensity, and healthcare encounters. The data visualization tool helped determine the assessment window for strategy identification. It also illustrated that a longitudinal treatment decision design with intervals anchored by the TSAT laboratory tests had advantages over the fixed-length interval design for this current study (results not shown). Using this tool, it is easy to view the whole patient journal across time in a fast manner, including outcomes of

interest. However, caution needs to be exercised to not condition the study or cohort construction on the outcome status when using this tool.

4.5. Conclusion

With the increasing availability of detailed healthcare data and sophistication of methods, we have a great opportunity to improve the clinical management of complex patient care using existing data. We illustrated the use of an approach to identify dynamic treatment regimes that could be evaluated in a large observational database. Furthermore, we demonstrated the use of data visualization that provided insights into the complexity of data structure and helped us identify appropriate exposure assessment, study design, and analytical approaches for study questions of interest.

Table 4.8. Baseline characteristics for eligible patients included in the cohort, 2004-2012

		Overall (N = 43,166)	
		N	%
Age, year			
Mean (SD)		75.8 (6.8)	
Median (IQR)		75 (70-81)	
65-74		19,959	46.2
75-84		18,150	42.0
85-94		4,951	11.5
95-		106	0.2
Sex of patient			
Male		22,249	51.5
Female		20,914	48.5
Unknown		<11	0.0
Race			
White		31,080	72.0
Black		10,109	23.4
Other		1,977	4.6
Region			
Midwest		9,510	22.0
Northeast		6,380	14.8
South		19,035	44.1
West		8,234	19.1
Others		<11	0.0
Primary cause of ESRD			
Diabetes		19,447	45.1
Glomerulonephritis		2,267	5.3
Hypertension		15,756	36.5
Other reason		5,633	13.0
Missing		63	0.1
Year of protocol start			
	2004	3,724	8.6
	2005	5,287	12.2
	2006	5,118	11.9
	2007	5,182	12.0
	2008	5,053	11.7
	2009	5,397	12.5
	2010	5,290	12.3
	2011	4,191	9.7
	2012	3,924	9.1
Time on dialysis			
	0	43,166	100

Comorbidities		
Vascular access infection, baseline last month	534	1.2
Pneumonia, baseline last month	868	2.0
Sepsis, baseline last month	846	2.0
Infection, ADR definition, baseline last month	1,238	2.9
Antibiotic use, baseline last month	6,716	15.5
IV antibiotics in clinic, baseline last month	4,600	10.6
Infection (broad definition) baseline last month	8,910	20.6
Diabetes	29,203	67.5
Hypertensive disease	41,738	96.5
Congestive heart failure	27,528	63.7
Myocardial infarction, acute	4,297	9.9
Angina	3,726	8.6
Coronary artery disease/atherosclerosis	24,601	56.9
Ischemic stroke	3,429	7.9
Intracerebral hemorrhage	120	0.3
Subarachnoid hemorrhage	46	0.1
Hemorrhagic stroke	287	0.7
Cerebrovascular disease	9,164	21.2
Chronic obstructive pulmonary disease & asthma	14,134	32.7
Hyperlipidemia	23,359	54.0
Cancer	8,601	19.9
Liver disease	1,661	3.8
Gastrointestinal bleeding & ulcer	1,206	2.8
Peripheral vascular disease	11,483	26.6
Rheumatic heart disease	2,871	6.6
Psychiatric disorder	2,233	5.2
Substance abuse	2,386	5.5
Autoimmune disorder	1,755	4.1
Blood loss anemia	2,481	5.7
Other neurological disorders	4,645	10.7
Hyperparathyroidism	1,678	3.9
Chronic heart disease procedures	2,519	5.8
Blood transfusion	14,163	32.7
Rheumatoid arthritis/collagen vascular disease	1,130	2.6
Neuropathy	8,335	19.3
Osteoarthritis	7,522	17.4
Osteoporosis	1,555	3.6
History of fall	1,603	3.7
Anemia Management in last month of baseline period		
Access		
Catheter	27,410	63.5

Fistula	10,033		23.2
Graft	5,331		12.4
Missing	392		0.9
Pre-treatment SBP, mmHg	143.0 (129.0-158.5)	144.2 (22.2)	
Post-treatment weight, kg	71.8 (61.0-84.2)	73.9 (18.2)	
Hospital days	0 (0-0)	0.6 (1.9)	
Anemia Management at last month of baseline period[a]			
Total EPO dose, 1000 units/month	60.5 (24.2-118.8)	85.1 (84.2)	
Total iron dose, mg	200 (75-500)	337 (357)	
TSAT, %	22 (17-29)	24.4 (11.9)	
Ferritin, ng/mL	292 (155-520)	398.5 (402.4)	
Hemoglobin, g/dL	12.1 (11.1-13.2)	12.1 (1.6)	
Albumin, g/dL	3.6 (3.3-3.9)	3.6 (0.5)	
Creatinine, mg/dL	5.0 (3.8-6.4)	5.2 (2.0)	
Anemia Management on index date[b]			
TSAT, %	25 (18-33)	27.5 (13.6)	
Ferritin, ng/mL	341 (184-582)	440.2 (405.4)	
Hemoglobin, g/dL	12.3 (11.3-13.3)	12.3 (1.5)	
Albumin, g/dL	3.7 (3.4-3.9)	3.6 (0.4)	
Creatinine, mg/dL	5.20 (3.92-6.61)	5.4 (2.1)	

SD=Standard deviation; IQR=interquartile range; ESRD=end stage renal disease; ADR=annual data report; TSAT=transferrin saturation; EPO=Epoetin

[a]If laboratory tests in the last month of baseline were missing, the previous test values were used;
[b]If a laboratory test was missing on index date, the last non-missing test values were used.
For all continuous variables, the first column is median (IQR), and the second column is mean (SD).

Table 4.9. Identified IV iron administration strategies in 2004-2012

Number	Number of consistent strategies		Strategy	Prevalence of initiation	
	N	%[a]		N	%[b]
0	9,023	20.9	strategy 1	22,532	52.2
1	5,188	12.0	strategy 2	23,663	54.8
2	5,731	13.3	strategy 3	22,570	52.3
3	5,901	13.7	strategy 4	18,100	41.9
4	2,394	5.5	strategy 5	14,782	34.2
5	1,728	4.0	strategy 6	16,146	37.4
6	621	1.4	strategy 7	18,900	43.8
7	1,162	2.7	strategy 8	19,080	44.2
8	11,418	26.5	Other	9,023	20.9

[a]These percentages describe the proportion of 43,166 patients were consistent with a specific number of strategies, so they sum up to 100%.
[b]These percentages describe the proportion of 43,166 patients were consistent with a specific strategy. Because multiple strategies could be consistent to one patient's treatment history, so these percentages do not sum up to 100%.

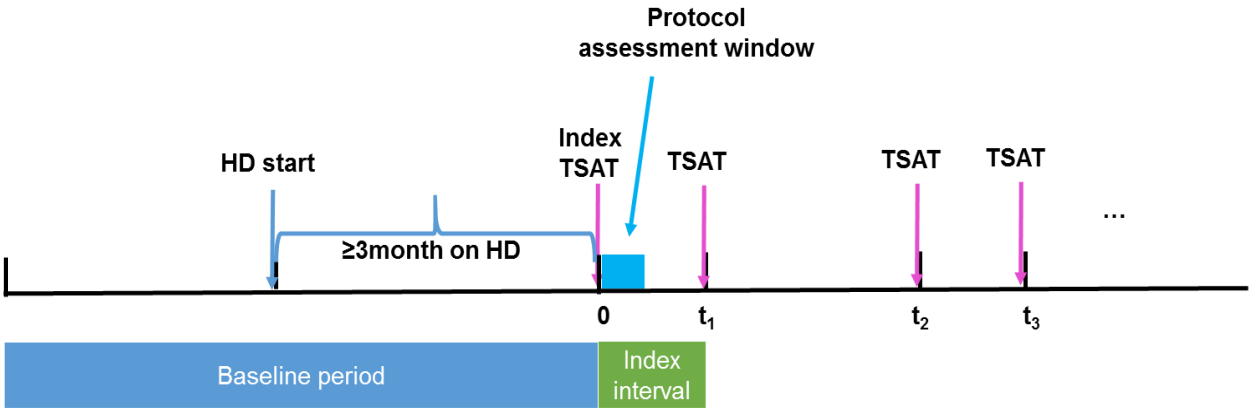

Figure 4.6. The scheme of study design describes the index date and index interval in relation to hemodialysis initiation and iron management parameters
HD=hemodialysis IV=intravenous; TSAT=transferrin saturation.

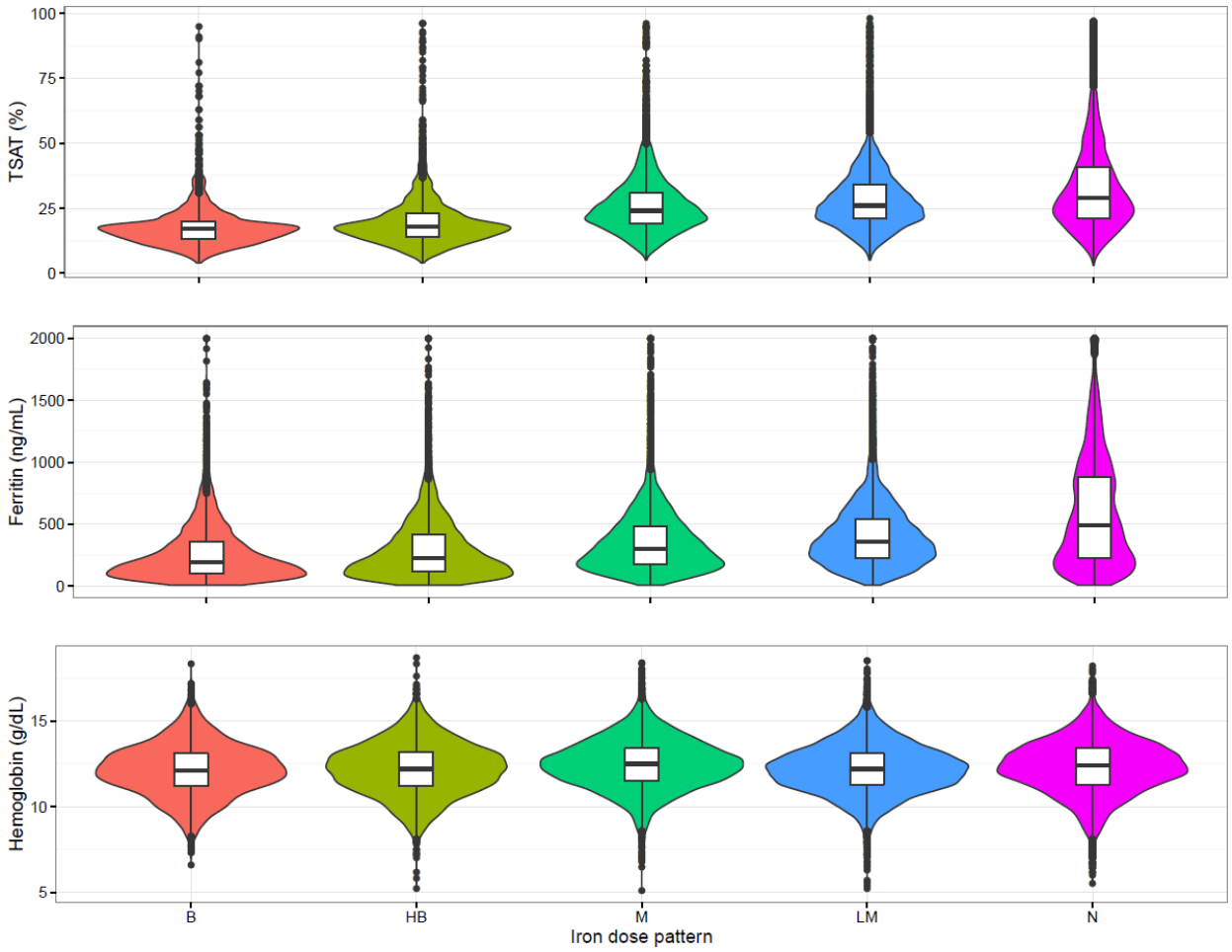

Figure 4.7. Distribution of laboratory tests across dosage patterns in the assessment window B=bolus dosing (> 500 mg); HB=half bolus dosing (201-500 mg); M=maintenance dosing (101-200 mg), LM=low maintenance dosing (1-100 mg); N=none (0 mg).

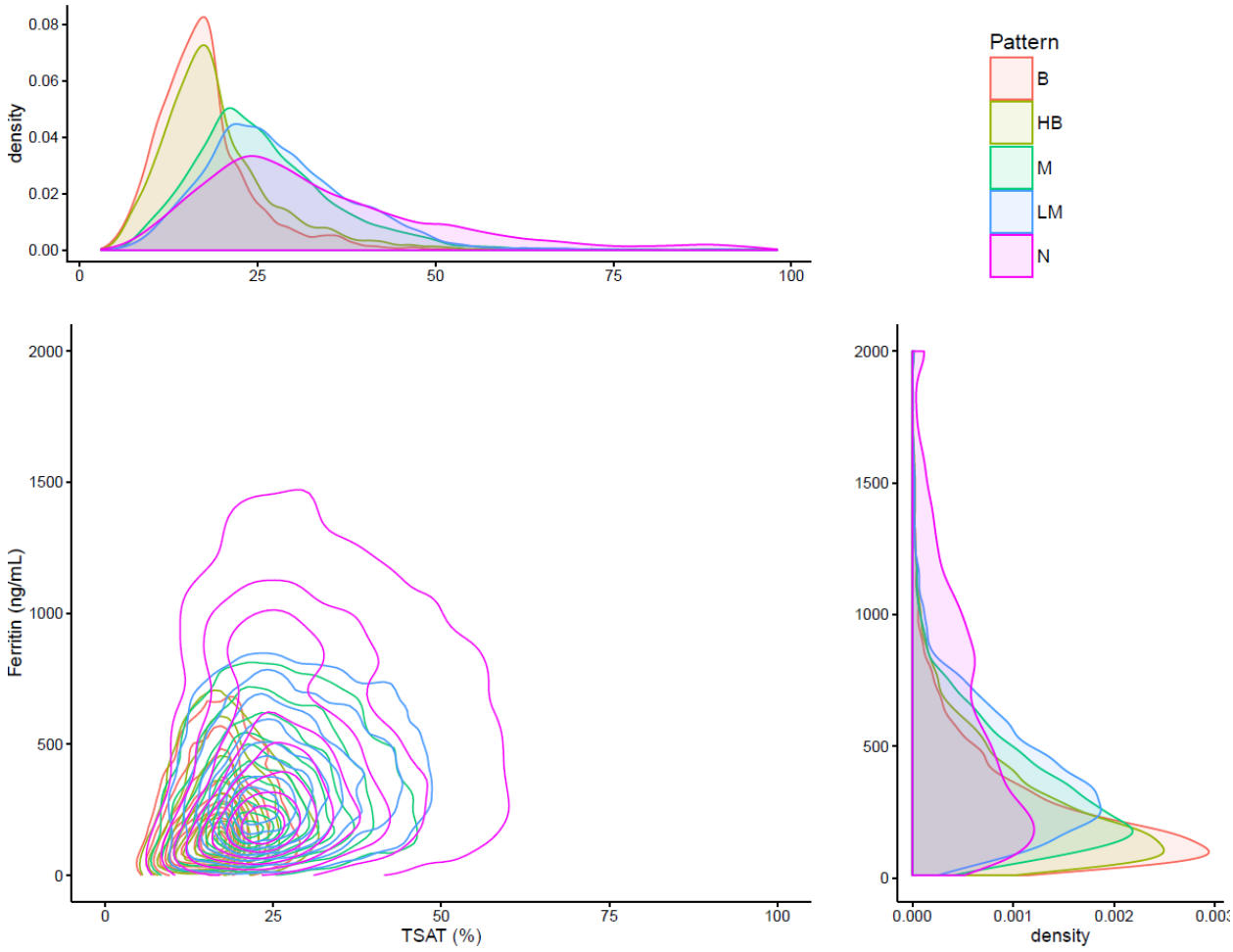

Figure 4.8. The joint density of dosage patterns across levels of TSAT and ferritin
B=bolus dosing (> 500 mg); HB=half bolus dosing (201-500 mg); M=maintenance dosing (101-200 mg), LM=low maintenance dosing (1-100 mg); N=none (0 mg).

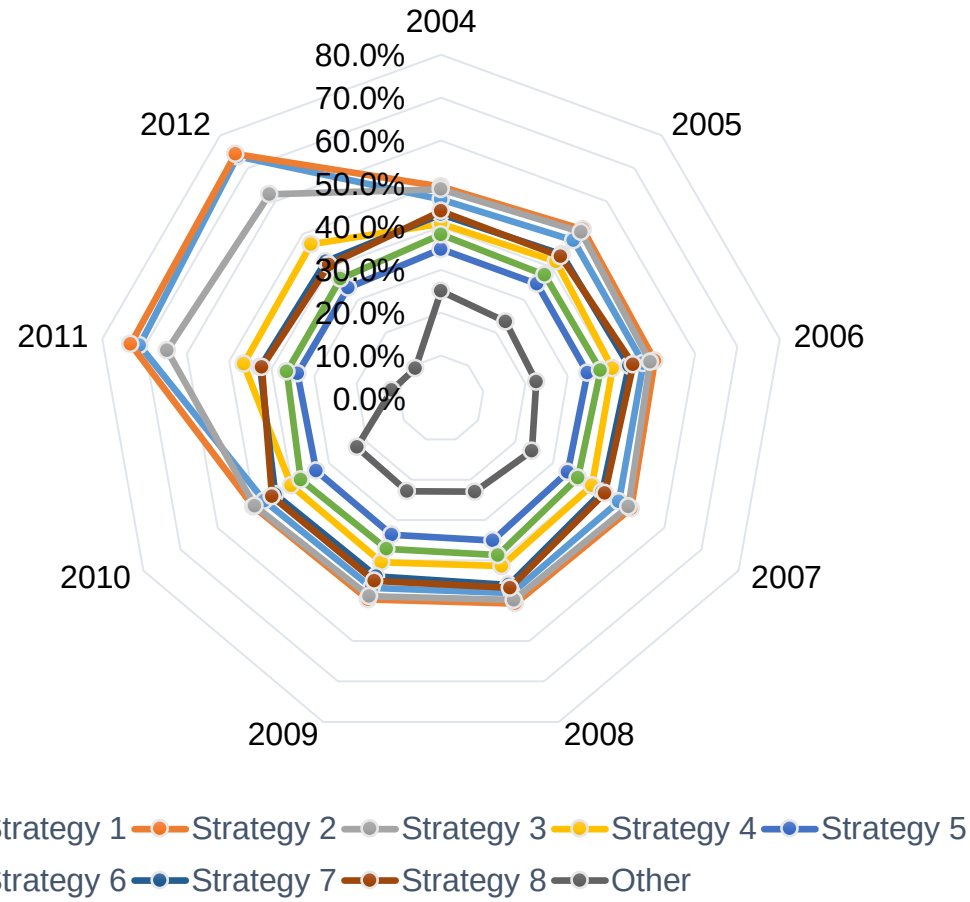

Figure 4.9. Trend of matched IV iron administration strategies across calendar year in the study period 2004-2012

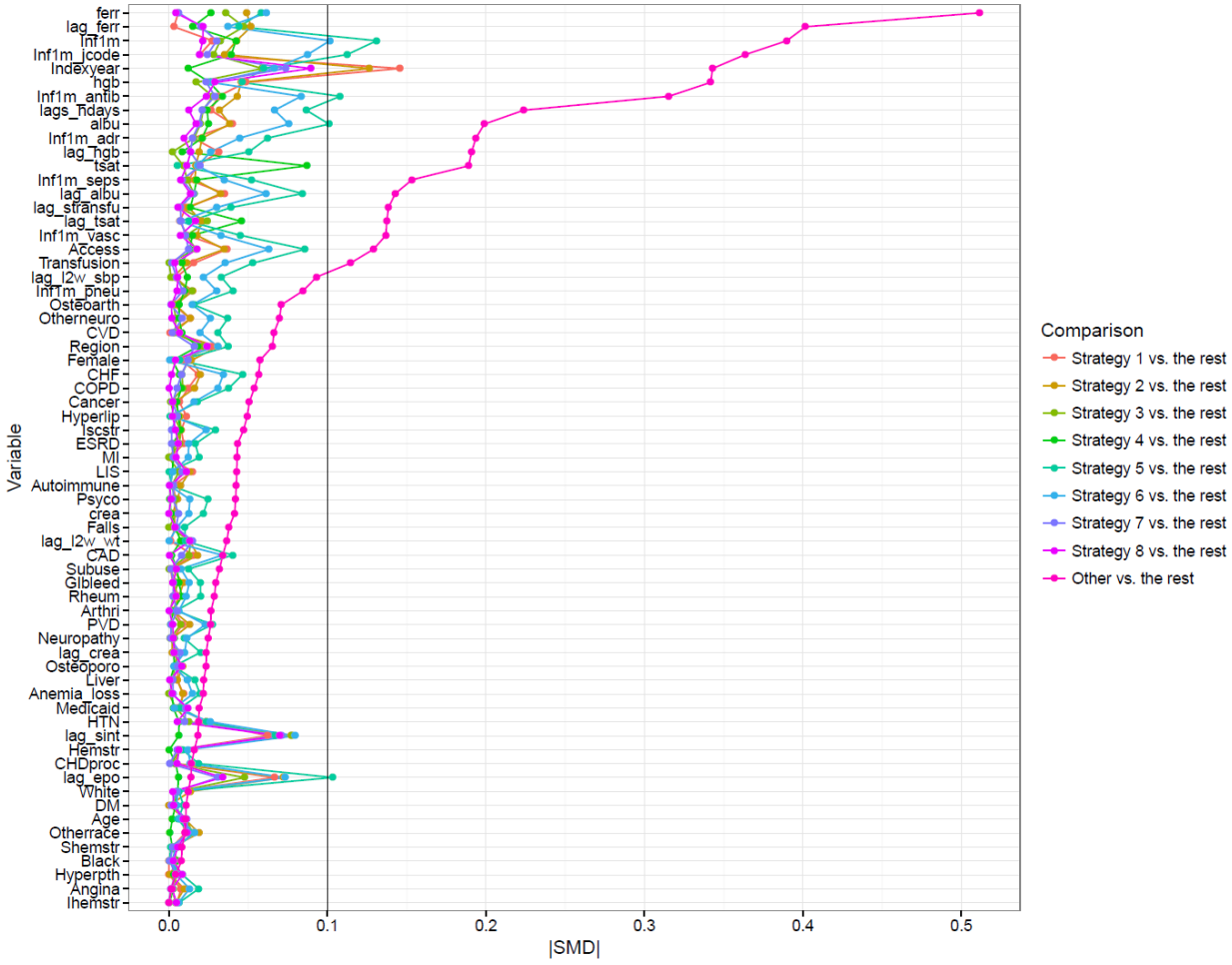

Figure 4.10. Absolute standardized mean difference (SMD) for baseline predictors of initiation comparing patients initiating one strategy versus patients initiating other strategies

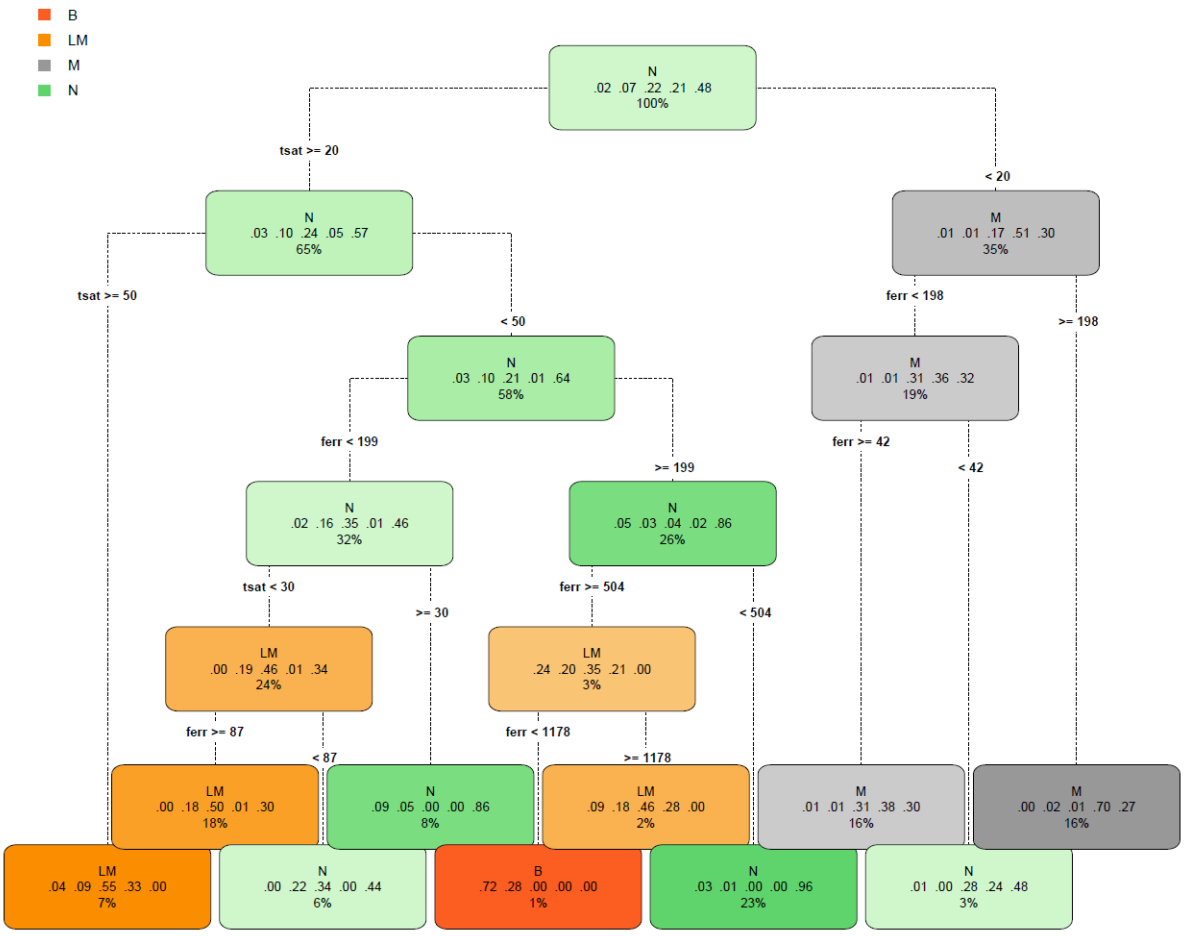

Figure 4.11. Decision tree for dosage patterns among patients who could not be matched with strategies under consideration

B=bolus dosing (> 500 mg); HB=half bolus dosing (201-500 mg); M=maintenance dosing (101-200 mg), LM=low maintenance dosing (1-100 mg); N=none (0 mg).

CHAPTER 5: COMPARATIVE EFFECTIVENESS OF INTRAVENOUS IRON ADMINISTRATION STRATEGIES IN HEMODIALYSIS PATIENTS

5.1. Introduction

Anemia, a common complication of end stage renal disease (ESRD),[1] is associated with elevated morbidity, mortality, and healthcare costs.[2] A primary cause of anemia in ESRD is iron deficiency, particularly among patients requiring hemodialysis. Iron deficiency can be classified into absolute iron deficiency and functional iron deficiency; their causes are multifactorial.[3] Absolute iron deficiency, depleted iron stores, is frequently a result of blood loss, reduced intake, and impaired intestinal absorption of dietary iron.[3] Functional iron deficiency, insufficient iron availability at the site of erythropoiesis despite adequate iron stores, can be caused by chronic inflammation associated with ESRD or elevated hepcidin levels.[3] Overall, hemodialysis patients lose an average of 1-2 g of iron per year, and some as much as 4-5 g per year.[4] Management of iron deficiency to meet the need for erythropoiesis is thus essential for optimal management of anemia in ESRD patients.

In contemporary clinical practice, intravenous (IV) iron is either provided intermittently via large doses over consecutive dialysis sessions (often termed "bolus dosing") or via small doses provided every one to two weeks (often termed "maintenance dosing"). Administration of IV iron is always anchored on regular laboratory tests of iron status parameters - ferritin and transferrin saturation (TSAT).[13-15] Decisions regarding dose, frequency, and duration of IV iron (i.e., maintenance dosing, bolus dosing, or other variation) are specified by protocols adopted by dialysis clinics. Surprising variation exists in dosing protocols used in clinical practice with

respect to IV iron administration.[19-21] For example, one (intense) protocol may specify 100 mg of IV iron administered over 10 consecutive dialysis sessions for TSAT <30% and ferritin <1200 ng/mL while another (conservative) protocol would hold iron for any ferritin >500 ng/mL regardless of TSAT.

Several existing studies consistently demonstrated short-term benefits of bolus iron administration on hemoglobin levels and iron status compared to more conservative maintenance dosing.[6,22] No difference in cardiovascular risks was associated with either dosing approach; [23,24] however, a modestly increased risk of infection was associated with bolus dosing among patients with a history of infection and those with a central venous hemodialysis catheter.[24,25] A recent observational study has reported association between lower mortality risk and maintenance strategy relative to non-maintenance strategies.[26]

Compared to short-term effects, less is known about the long-term safety and effectiveness of different iron protocols. Clinical trials assessing the long-term use of iron administration strategies are lacking; existing large observational studies have focused on the effect of cumulative iron exposure over a long period, which were not large enough to resolve clinically meaningful effects of iron exposure on infection outcomes.[20,27] The cumulative exposures do not align well with the treatment decisions that a physician needs to make regarding iron use in routine care.[28]

Given the growing use of IV iron for anemia management and data suggesting some risk, it is of great interest to examine the long-term effectiveness and safety of different IV iron dosing protocols and to identify optimal treatment strategies for hemodialysis patients that can maximize the known benefits of IV iron, while avoiding its potential risks. In this study, we identified a set of commonly used IV iron administration strategies in a contemporary cohort of

hemodialysis patients. We then compared their effect on risks of mortality and infection-related morbidity and mortality.

5.2. Results

Between 2009 and 2012, 18,697 patients met our study entry criteria (Figure 4.6 & Appendix G). Among them, 15,481 (82.8%) patients were matched with at least one IV iron administration strategy, and 13,249 (70.9%) patients initiated one of the five most commonly used strategies. At strategy initiation, the average age was 76.0 years (standard deviation (SD) 6.9 years). About half of the cohort were female, and 22.7% were African American. The most commonly initiated strategy was strategy 2, and the least commonly initiated strategy was strategy 5. Strategies 4 and 5 recommended more aggressive iron therapy in much broader ranges of TSAT and ferritin levels. For example, strategy 5 recommended bolus dosing patterns (100 mg IV iron sucrose for 10 consecutive dialysis sessions) if TSAT fell below 30% and ferritin was not greater than 1200 ng/mL. The strategy recommended half bolus dosing (100 mg for 5 consecutive dialysis sessions) if TSAT was between 30-40% and 100 mg weekly if TSAT was between 40-50%. The definitions of the administration strategies are listed in Table 5.10.

Table 5.11 presents patients' baseline characteristics stratified by strategy. Baseline characteristics were similar among initiators of strategies 1, 2, and 3. Compared to these patients, initiators of strategies 4 and 5 were more likely to initiate in early years and used a catheter. Recent history of infections and comorbidities were more common in strategy 5 initiators, including congestive heart failure, ischemic stroke, chronic obstruction pulmonic disease, and cancer. Strategy 5 initiators were also more likely to have had a gastrointestinal bleed or received blood transfusion during the baseline period. During the last month of baseline period, the strategy 5 initiators received higher doses of epoetin and IV iron and spent more days in the

hospital. Levels of index TSAT and ferritin tests were also higher among initiators of strategy 5 compared to other patients.

During follow-up, patients deviated from their index administration strategy quickly. The median time to deviation was shortest in the strategy 5 group and longest in the strategy 2 group with 49 days (95% confidence interval (CI): 42, 54 days) and 131 days (95% CI: 126, 147 days), respectively. Between 40-80% of patients deviated from their index strategy by the end of 4 months. Factors that increased probability of deviation included vascular access-related infection in the last month of baseline, use of a catheter, higher albumin level, fewer dialysis sessions, and higher EPO doses in the previous treatment interval. In contrast, having blood transfusions and more days of hospitalization in the previous treatment interval reduced the probability of deviation.

The estimated cumulative incidence differences and their 95% CIs of all-cause mortality among strategy groups in the 4 months of treatment are presented in Figure 5.13 and Table 5.12. Compared with initiators of strategy 1, initiators of strategies 2 and 3 showed reduced but non-statistically significant mortality risks; strategy 4 showed increased risks, and the risk differences (RD) and 95% CIs at 2 months and 4 months were 0.6% (0.3, 1.1%) and 1.5% (0.1, 3.1%), respectively. The highest risks were seen among the strategy 5 group and the RDs at 2 months and 4 months were 1.3% (0.8, 2.1%) and 3.1% (1.0, 5.6%), respectively.

A similar trend was observed for the composite outcome of infection-related hospitalization or mortality at 2 months and 4 months (Figure 5.14 and Table 5.12). Compared to the strategy 1 group, users of strategy 4 and strategy 5 had increased risks, while strategy 2 and strategy 3 users had little difference. At 2 months, RDs for strategy 4 and strategy 5 users were

0.8% (0.3, 1.3%) and 1.8% (1.2, 2.6%), respectively. At 4 months, RDs for these two groups were 1.7% (0.4, 2.9%) and 4.3 (2.2, 6.8%).

Appendix H & Appendix I show the estimated cumulative incidence differences and 95% CIs of both outcomes among strategy groups in sensitivity analyses. Models with different sets of covariates were used to estimate the censoring weights for strategy deviation. Little difference was seen among the estimates except the intercept-only model that did not consider any covariates.

5.3. Discussion

In a large contemporary cohort of hemodialysis patients, we compared a set of five commonly initiated IV iron administration strategies to assess their risks of mortality and infection-related events over 4 months. Increased risks of these outcomes were observed among strategies 4 and 5 that recommended aggressive dosing approaches at higher levels of TSAT and ferritin. Compared with strategy 1, strategy 5 may result in an additional 13 deaths or 18 infection-related events per 2 months per 1000 patients treated. Increased risks were also observed with strategy 4 but with a slightly smaller magnitude.

To our knowledge, this study is one of the first to assess the longer-term safety profile of IV iron administration strategies that align with clinical practice patterns among hemodialysis patients. In routine care, the treatment decision for IV iron use is dynamic. Physicians make frequent adjustments to treatment based on the evolving clinical characteristics of patients. Following the availability of iron status test results, treatment decisions occur, and physicians make recommendations on how much iron to provide and how frequent to provide according a certain treatment protocol.[13-15] We designed our study by mimicking this dynamic treatment

decision process in routine care and aligning our exposure assessment with points of possible treatment decisions.[203] The multidimensional strategies we compared in this study were adopted from complex protocols that actually occur in clinical practice. The comparative analyses of these strategies provided evidence that could be directly used to inform clinical decisions.

Our findings–that more intense strategies were associated with higher risks of infection–confirm and complement findings from prior studies. In a large cohort of hemodialysis patients, increased risk of infection-related hospitalizations or deaths was observed with more aggressive bolus dosing strategy compared with maintenance dosing.[25] The bolus dosing was defined as having at least two consecutive dialysis sessions of ≥100 mg iron or two or more administrations of >100 mg iron with the potential to exceed 600 mg in a month. Yet, the magnitude of the current results were relatively larger. The observed difference may be due to the difference in age and strategy definition. Our study cohort included hemodialysis patients who were at least 65 years old at dialysis initiation. Eligible patients averaged around 76 years old, which was 16 years older than that of the previous study. Another recent cohort study also showed higher mortality risk associated with non-maintenance strategies of IV iron compared with maintenance strategies.[26] No direct comparisons could be done for the estimates of effects as their definitions of the strategies were substantially different from ours. They defined maintenance strategy as having IV iron in a regular schedule and non-maintenance strategy as having any other iron administrations practice.

Among the commonly used administration strategies, the main difference is the level of ferritin at which iron treatment needs to be held. Among strategies 1-3, the TSAT levels indicating a particular dosage pattern were the same, but the ferritin levels for stopping iron decreased from 1200 ng/mL in strategy 1 to 500 ng/mL in strategy 3. Although not statistically

significant, the risks for all-cause mortality were modestly lower associated with strategies 2 and 3 that had lower stopping ferritin levels compared with strategy 1. The findings suggest that aggressive iron treatment with high ferritin level could have contributed to the increased risk. Compared with the first three strategies, strategies 4 and 5 made more intensive treatment recommendations. The TSAT levels for indicating a particular dosage pattern are much higher with these two strategies. For example, both strategies recommended bolus dosing when TSAT <30% while the other strategies would not recommend bolus dosing until TSAT <20%. In addition, the ferritin levels for holding iron were >1200 ng/mL, and the dosage pattern at high ferritin levels were either bolus in strategy 5 or at least half bolus in strategy 4. Increased risks of both mortality and infection-related events associated with these two strategies could potentially be explained by the aggressive treatment at high levels of ferritin. These results suggest that level of ferritin should be routinely evaluated in determining iron administration, calling into question the common practice of checking ferritin every 3 months rather than monthly.

Our analyses were subject to possible bias from unmeasured confounding or residual selection bias. Residual confounding bias would occur if unknown confounders for strategy initiation and outcomes were not included in the treatment model for estimation of standardized mortality ratio (SMR) weights. Residual confounding could also occur if initiators of more aggressive strategies were inherently different from initiators of other strategies and they were treated more aggressively for a reason. We did not have access to individual's indication for the use of a certain dosage approach. If the indication were a risk factor for the outcome, then the observed effect would be subject to bias. Residual selection bias would occur if there were unmeasured risk factors for both strategy deviation and adverse outcomes. The clinical research database and the USRDS database contain rich, frequently measured clinical, laboratory,

treatment, and demographic variables. We examined the impact of different sets of covariates on the estimated effects in sensitivity analyses. The results were robust to changes in the models, suggesting the possibility that the association between strategy deviation and the outcomes studied may not be strongly confounded by the measured covariates. However, there might exist some unmeasured variables for deviation adjustment of which would potentially attenuate the effect estimates.

In conclusion, administration strategies that recommended more aggressive treatment at higher levels of ferritin and TSAT were associated with increased risks of all-cause mortality and infection-related hospitalization or mortality. Our findings suggest iron may need to be used more sparingly in patients with elevated ferritin levels, but further exploration is needed to assess the extent of potential residual confounding and selection bias.

5.4. Concise Methods

Data sources

We constructed our study cohort using data derived from the clinical research database of a large dialysis provider in the United States, linked with the United States Renal Data System (USRDS) (2009-2012). We obtained detailed clinical information regarding patients' dialysis treatments, vascular access, routine laboratory tests, IV medications, and anemia management using the clinical research database. 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, Chapel Hill, North Carolina, USA.

Study design and study population

Detailed methods for cohort construction have been described elsewhere (Chapter 4). Briefly, 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 TSAT measurement on the index date was defined as the index TSAT. We used the 14-day window following the index TSAT as the index strategy assessment window to assess the IV iron administration strategy a patient was initiated on. 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 starting on day 15 following the index strategy assessment window (Figure 4.6).

Our study population comprised outpatient hemodialysis patients who initiated in-center hemodialysis between 1 January, 2009 and 16 September, 2012. We included patients who had Medicare as their primary insurer, continued hemodialysis for at least 90 days, and had complete information on baseline covariates. To ensure patients were receiving regular in-center hemodialysis and anemia management, we excluded patients who had fewer than nine dialysis sessions in the last month of baseline period or no TSAT measurement during the 136 days following dialysis initiation. We also excluded patients if they had polycystic kidney disease because their administration strategies of IV iron could differ. The cohort construction is outlined in Appendix G.

IV iron administration strategies

We identified the IV iron administration strategies initiated by eligible patients in the index assessment window using an approach outlined in Chapter 4. As the set of commonly used strategies were not known a priori, this identification approach matched a patient's treatment

pattern in the 14-day assessment window and current laboratory test values with candidate strategies by consistency. The length of assessment window was chosen so that it maximized the representativeness of treatment experience in the assessment window for the treatment experience in the entire treatment course while minimizing the days required for the assessment window to maximize follow-up time for outcomes. Each candidate strategy consisted of a set of decision rules that specified a range of acceptable iron therapy values (including dosage and frequency) during a treatment course given a patient's current laboratory test values.

To evaluate the effect of long-term exposure, we assessed whether a patient deviated from her index strategy during follow-up. We discretized the observation of an individual into intervals anchored by dates of TSAT laboratory tests. At each measurement of TSAT, we evaluated the treatment pattern in the 14-day assessment window, 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 assessment 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 bias introduced by this artificial censoring was adjusted for by inverse-probability censoring weighting as described in the statistical analysis section below.

Outcomes

Two adverse outcomes were examined: all-cause mortality and a composite outcome of infection-related hospitalization or death. These events were identified using the Medicare

inpatient and outpatient claims and death notification data. For analyses of all-cause mortality, patients were followed up until death, receipt of kidney transplantation, the time of switching modality, loss to follow-up, disenrollment from the dialysis provider, loss of Medicare coverage, 120 days after the index exposure window, or the administrative end of follow-up (December 31, 2012). For analyses of infection-related events, patients were followed up until death attributed to reasons other than infection. For both analyses, patients were also censored by deviation from index strategy. Infection-related hospitalization included sepsis, vascular access infection, or pneumonia. The detailed definitions for the outcomes are listed in Table 3.6.

Covariates

We evaluated both baseline and time-varying covariates using Medicare claims and the clinical research database. Baseline covariates included demographic characteristics (e.g. age, sex, race, region of residence, year of strategy initiation), clinical characteristics (e.g., cause of ESRD, body mass index), and a list of comorbidities. Time-varying covariates included time-varying laboratory values (TSAT, ferritin, hemoglobin, albumin, creatinine), clinical characteristics (e.g., type of vascular access, 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 (Table 3.7**)**.

Statistical analysis

We compared different IV iron administration strategies with respect to risk of all-cause mortality and risk of infection-related hospitalization or mortality using inverse probability of weighted estimation of Cox marginal structural models.[172] We chose one frequently used strategy as the referent strategy. Standardized mortality ratio weighting was used to adjust for

potential baseline confounders. Inverse probability of censoring weighting was used to adjust for potential selection bias introduced by artificially censoring patients who deviated from index administrations strategy. Variables included in the censoring model included time-dependent prognostic factors both for outcomes of interest and for censoring (lengths 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 etc), and time-independent factors (gender, cause of ESRD, comorbidities, and etc). We estimated the cumulative incidence differences between each strategy and the referent strategy during the follow-up period. The 95% confidence intervals (CI) for cumulative incidence differences were estimated using a non-parametric bootstrap procedure with 200 repetitions. We conducted sensitivity analyses by using different covariates for censoring weighting estimation. We also conducted three additional analyses to estimate different effects of administration strategy exposure. Detailed methods and results are described in Supplemental Material. All statistical analyses were conducted using the R Statistical Software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

ACKNOWLEDGMENTS

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5.5. Detailed Methods

Data sources

We constructed our study cohort using data derived from the clinical research database of a large dialysis provider 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. We obtained detailed clinical information regarding patients' dialysis treatments, vascular access, routine laboratory tests, IV medications, and anemia management using the clinical research database. 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, Chapel Hill, North Carolina, USA.

Study design and study population

Detailed methods for cohort construction have been described elsewhere (Chapter 4). Briefly, 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 TSAT measurement on the index date was defined as the index TSAT. We used the 14-day window following the index TSAT as the index strategy assessment window to assess the IV iron administration strategy a patient was initiated on. 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 starting on day 15 following the index strategy assessment window (Figure 4.6).

Our study population comprised outpatient hemodialysis patients who initiated in-center hemodialysis between 1 January, 2009 and 16 September, 2012. We included patients who had Medicare as their primary insurer, continued hemodialysis for at least 90 days, and had complete information on baseline covariates. To ensure patients were receiving regular in-center hemodialysis and anemia management, we excluded patients who had fewer than nine dialysis sessions in the last month of baseline period or no TSAT measurement during the 136 days following dialysis initiation. We also excluded patients if they had polycystic kidney disease because their administration strategies of IV iron could differ. The cohort construction is outlined in Appendix G.

IV iron administration strategies

We identified the IV iron administration strategies initiated by eligible patients in the index assessment window using an approach outlined in (Li unpublished). As the set of commonly used strategies were not known a priori, this identification approach matched a patient's treatment pattern in the 14-day assessment window and current laboratory test values with candidate strategies by consistency. The length of assessment window was chosen so that it maximized the representativeness of treatment experience in the assessment window for the treatment experience in the entire treatment course while minimizing the days required for the assessment window to maximize follow-up time for outcomes. Each candidate strategy consisted of a set of decision rules that specified a range of acceptable iron therapy values (including dosage and frequency) during a treatment course given a patient's current laboratory test values.

To evaluate the effect of long-term exposure, we assessed whether a patient deviated from her index strategy during follow-up. We discretized the observation of an individual into intervals anchored by dates of TSAT laboratory tests. At each measurement of TSAT, we

evaluated the treatment pattern in the 14-day assessment window 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 assessment 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 artificial censoring was adjusted for by inverse-probability censoring weighting as described in the statistical analysis section below.

Outcomes

Two adverse outcomes were examined: all-cause mortality and a composite outcome of infection-related hospitalization or death. These events were identified using the Medicare inpatient and outpatient claims and death notification data. For analyses of all-cause mortality, patients were followed up until death, receipt of kidney transplantation, the time of switching modality, loss to follow-up, disenrollment from this dialysis privder, loss of Medicare coverage, 120 days after the index exposure window, or the administrative end of follow-up (December 31, 2012). For analyses of infection-related events, patients were followed up until death attributed to reasons other than infection. For both analyses, patients were also censored by deviation from index strategy. Infection-related hospitalization included sepsis, vascular access infection, or pneumonia. The detailed definitions for the outcomes are listed in Table 3.6.

Covariates

We evaluated both baseline and time-varying covariates using Medicare claims and the clinical research database. Baseline covariates included demographic characteristics (e.g. age, sex, race, region of residence, year of strategy initiation), clinical characteristics (e.g., cause of ESRD, body mass index), and a list of comorbidities. Time-varying covariates included time-varying laboratory values (TSAT, ferritin, hemoglobin, albumin, creatinine), clinical characteristics (e.g., type of vascular access, 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 (Table 3.7).

Statistical analysis

We compared different IV iron administration strategies with respect to risk of all-cause mortality and risk of infection-related hospitalization or mortality using inverse probability of weighted estimation of Cox marginal structural models. We chose one frequently used strategy as the referent strategy.

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 follow up and estimated the effect of initiating one administration strategy versus the referent strategy on outcomes of interest. No adjustment was done for baseline confounding between initiation of strategies.

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

The third analysis used standardized mortality ratio (SMR) weights at the index date to adjust for baseline confounding. This analysis used the same structure as the analysis by censoring patients when they deviated from index strategy. No adjustment was done 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 regimen non-adherence using a product of SMR weights (SW_i^T) for baseline confounding control and inverse probability of censoring weights (IPCW) for deviation (SW_{ij}^D) for selection bias.

During the index assessment window, a patient's treatment experience might be consistent with multiple administration strategies. We created k copies of the same patient for k strategies she was consistent with initially. 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 strategy were artificially censored at the end of 14-day assessment window. The remaining patients were weighted by the probability that they stayed on the index strategy 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 reweighted to account for possible dependent censoring related to these additional events.

We fit 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. These covariates included baseline covariates and the most recent time-varying covariates in the

interval prior to the 14-day assessment window in which deviation was thought to have occurred. 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 incidence of adverse outcomes in initiators of each administration strategy separately. We then estimated the cumulative incidence differences between each strategy and the referent strategy during the follow-up period. The 95% confidence intervals (CI) for cumulative incidence differences were estimated using a non-parametric bootstrap procedure with 200 repetitions. We conducted sensitivity analyses by using different covariates for censoring weighting estimation. All statistical analyses were conducted using the R Statistical Software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Table 5.10. Definitions of IV iron administration strategies

A. Strategies without hemoglobin restriction

Strategy 1

		Ferritin, ng/mL		
		<200	200-1200	>1200
TSAT, %	<20	B	LM	N
	20-50	M	LM	N
	>50	N	N	N

Strategy 2

		Ferritin, ng/mL		
		<200	200-800	>800
TSAT, %	<20	B	LM	N
	20-50	M	LM	N
	>50	N	N	N

Strategy 3

		Ferritin, ng/mL		
		<200	200-500	>500
TSAT, %	<20	B	LM	N
	20-50	M	LM	N
	>50	N	N	N

Strategy 4

		Ferritin, ng/mL		
		<800	800-1200	>1200
TSAT, %	<30	B	HB	N
	30-50	LM	LM	N
	>50	N	N	N

Strategy 5

		Ferritin, ng/mL	
		<1200	≥1200
TSAT, %	<30	B	N
	30-40	HB	N
	41-49	M	N
	≥50	N	N

Note:TSAT = transferrin saturation; Hgb = hemoglobin

B. Dose pattern definition

Dose Pattern	Iron Dosage Level	
	2-Week	**Monthly equivalence**
Bolus (B)	>500	100 mg × 10 consecutive sessions
Half bolus (HB)	201-500	100 mg × 5 consecutive sessions
Maintenance (M)	101-200	100 mg weekly
Low maintenance (LM)	1-100	25 or 50 mg weekly
None (N)	0	0 mg

Table 5.11. Baseline characteristics of hemodialysis patients by initiated IV iron administration strategy, 2009-2012

Characteristics	Overall	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5
N	13,249	10,882	11,293	10,397	8,089	6,305
Age, Mean (SD)	75.97 (6.92)	75.91 (6.94)	75.95 (6.94)	75.92 (6.93)	75.94 (6.95)	75.89 (6.97)
Female, %	49.4	49.4	49.5	49.3	48.9	49.4
Race, %						
Black	22.7	22.4	22.5	22.2	21.9	22.5
White	72.0	72.5	72.3	72.6	73.1	72.8
Other	5.3	5.1	5.2	5.2	5.0	4.7
Medicaid, %	29.3	29.3	29.3	29.2	29.3	29.8
Lower income subsidy, %	34.4	34.5	34.5	34.4	34.8	35.2
Region, %						
Midwest	23.0	23.3	23.3	23.5	23.0	23.1
Northeast	14.0	14.0	13.7	13.8	13.8	13.5
Other	0.0	0.0	0.0	0.0	0.0	0.0
South	42.1	41.3	41.5	41.8	42.7	43.3
West	21.0	21.3	21.5	20.9	20.4	20.0
Cause of ESRD, %						
Diabetes	44.7	45.0	44.7	45.0	44.5	43.9
Glomerulonephritis	5.1	4.9	4.9	4.9	5.1	5.0
Hypertension	36.3	36.1	36.2	35.7	36.3	35.9
Missing	0.3	0.4	0.4	0.4	0.4	0.4
Other	13.5	13.6	13.8	14.0	13.8	14.8
Index year, %						
2009	25.0	23.1	23.6	25.2	26.9	28.6
2010	24.8	23.0	23.5	25.4	26.3	28.1
2011	25.5	27.3	27.1	26.0	24.1	22.4
2012	24.7	26.5	25.8	23.4	22.8	20.9
Comorbidities, %						
Vascular access infection[a]	1.1	1.2	1.2	1.3	1.6	2.0

Pneumonia[a]	2.2	2.4	2.3	2.4	2.7	3.3
Sepsis[a]	2.3	2.5	2.5	2.6	3.1	3.8
Infection (ADR definition)[a]	3.6	4.0	3.9	4.1	4.9	6.0
Antibiotic use[a]	19.5	21.1	20.7	21.2	23.9	27.6
IV antibiotics (dialysis center)[a]	11.1	12.1	11.9	12.5	14.4	17.3
Infection (broad definition)[a]	24.3	26.1	25.7	26.3	29.4	34.1
Diabetes	69.3	69.6	69.4	69.6	69.3	69.8
Hypertensive disease	95.6	95.3	95.4	95.8	96.2	96.6
Congestive heart failure	62.4	62.5	62.7	63.4	64.0	66.3
Myocardial infarction, acute	9.7	9.6	9.7	9.9	9.6	9.8
Angina	6.9	6.9	7.0	7.1	6.9	7.2
Coronary artery disease/atherosclerosis	56.1	56.3	56.3	56.9	57.5	59.1
Ischemic stroke	7.5	7.7	7.7	7.7	7.9	8.6
Intracerebral hemorrhage	0.3	0.3	0.3	0.3	0.3	0.3
Subarachnoid hemorrhage	0.1	0.1	0.1	0.1	0.1	0.1
Hemorrhagic stroke	0.7	0.7	0.7	0.7	0.8	0.8
Cerebrovascular disease	23.8	24.1	24.1	24.2	24.4	25.4
Chronic obstructive pulmonary disease & asthma	33.0	33.4	33.4	33.9	34.5	36.2
Hyperlipidemia	60.5	60.5	60.4	60.6	60.5	60.3
Cancer	21.4	21.6	21.7	21.7	22.2	23.2
Liver disease	4.2	4.2	4.2	4.3	4.4	4.8
GI bleeding & ulcer	2.7	2.8	2.8	2.8	3.1	3.4
Blood transfusion	36.2	36.1	36.4	37.1	38.0	40.5
Blood loss anemia	5.2	5.1	5.2	5.3	5.6	5.8
Peripheral vascular disease	26.4	26.7	26.5	27.0	27.0	28.1
Rheumatic heart disease	6.1	6.1	6.1	6.1	6.3	6.7
Psychiatric disorder	5.9	6.0	6.0	6.0	6.0	6.7
Substance abuse	6.3	6.5	6.4	6.5	6.8	7.1
Autoimmune disorder	4.8	4.8	4.8	4.7	4.9	4.9
Other neurological disorders	13.5	13.7	13.7	14.3	14.6	16.1

Hyperparathyroidism	3.7	3.7	3.6	3.6	3.8	3.7
Chronic heart disease procedures	5.5	5.5	5.6	5.7	5.5	5.9
Rheumatoid arthritis	2.8	2.7	2.7	2.7	2.7	2.8
Neuropathy	20.8	21.3	21.2	21.4	21.4	21.7
Osteoarthritis	19.8	20.2	20.2	19.9	20.1	20.6
Osteoporosis	4.6	4.6	4.7	4.6	4.6	4.6
History of fall	5.5	5.5	5.5	5.5	5.7	5.9
Last month of baseline period, Mean (SD)[b]						
Total EPO dose, 1000 units/month	68.46 (73.30)	68.26 (73.02)	68.22 (72.91)	70.65 (74.57)	72.99 (79.39)	83.32 (83.03)
Total iron dose, mg	299.04 (310.93)	292.50 (295.98)	287.87 (299.13)	289.11 (307.68)	310.18 (321.75)	334.24 (342.57)
TSAT, %	24.99 (12.41)	24.90 (12.34)	25.02 (12.50)	25.06 (12.72)	25.48 (13.26)	24.67 (13.75)
Ferritin, ng/mL	489.93 (435.28)	470.50 (437.11)	486.75 (445.72)	484.10 (462.63)	487.68 (481.96)	510.90 (525.13)
Hemoglobin, g/dL	11.47 (1.43)	11.43 (1.42)	11.45 (1.43)	11.47 (1.45)	11.49 (1.49)	11.38 (1.53)
Albumin, g/dL	3.57 (0.45)	3.57 (0.46)	3.57 (0.46)	3.57 (0.46)	3.55 (0.47)	3.51 (0.47)
Creatinine, mg/dL	5.07 (1.91)	5.07 (1.91)	5.07 (1.90)	5.06 (1.91)	5.06 (1.92)	5.01 (1.94)
Pre-treatment SBP, mmHg	143.03 (22.15)	142.87 (22.08)	142.84 (22.16)	142.90 (22.26)	142.41 (22.13)	141.87 (22.40)
Post-treatment weight, kg	74.40 (18.49)	74.66 (18.65)	74.49 (18.63)	74.60 (18.72)	74.52 (18.61)	74.39 (18.76)
Hospital days	0.71 (1.97)	0.75 (2.03)	0.74 (2.02)	0.77 (2.06)	0.87 (2.18)	1.03 (2.34)
Number of transfusions	0.03 (0.20)	0.03 (0.22)	0.03 (0.21)	0.03 (0.22)	0.04 (0.25)	0.05 (0.27)
Access, %						
Catheter	62.8	63.4	63.7	64.7	65.9	70.1
Fistula	26.6	26.1	25.9	24.9	24.1	20.7
Graft	10.6	10.4	10.5	10.4	10	9.2
Index date, Mean (SD)[c]						
Index TSAT, %	28.43 (13.90)	28.56 (14.48)	28.58 (14.37)	28.69 (14.74)	30.65 (16.11)	29.12 (17.74)
Index Ferritin, ng/mL	546.02 (463.50)	526.22 (488.18)	542.53 (486.91)	535.54 (506.28)	559.52 (548.57)	583.85 (607.72)
Index Hemoglobin, g/dL	11.57 (1.31)	11.52 (1.30)	11.54 (1.30)	11.58 (1.32)	11.55 (1.36)	11.51 (1.42)
Index Albumin, g/dL	3.61 (0.45)	3.60 (0.46)	3.60 (0.45)	3.60 (0.46)	3.57 (0.47)	3.53 (0.47)
Index Creatine, mg/dL	5.24 (1.98)	5.24 (1.99)	5.24 (1.98)	5.23 (1.98)	5.23 (2.01)	5.18 (2.01)

SD=Standard deviation; IQR=interquartile range; ESRD=end stage renal disease; ADR=annual data report; TSAT=transferrin saturation; EPO=Epoetin

[a]Prevalence during the last month of baseline period;

[b]If laboratory tests in the last month of baseline were missing, the previous test values were used;

[c]If a laboratory test was missing on index date, the last non-missing test values were used.

Table 5.12. Adjusted cumulative incidence differences and 95% confidence intervals at 2 months and 4 months

		Death		Infection-related hospitalization or death	
Strategy	**Total**	**2-month**	**4-month**	**2-month**	**4-month**
1	10,882	referent	referent	referent	referent
2	11,293	-0.2 (-0.4, 0.0)	-0.7 (-1.2, 0.0)	0.1 (-0.1, 0.3)	-0.2 (-0.5, 0.3)
3	10,397	-0.1 (-0.4, 0.2)	-0.6 (-1.6, 0.7)	0.2 (-0.1, 0.5)	0.2 (-0.6, 1.0)
4	8,089	0.6 (0.3. 1.1)	1.5 (0.1, 3.1)	0.8 (0.3. 1.3)	1.7 (0.4, 2.9)
5	6,305	1.3 (0.8, 2.1)	3.1 (1.0, 5.6)	1.8 (1.2, 2.6)	4.3 (2.2, 6.8)

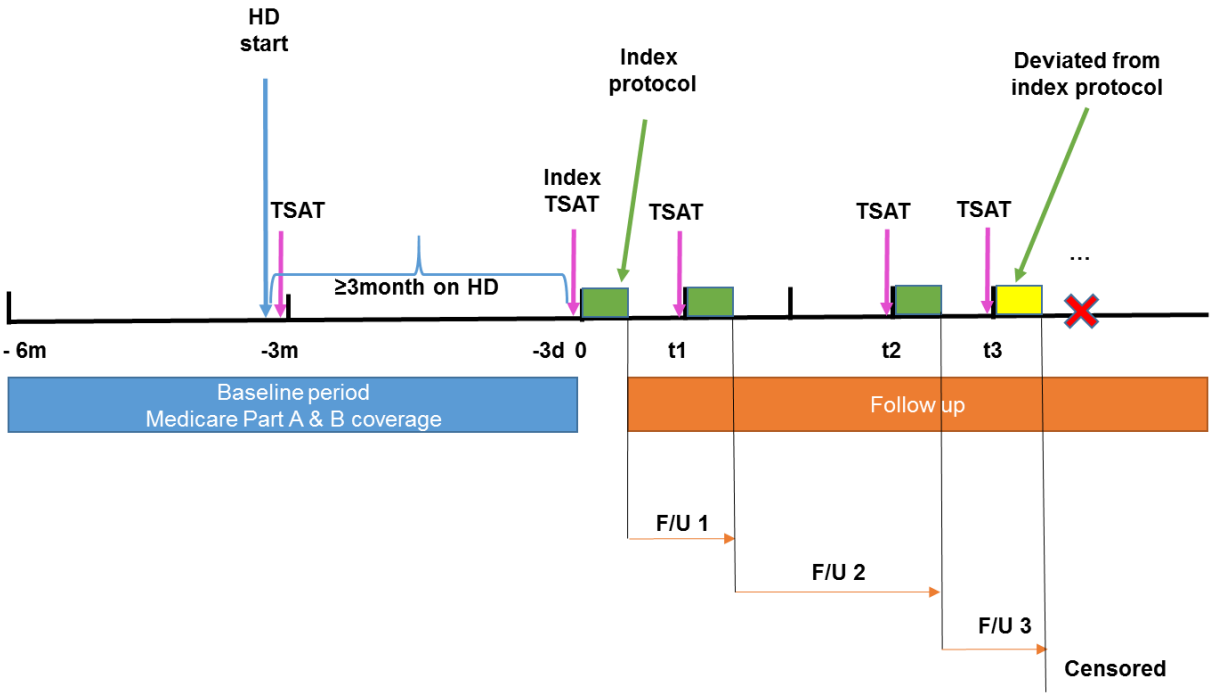


Figure 5.12. Study design for assessing the effect of initiating and staying on a particular IV iron administration strategy

Patients are followed starting on the end of the 1st 14-day iron exposure window for all-cause mortality. Those deviated from the index strategy are artificially censored.

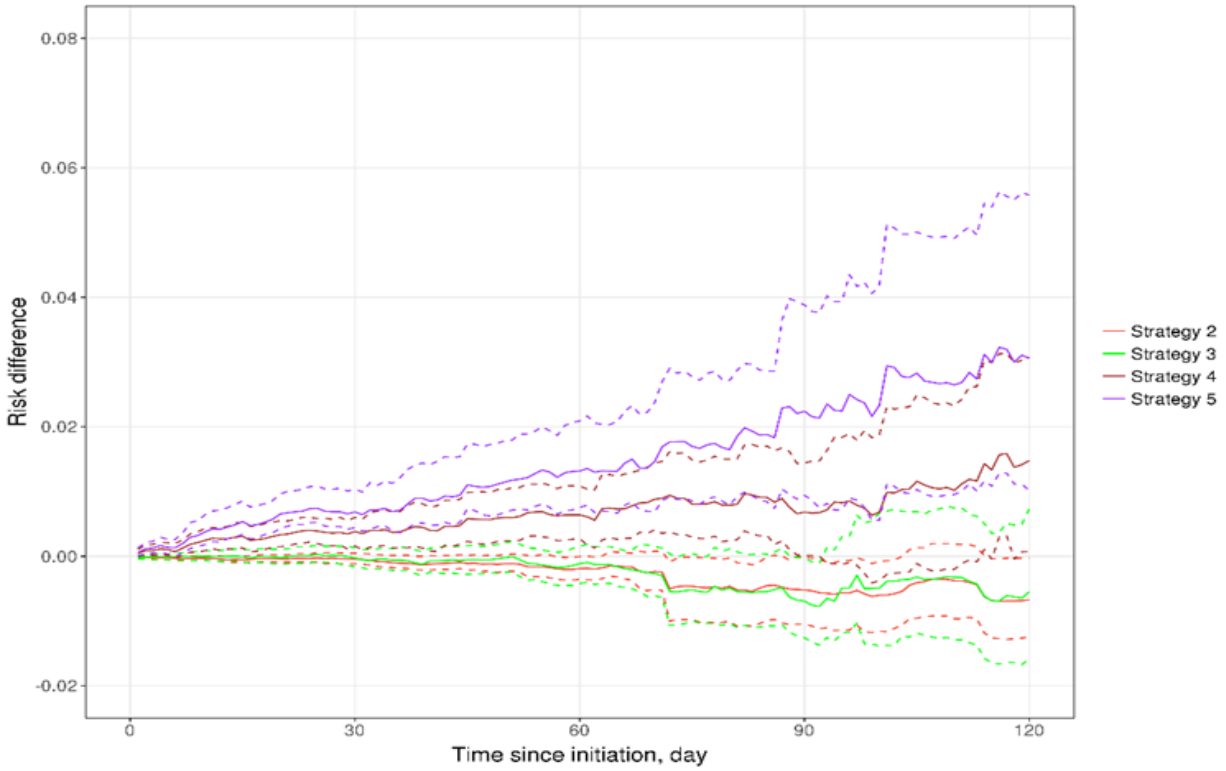


Figure 5.13. Estimated 4-month cumulative incidence differences and 95% confidence intervals of mortality, 2009-2012

The observed cumulative incidence difference represents elevated risks of all-cause mortality comparing new users of an IV iron administration strategy with that of strategy 1.

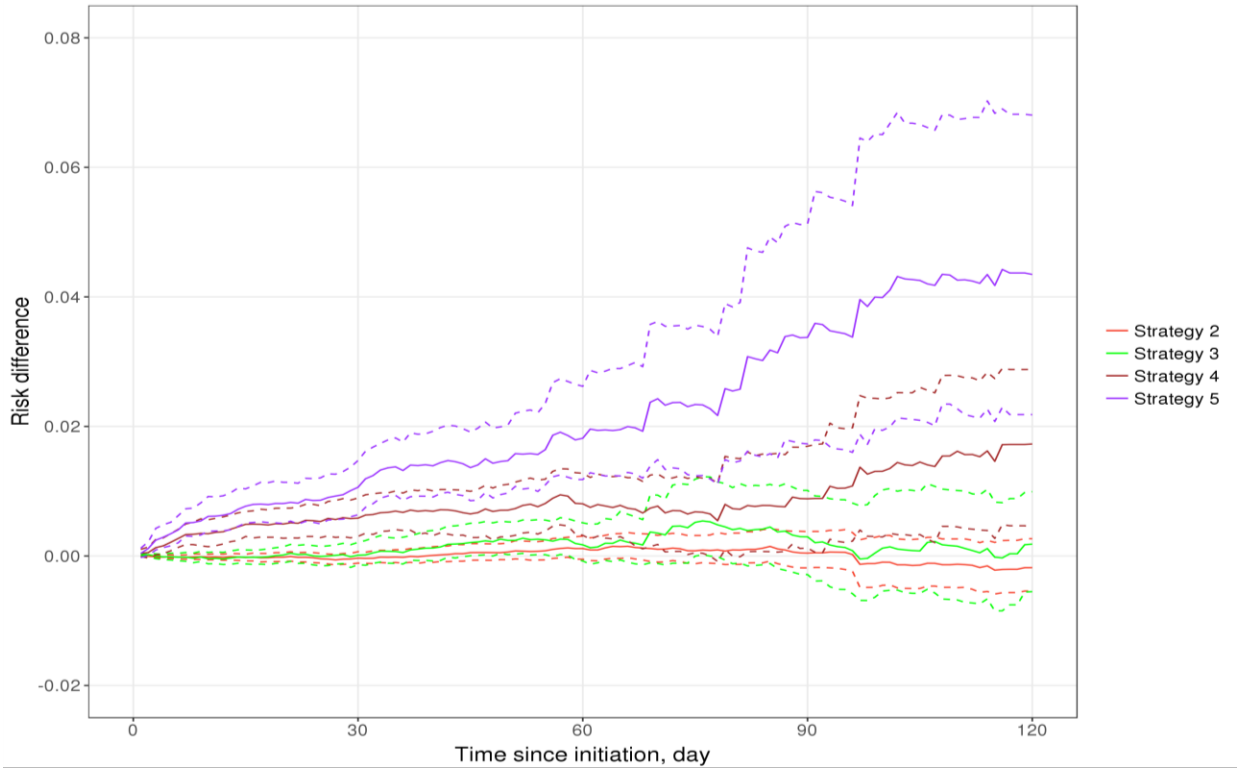


Figure 5.14. Estimated 4-month cumulative incidence differences and 95% confidence intervals of infection-related hospitalization or mortality, 2009-2012
Users of IV iron administration strategy 1 were used as the referent group.

CHAPTER 6: DISCUSSION

6.1. Summary of Findings

The primary objective of this first specific aim was to develop an approach to systematically identify dynamic treatment regimes in secondary databases for comparative effectiveness and safety studies when a priori regimes are not available. We developed an approach that identifies regimes using treatment experience in an assessment window and current laboratory tests at a point of treatment decision. Candidate regimes under consideration were assigned to a patient if they were consistent with treatment experience in the assessment window. We exploited data visualization of patient-level data to inform regime construction and identification. We applied this identification process in an empirical example of IV iron dosing protocols for anemia management in hemodialysis patients, using measurements of iron status tests and iron treatment experience in a two-week assessment window. Among 43,166 patients initiated hemodialysis in 2004-2012, 79.1% of them were matched with candidate protocols. The prevalence of protocol matches increased from 75.0% in 2004 to 90.7% in 2012. Due to the unavailability of exact protocols that were used, we could not evaluate the performance of the identification approach; however, higher prevalence of knowingly implemented protocols confirmed the performance of this identification approach.

The primary objective of the second specific aim was to evaluate the comparative safety of continuous exposure to different commonly used IV iron treatment protocols. We estimated the effect of continuous exposure to the five most commonly initiated protocols in 2009-2012 on

risks of mortality and infection-related events. Two less commonly initiated protocols were more aggressive, recommending a large amount of iron at higher iron status levels; their initiators were sicker at baseline. Compared with the protocol that recommended less intensive treatment at lower ferritin levels, protocols that indicated a large amount of iron at higher levels of iron status tests were at elevated risk of all-cause mortality. We observed similar trends in elevated risks for a composite outcome of infection-related hospitalization and death among more aggressive protocols. Protocols that recommend less intensive use of iron at high levels of ferritin and TSAT may lower risks of mortality and infection-related events, but further exploration is needed to address potential residual confounding and selection bias.

6.2. Public Health Implications

This dissertation project aimed to find evidence to inform IV iron use for anemia management in ESRD patients maintained on hemodialysis. The important question regarding IV iron is not whether we should use IV iron. Data have consistently shown the benefit of IV iron use relative to no use.[5,6] Instead, the important question is on how best to provide IV iron, and identifying optimal management strategies is essential. Our study is one of the first to assess longer-term safety of commonly used IV iron administration protocols. We used a study design that mimics the dynamic treatment decision regarding IV iron use in routine care and compared multidimensional protocols that commonly used in clinical practice. Doing so, we were able to obtain clinically-relevant evidence that could be directly used to inform clinical decisions.

We observed that certain protocols that recommend aggressive use of iron at high iron status levels were at elevated risk of adverse outcomes in the longer term. This finding suggests that thorough examination is needed on the initiating levels of iron status tests for various iron

dosing approaches, which is urgently important in current practice with increasing reliance on IV iron. In the U.S, there were more than 468,000 hemodialysis patients, and 69% of more than hemodialysis patients were receiving IV iron in April 2014.[204] Inappropriate IV iron treatment could potentially cause harm to a large number of patients.

6.3. Future Research

In the second aim, our analyses suggested that protocols that recommend intensive iron therapy at high levels of iron status tests are associated with elevated risks of infection-related outcomes, compared to protocols that recommend less intensive strategies. The differences in the baseline clinical characteristics among their initiators, however, casts some doubt on potential residual confounding bias and selection bias. Although the differences in distributions of observed covariates diminished after adjustment with SMR weighting, it is possible that we did not have access to some important risk factors for the outcome that also had contributed to the initiation of these aggressive protocols. Further investigation should examine the extent of potential unmeasured confounding and selection bias.

As a leading cause of death for ESRD patients, cardiovascular outcomes are another big concern. Prior studies have not established a difference in cardiovascular risks between maintenance and bolus dosing administration, but they remain a constant concern. We observed elevated risks of infection-related outcomes in protocols that recommend intensive iron therapy at high levels of iron status tests. It would be important to examine the effect of these protocols on risks of cardiovascular outcomes.

Within these two aims, we set up a working framework to compare the safety of dynamic treatment regimes using complex longitudinal data using causal inference methods. In the first

aim, we developed an approach to identify commonly used regimes. In the second aim, we established the longitudinal treatment decision design for evaluation of comparative safety of the regimes. This framework could be easily generalized to assess the comparative effectiveness of the regimes. For this example of IV iron in hemodialysis patients, it is equally important to know which protocols can achieve better anemia management goals including hemoglobin response and ESA dose requirement reduction. More aggressive IV iron treatment protocols may lead to better anemia response.

This study identified a number of commonly used dosing protocols. Pragmatic trials could be carried out within dialysis clinics to directly compare these protocols and evaluate their real-world effectiveness and safety.

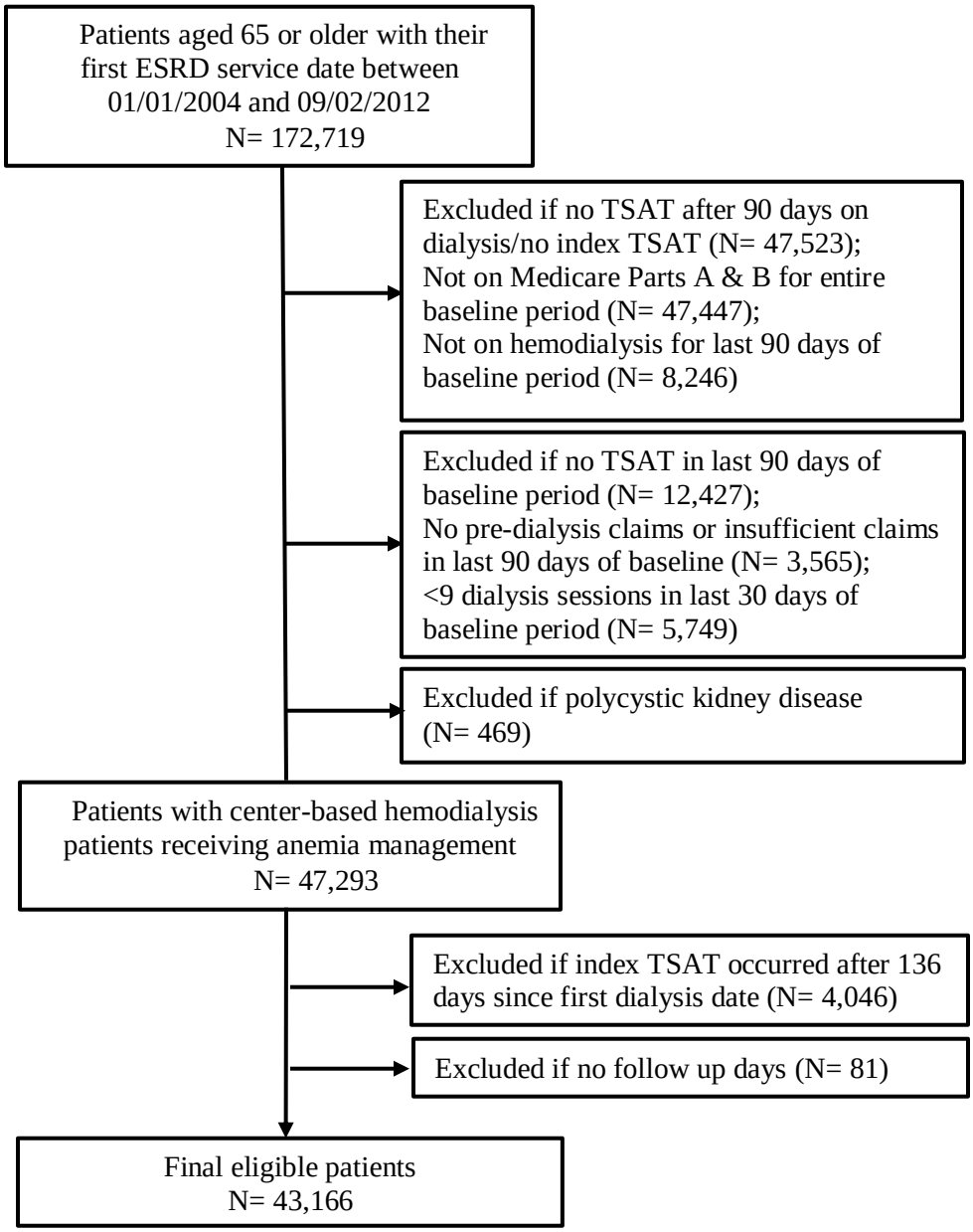
6.4. Conclusions

Starting around 2009, more and more IV iron treatment patterns in ESRD patients on hemodialysis were matched with IV iron dosing protocols. These dosing protocols differed in IV iron administration approaches and their corresponding levels of iron status tests. Protocols that recommend less intensive use of iron at high levels of iron status tests may lower risks of mortality and infection-related events, but further exploration is needed to address potential residual confounding and selection bias.

Increasingly available large healthcare databases containing rich, granular patient-level information can make estimation of effect of dynamic treatment regimes more feasible. With appropriate study design and statistical methods, we can compare the regimes in comparative effectiveness and safety research to provide evidence to assist decision-making in clinical practice.

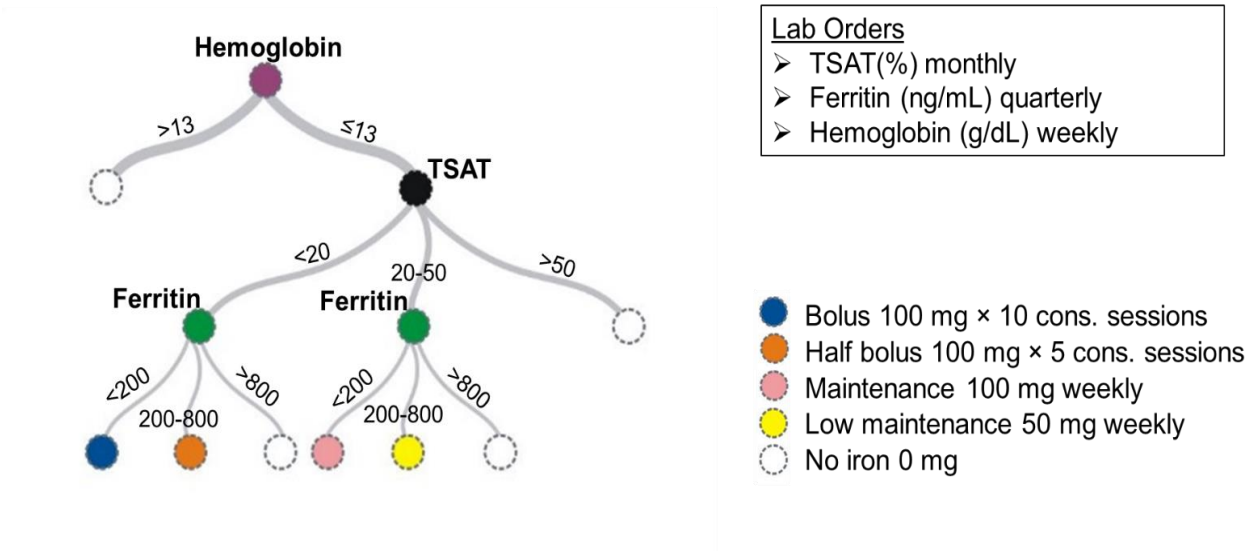
APPENDIX A: FLOW DIAGRAM OF STUDY POPULATION FOR CHAPTER 4

Figure A.1: Flow diagram of study population for Chapter 4



APPENDIX B: IV IRON DOSING PROTOCOL EXAMPLE

Figure B.1: Example intravenous iron dosing strategy for end-stage renal failure patients on chronic hemodialysis



APPENDIX C: DEFINITIONS OF CANDIDATE ADMINISTRATION STRATEGIES

A. Strategies without hemoglobin restriction

Strategy 1

		Ferritin, ng/mL		
		<200	200-1200	>1200
TSAT, %	<20	B	LM	N
	20-50	M	LM	N
	>50	N	N	N

Strategy 2

		Ferritin, ng/mL		
		<200	200-800	>800
TSAT, %	<20	B	LM	N
	20-50	M	LM	N
	>50	N	N	N

Strategy 3

		Ferritin, ng/mL		
		<200	200-500	>500
TSAT, %	<20	B	LM	N
	20-50	M	LM	N
	>50	N	N	N

Strategy 4

		Ferritin, ng/mL		
		<800	800-1200	>1200
TSAT, %	<30	B	HB	N
	30-50	LM	LM	N
	>50	N	N	N

Strategy 5

		Ferritin, ng/mL	
		<1200	≥1200
TSAT, %	<30	B	N
	30-40	HB	N
	41-49	M	N
	>=50	N	N

Strategy 6

		Ferritin, ng/mL			
		<200	200-<800	800-<1200	≥1200
TSAT, %	<20	B	B	HB	N
	20-29	B	HB	M	N
	30-39	HB	M	LM	N
	40-49	M	M	LM	N
	>=50	N	N	N	N

Strategy 7

		Ferritin, ng/mL	
		<1200	≥1200
TSAT, %	<20	B	N
	20-40	M	N
	41-49	LM	N
	>=50	N	N

Strategy 8

		Ferritin, ng/mL	
		<1200	≥1200
TSAT, %	<20	HB	N
	20-40	M	N
	41-49	LM	N
	>=50	N	N

B. Strategies with hemoglobin restriction

Strategy 1 If hgb > 13 g/dL then N; else do:

		Ferritin, ng/mL		
		<200	200-1200	>1200
TSAT, %	<20	B	LM	N
	20-50	M	LM	N
	>50	N	N	N

Strategy 2 If hgb > 13 g/dL then N; else do:

		Ferritin, ng/mL		
		<200	200-800	>800
TSAT, %	<20	B	LM	N
	20-50	M	LM	N
	>50	N	N	N

Strategy 3 If hgb > 13 g/dL then N; else do:

		Ferritin, ng/mL		
		<200	200-500	>500
TSAT, %	<20	B	LM	N
	20-50	M	LM	N
	>50	N	N	N

Strategy 4 If hgb > 13 g/dL then N; else do:

		Ferritin, ng/mL		
		<800	800-1200	>1200
TSAT, %	<30	B	HB	N
	30-50	LM	LM	N
	>50	N	N	N

Strategy 5 If hgb > 13 g/dL then N; else do:

		Ferritin, ng/mL	
		<1200	≥1200
TSAT, %	<30	B	N
	30-40	HB	N
	41-50	M	N
	>50	N	N

Strategy 6 If hgb > 13 g/dL then N; else do:

		Ferritin, ng/mL			
		<200	200-<800	800-1200	>1200
TSAT, %	<20	B	B	HB	N
	20-30	B	HB	M	N
	30-40	HB	M	LM	N
	40-50	M	M	LM	N
	>50	N	N	N	N

Strategy 7 If hgb > 13 g/dL then N; else do:

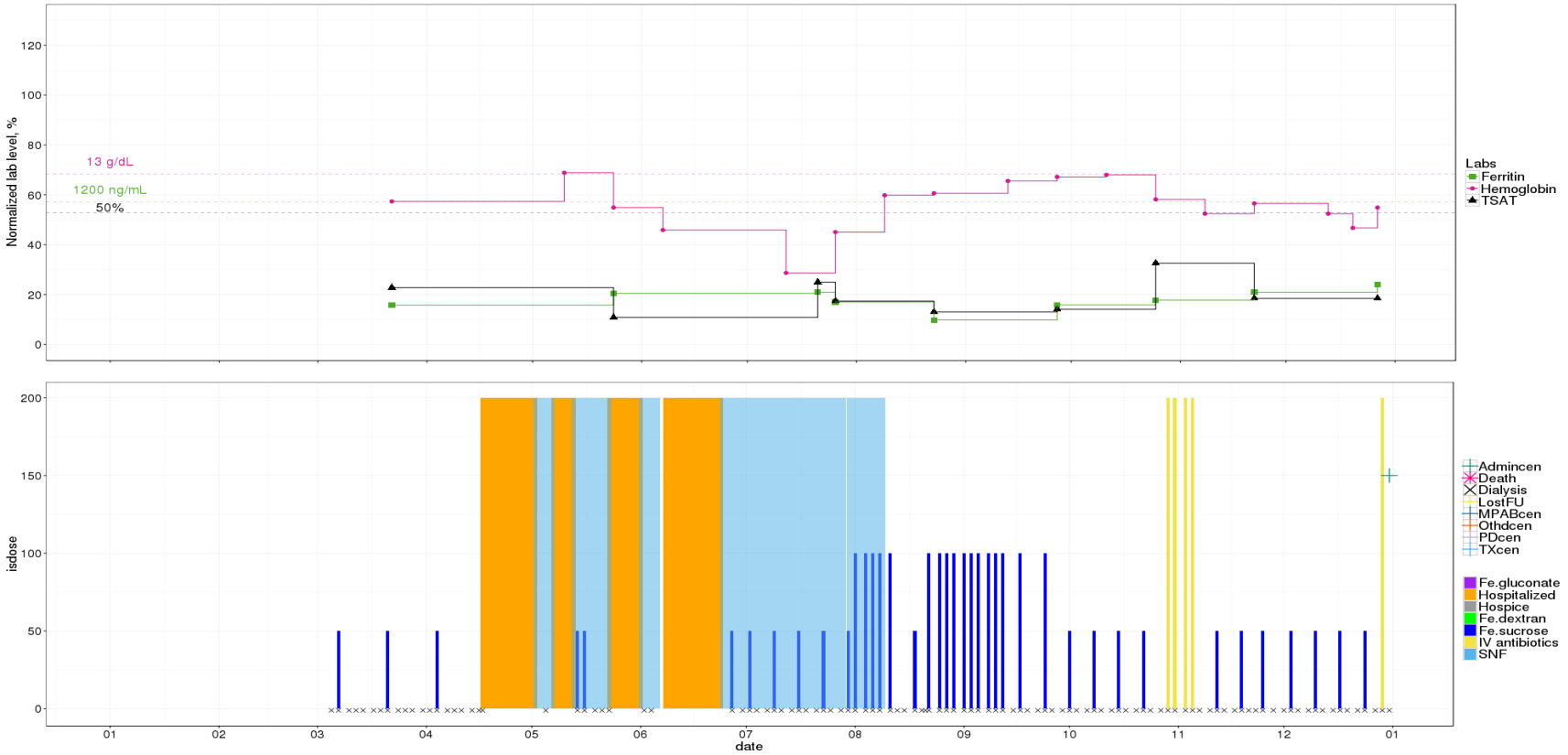
		Ferritin, ng/mL	
		<1200	≥1200
TSAT, %	<20	B	N
	20-40	M	N
	40<-50	L	N
	>50	N	N

Strategy 8 If hgb > 13 g/dL then N; else do:

		Ferritin, ng/mL	
		<1200	≥1200
TSAT, %	<20	HB	N
	20-40	M	N
	40<-50	L	N
	>50	N	N

APPENDIX D: PATIENT JOURNEY – A VISUALIZATION TOOL

Figure D.1: Patient journey, a data visualization tool that depicts the patient journey with treatment and her clinical condition evolution across time using two panels. The top panel illustrated the changes in anemia management parameters, while the bottom panel presents the IV iron dosage level received at each dialysis session, healthcare system encounters and outcome information.



APPENDIX E: DISTRIBUTION OF IRON DOSAGE PATTERNS

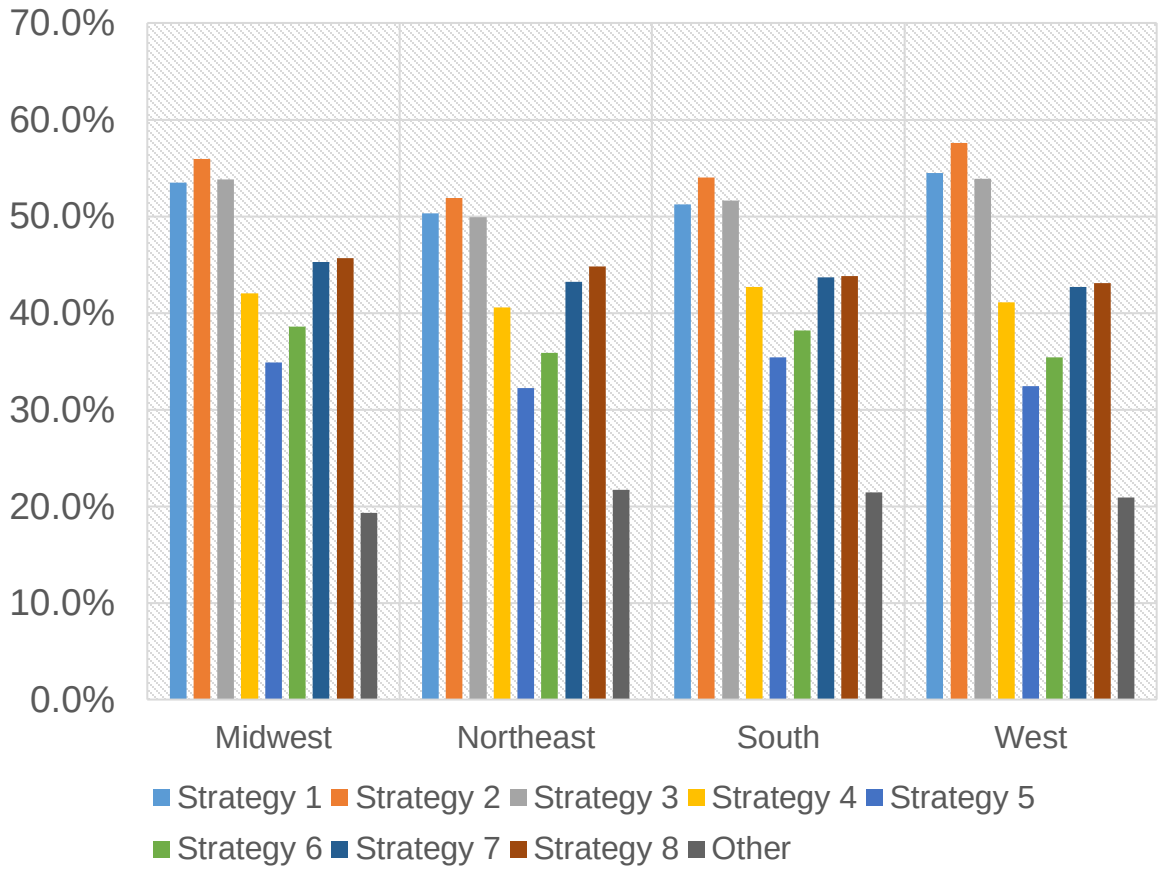
Table E.1: Distribution of iron dosage pattern

Dose pattern	Definition: 2-week	Definition: Monthly equivalence	N	%	Iron dose, mg: Median (IQR)	Iron dose, mg: Mean (SD)	TSAT, %: Median (IQR)	Ferritin, ng/mL: Median (IQR)	Hgb, g/dL: Median (IQR)
Bolus	>500	100 mg × 10 consecutive sessions	3,218	7.5	600 (600-600)	627.6 (279.9)	17 (13-20)	192 (101-360.8)	12.1 (11.2-13.1)
Half bolus	201-500	100 mg × 5 consecutive sessions	4,853	11.2	400 (300-500)	393.3 (88.5)	18 (14-23)	226 (116-415)	12.2 (11.2-13.2)
Maintenance	101-200	100 mg weekly	7,902	18.3	200 (200-200)	189.2 (23.8)	24 (19-31)	299 (174-480)	12.5 (11.5-13.4)
Low maintenance	1-100	25 or 50 mg weekly	14,182	32.9	100 (50-100)	83.9 (24.3)	26 (21-34)	358 (224-543)	12.2 (11.3-13.1)
None	0	0 mg	13,011	30.1	0 (0-0)	0 (0)	29 (21-41)	492 (227.3-884)	12.4 (11.3-13.4)

Note: IQR = interquartile range; SD = standard deviation; TSAT = transferrin saturation; Hgb = hemoglobin

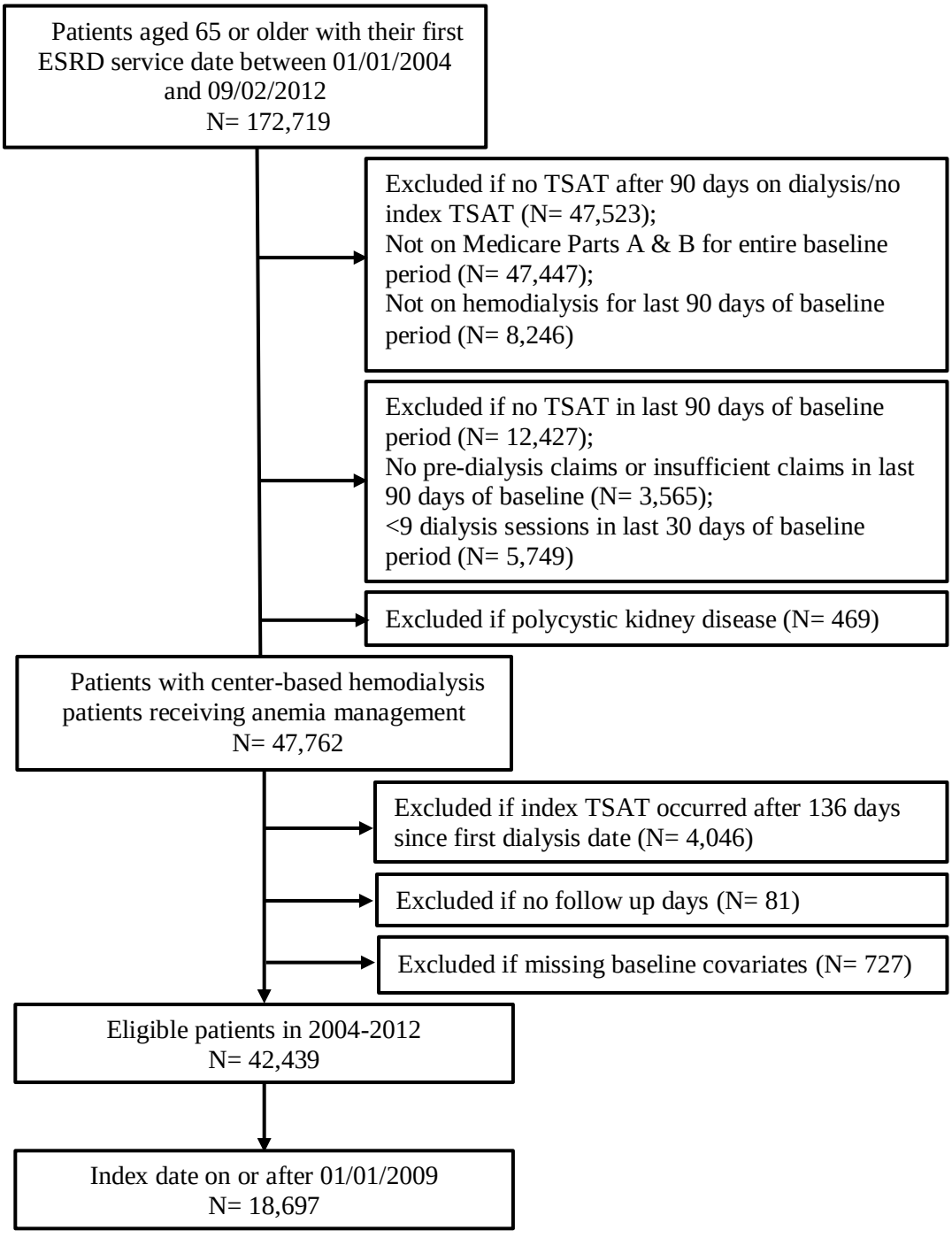
APPENDIX F: REGIONAL TREND OF MATCHED IV IRON ADMINISTRATION STRATEGIES

Figure F.1: Distribution of matched IV iron administration strategies was similar among residential regions in 2004-2012.



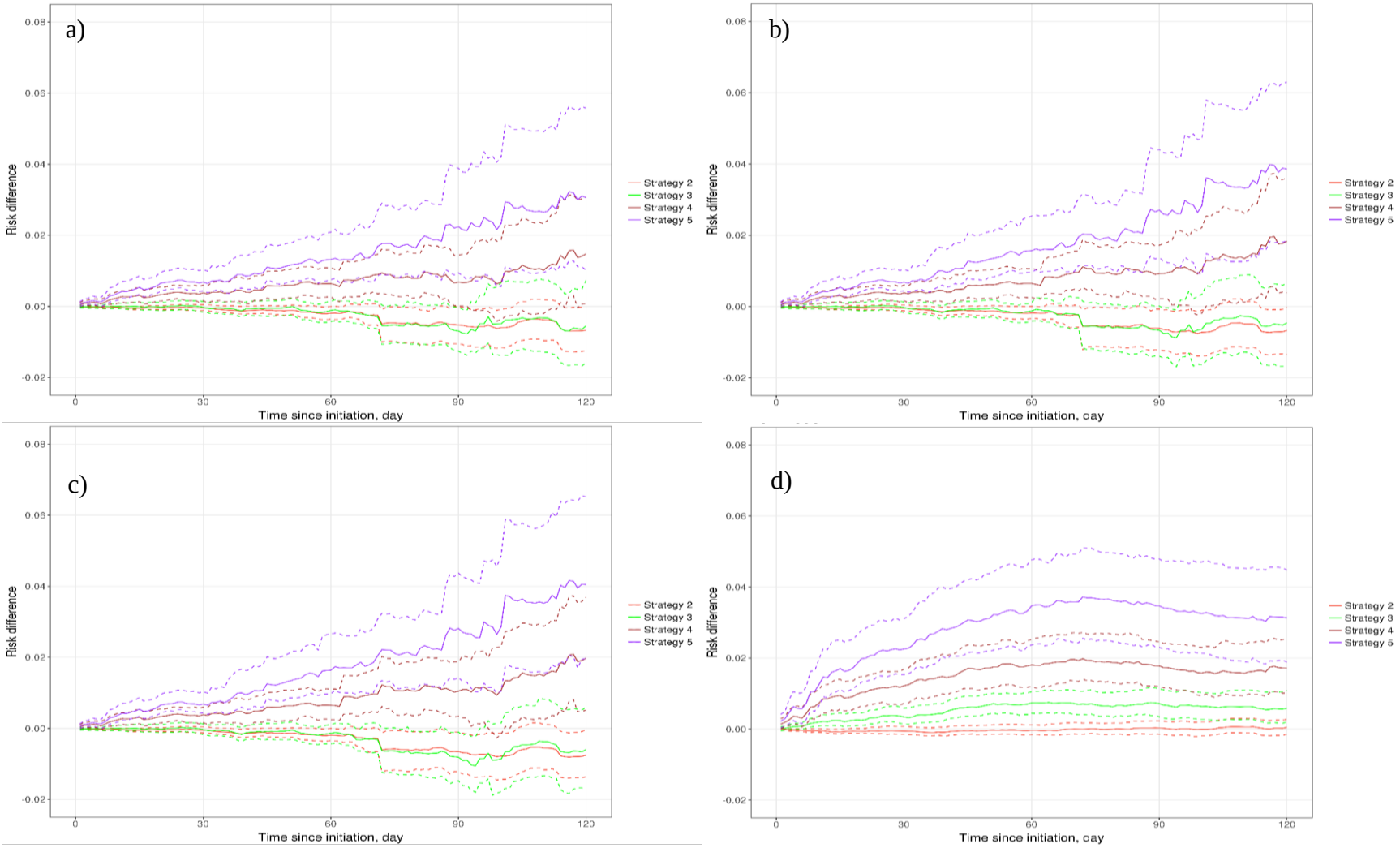
APPENDIX G: FLOW DIAGRAM OF STUDY POPULATION FOR CHAPTER 5

Figure G.1: Flow diagram of study population for Chapter 5, 2009-2012



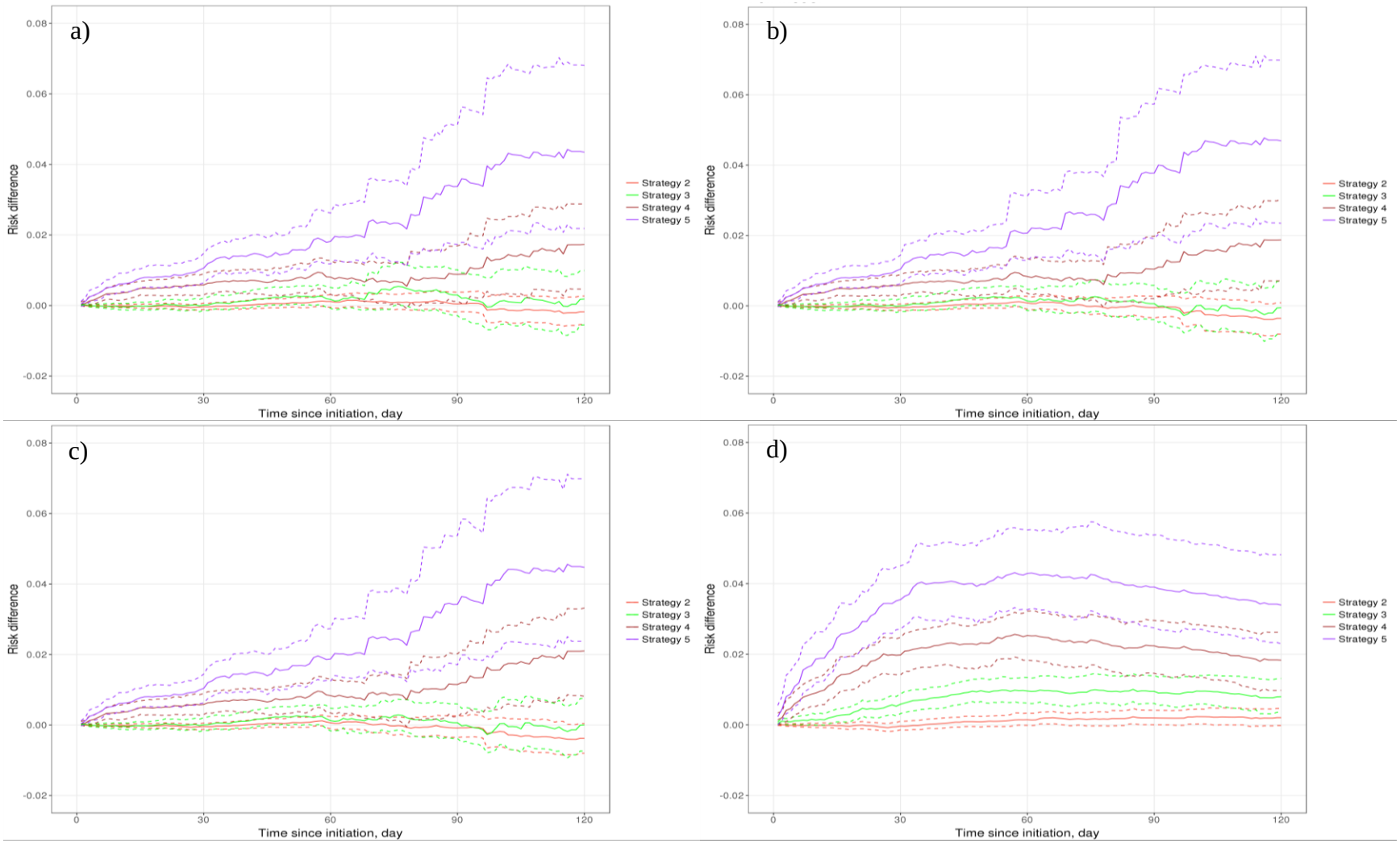
APPENDIX H: SENSITIVITY ANALYSIS VARYING MODELS FOR DEVIATION – ALL CAUSE MORTALITY

Figure H.1: 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



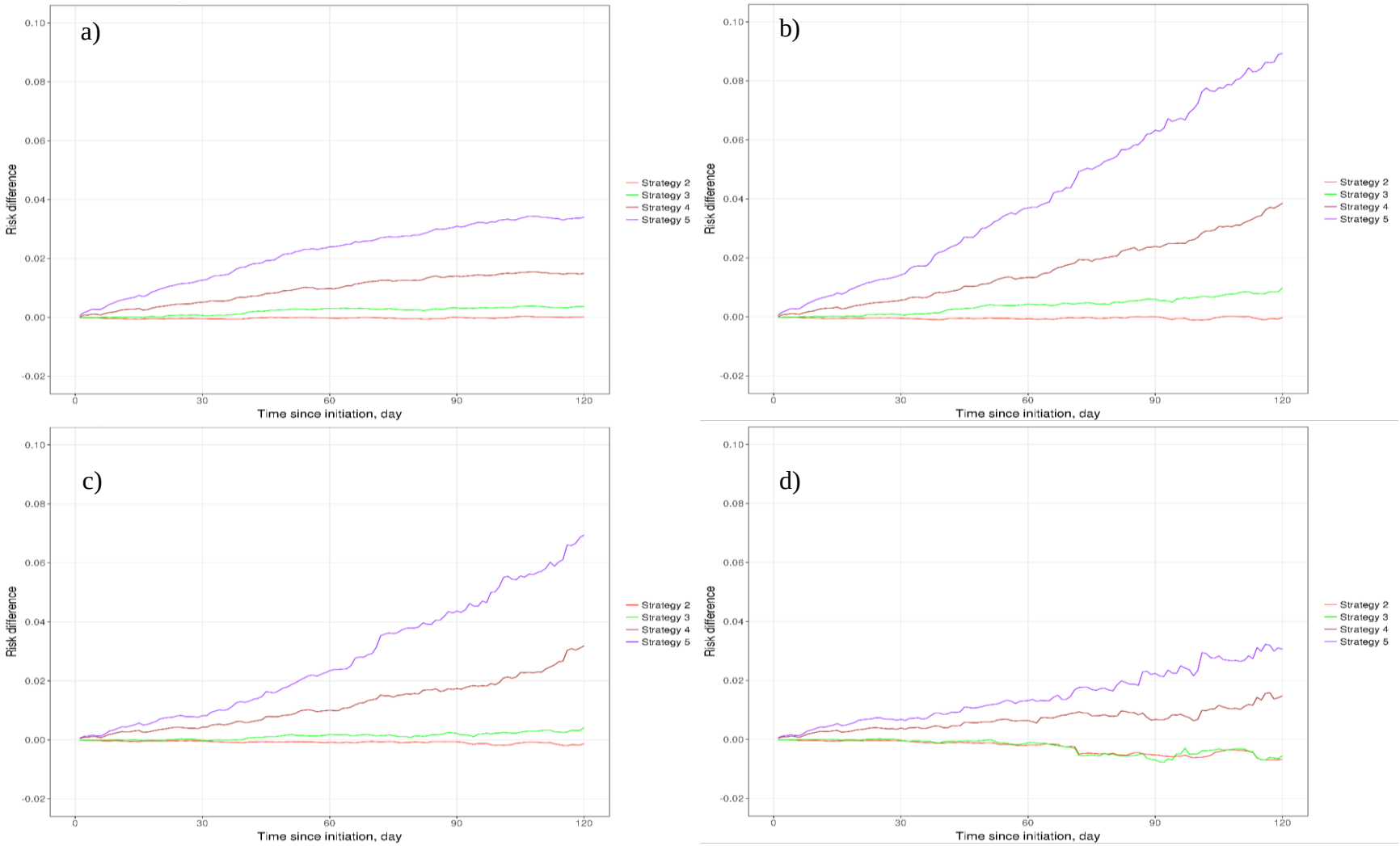
APPENDIX I: SENSITIVITY ANALYSIS VARYING MODELS FOR DEVIATION – INFECTION-RELATED EVENTS

Figure I.1: 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



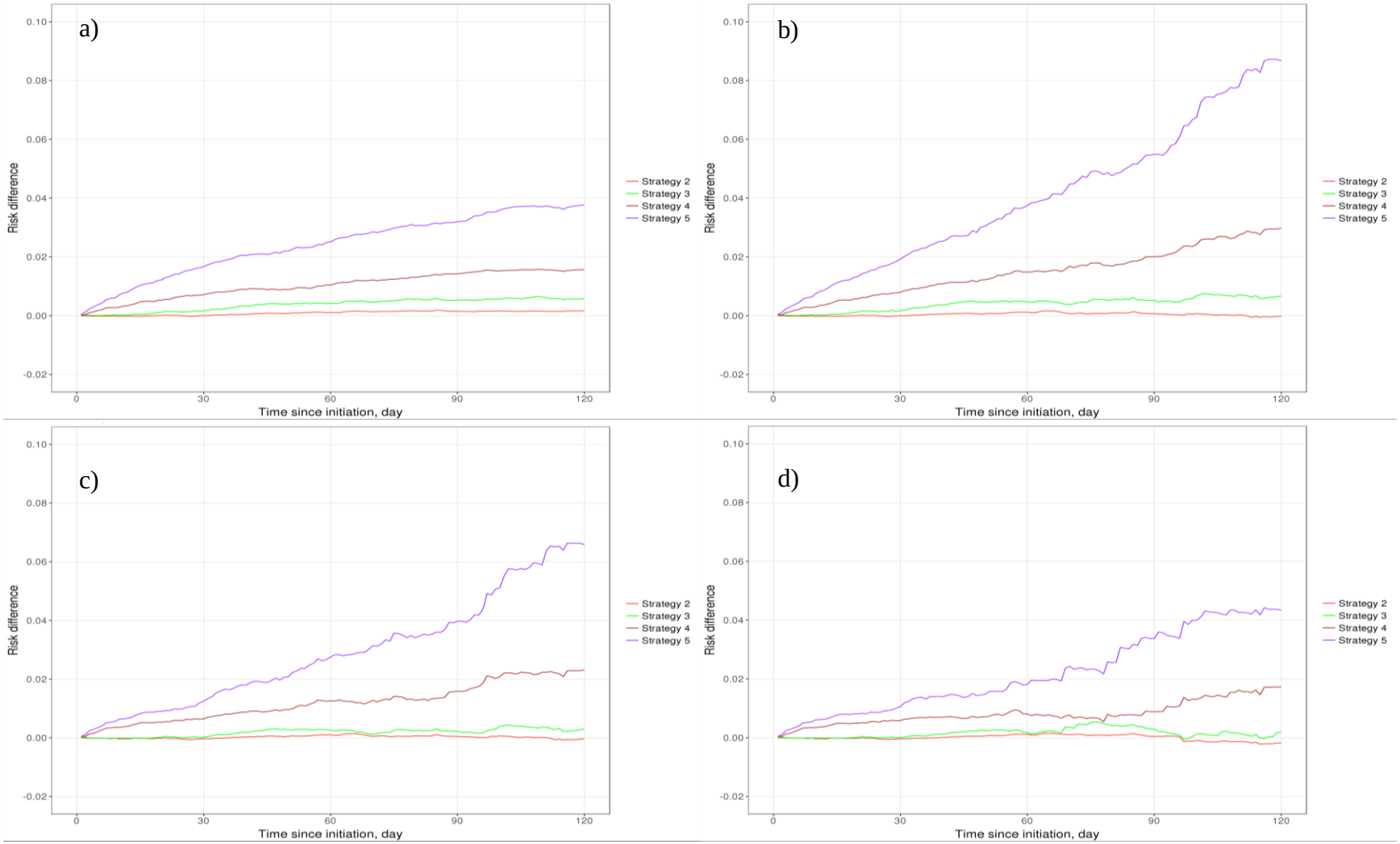
APPENDIX J: FOUR DIFFERENT ESTIMATION MODELS – ALL-CAUSE MORTALITY

Figure J.1: Cumulative risk difference curves for all-cause mortality varying estimation models (a) crude-intention-to-treat; (b) crude-as treated; (c) SMRW-as treated; (d) SMRW-IPCW



APPENDIX K: FOUR DIFFERENT ESTIMATION MODELS – INFECTION-RELATED EVENTS

Figure K.1: Cumulative risk difference curves for infection-related events varying estimation models (a) crude-intention-to-treat; (b) crude-as treated; (c) SMRW-as treated; (d) SMRW-IPCW



REFERENCES

1. Eschbach JW, Adamson JW. Anemia of end-stage renal disease. Kidney Int. 1985;28:1–5.

2. Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. J Am Soc Nephrol. 2001;12:2465–2473.

3. Gaweda AE, Ginzburg YZ, Chait Y, et al. Iron dosing in kidney disease: inconsistency of evidence and clinical practice. Nephrol Dial Transplant. 2015;30:187–196.

4. Macdougall IC, Bircher AJ, Eckardt K, et al. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2016;89:28–39.

5. Kapoian T, O'Mara NB, Singh AK, et al. Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin. J Am Soc Nephrol. 2008;19(2):372–379.

6. Coyne DW, Kapoian T, Suki W, et al. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. J Am Soc Nephrol. 2007;18(3):975–984.

7. Singh AK, Szczech L, Tang KL, et al; CHOIR Investigators: Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085–2098.

8. Drüeke TB, Locatelli F, Clyne N, et al; CREATE Investigators: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006;355:2071–2084.

9. Pfeffer MA, Burdmann EA, Chen CY, et al; TREAT Investigators: A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019–2032.

10. Centers for Medicare & Medicaid Services, HHS: Medicare Program; end-stage renal disease prospective payment system. Final rule. Fed Regist. 2010;75:49029–49214.

11. Freburger JK, Ng LJ, Bradbury BD, et al: Changing patterns of anemia management in US hemodialysis patients. Am J Med. 2012;125:906.e9–914.e9.

12. Miskulin DC, Zhou J, Tangri N, et al. Trends in anemia management in US hemodialysis patients 2004-2010. BMC Nephrology. 2013;14:264.

13. Kidney Disease: Improving Global Outcomes Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335.

14. Locatelli F, Bárány P, Covic A, et al. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrol Dial Transplant. 2013;28:1346–1359.

15. Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. Am J Kidney Dis. 2013;62:849–859.

16. Moist LM, Troyanov S, White CT, et al. Canadian Society of Nephrology commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. Am J Kidney Dis. 2013;62:860–873.

17. Fuller DS, Pisoni RL, Bieber BA, et al. The DOPPS practice monitor for U.S. dialysis care: update on trends in anemia management 2 years into the bundle. Am J Kidney Dis. 2013;62:1213–1216.

18. Karaboyas A, Zee J, Morgenstern H, et al. Understanding the recent increase in ferritin levels in United States dialysis patients: potential impact of changes in intravenous iron and erythropoiesis-stimulating agent dosing. Clin J Am Soc Nephrol. 2015;10:1814–1821.

19. Krishnan M, Weldon J, Wilson S, et al. Effect of Maintenance Iron Protocols on ESA Dosing and Anemia Outcomes [Abstract 153]. Am J Kidney Dis. 2011;57(4):A55.

20. Miskulin DC, Tangri N, Bandeen-Roche K, et al; Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network Patient Outcomes in End Stage Renal Disease Study Investigators: Intravenous iron exposure and mortality in hemodialysis patients. Clin J Am Soc Nephrol. 2014;9(11):1930–1939.

21. Implementing an IV iron administration protocol within a dialysis organization. http://www.nephrologynews.com/implementing-an-iv-iron-administration-protocol-within-a-dialysis-organization/. [Accessed 22 March 2015]

22. Kshirsagar AV, Freburger JK, Ellis AR, et al. The comparative short-term effectiveness of iron dosing and formulations in US hemodialysis patients. Am J Med. 2013;126(6): 541.

23. Kshirsagar AV, Freburger JK, Ellis AR, et al. Intravenous iron supplementation practices and short-term risk of cardiovascular events in hemodialysis patients. PLoS ONE. 2013;8(11):e78930.

24. Freburger JK, Ellis AR, Kshirsagar AV, et al. Comparative short-term safety of bolus versus maintenance iron dosing in hemodialysis patients: a replication study. BMC Nephrology. 2014;15:154.

25. Brookhart MA, Freburger JK, Ellis AR, et al. Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. J Am Soc Nephrol. 2013;24: 1151–1158.

26. Michels WM, Jaar BG, Ephraim PL, et al; DEcIDE Network Patient Outcomes in End Stage Renal Disease Study Investigators: Intravenous iron administration strategies and anemia management in hemodialysis patients. Nephrol Dial Transplant. 2016;0:1–9.

27. Tangri N, Miskulin DC, Zhou J, et al. Effect of intravenous iron use on hospitalizations in patients undergoing hemodialysis: a comparative effectiveness analysis from the DEcIDE-ESRD study. Nephrol Dial Transplant. 2015;30(4):667–675.

28. Brookhart MA, Li X, Kshirsagar AV. What are the considerations in balancing benefits and risks in Iron treatment? Semin Dial. 2016;30:25–27.

29. U.S. Renal Data System, USRDS 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014.

30. U.S. Renal Data System, USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009.

31. U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.

32. Brugnara C, Eckardt KU. Hematologic aspects of kidney disease. In: Taal MW, ed. Brenner and Rector's The Kidney. 9th ed. Philadelphia: Saunders; 2011:2081–2120.

33. Iron deficiency anemia: assessment, prevention, and control. A guide for programme managers. Geneva, World Health Organization, 2001 (WHO/NHD/01.3).

34. Primer on Kidney Diseases Sixth edition. National Kidney Foundation. Gilbert SJ, Weiner DE, Gipson DS, Perazella mA, & Tonelli M. (Eds). Philadelphia, PA: Elsevier Saunders; 2013.

35. Farag YM, Keithi-Reddy Sr, Mittal BV, et al. Anemia, inflammation and health-related quality of life in chronic kidney disease patients. Clin Nephrol. 2011;75(6):524–533.

36. Levin A, Singer J, Thompson CR, et al. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. Am J Kidney Dis. 1996;27(3):347–354.

37. Foley RN, Parfrey PS, Harnett JD, et al. The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. Am J Kidney Dis. 1996;28(1):53–61.

38. Besarab A, Coyne DW. Iron supplementation to treat anemia in patients with chronic kidney disease. Nat Rev Nephrol. 2010;6:699–710.

39. Weiss G, Gordeuk VR. Benefits and risks of iron therapy for chronic anaemias. Eur J Clin Invest. 2005;35[Suppl 3]:36–45.

40. Kalantar-Zadeh K, Rodriguez RA, Humphreys MH. Association between serum ferritin and measures of inflammation, nutrition and iron in haemodialysis patients. Nephrol Dial Transplant. 2004;19:141–149.

41. KDOQI; National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis. 2006;47(5 Suppl 3):S11–S145.

42. Wish JB. Assessing iron status: Beyond serum ferritin and transferrin saturation. Clin J Am Soc. Nephrol 2006;1[Suppl]:S4–S8.

43. Cavill I, Macdougall IC. Erythropoiesis and iron supply in patients treated with erythropoietin. Erythropoiesis. 1992;3:50–55.

44. Gaweda AE, Ginzburg YZ, Chait Y, et al. Iron dosing in kidney disease: inconsistency of evidence and clinical practice. Nephrol Dial Transplant 2015;30;187–196.

45. Sargent JA, Acchiardo SR. Iron requirements in hemodialysis. Blood Purif. 2004; 22:112–123.

46. Horl WH. Clinical aspects of iron use in the anemia of kidney disease. J Am Soc Nephrol. 2007;18:382–393.

47. Eschbach JW, Cook JD, Scribner BH, et al. Iron balance in hemodialysis patients. Ann Int Med. 1977;87:710–713.

48. Eschbach JW, Cook JD, Finch CA. Iron absorption in chronic renal disease. Clin Sci. 1970;38:191–201.

49. Al-Mueilo SH. Gastroduodenal lesions and Helicobacter pylori infection in hemodialysis patients. Saudi Med J. 2004;25:1010–1014.

50. Hershko C, Skikne B. Pathogenesis and management of iron deficiency anemia: emerging role of celiac disease, Helicobacter pylori, and autoimmune gastritis. Semin. Hematol. 2009;46:339–350.

51. Eschbach JW, Egrie JC, Downing MR, et al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med. 1987;316:73–78.

52. Szczech LA, Barnhart HX, Inrig JK, et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. Kidney Int. 2008;74:791–798.

53. Provenzano R, Schiller B, Rao M, et al. Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. Clin J Am Soc Nephrol. 2009;4:386–393.

54. Rozen-Zvi B, Gafter-Gvili A, Paul M, et al. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: Systematic review and meta analysis. Am J Kidney Dis. 2008;52:897–906.

55. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584–590.

56. Epogen Package Insert Revised April 2009. http://www.epogen.com/pdf/epogen_pi.pdf. [Accessed February 10, 2014]

57. US Food and Drug Administration. FDA public health advisory: erythropoiesis-stimulating agents (ESAs). http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103234s5122lbl.pdf. [Accessed February 10, 2014]

58. Ibrahim HN, Foley RN, Zhang R, et al. Parenteral iron use: possible contribution to exceeding target hemoglobin in hemodialysis patients. Clin J Am Soc Nephrol. 2009;4(3):623–629.

59. St Peter WL, Obrador GT, Roberts TL, et al. Trends in intravenous iron use among dialysis patients in the United States (1994-2002). Am J Kidney Dis. 2005;46(4):650–660.

60. Kliger AS, Fishbane S, Finkelstein FO. Erythropoietic Stimulating Agents and Quality of a Patient's Life: Individualizing Anemia Treatment. Clin J Am Soc Nephrol. 2012;7(2):354–357.

61. Tanhehco YC, Berns JS. Red blood cell transfusion risks in patients with end-stage renal disease. Semin Dial. 2012;25(5);539–544.

62. Reading FC, Brecher ME. Transfusion-related bacterial sepsis. Curr Opin Hematol. 2001;8:380–386.

63. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. Anesth Analg. 2009;108:759–769.

64. Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease: results of a phase III multicenter clinical trial. Ann Intern Med. 1989;111:992–1000.

65. Macdougall IC. Novel erythropoiesis stimulating protein. Semin Nephrol. 2000;20(4):375–381.

66. Tong EM, Nissenson AR. Erythropoietin and anemia. Semin Nephrol. 2001;21(2):190–203.

67. Epogen. http://www.epogen.com/patient/about-epogen/what-is-epogen.html [Accessed February 20, 2014]

68. United States Food and Drug Administration**.** Epogen® (epoetin alfa) injection, for intravenous or subcutaneous use. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103234Orig1s5166_103234Orig1s5266lbl.pdf [Accessed February 20, 2014]

69. United States Food and Drug Administration**.** Aranesp® (darbepoetin alfa) injection, for intravenous or subcutaneous use. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103951Orig1s5173_103951Orig1s5258lbl.pdf [Accessed February 20, 2014]

70. United States Food and Drug Administration**.** Mircera® (methoxy polyethylene glycol-epoetin Beta) injection. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125164toc.cfm [Accessed February 20, 2014]

71. Besarab A, Reyes CM, Hornberger J. Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. Am J Kidney Dis. 2002;40:439–446.

72. Centers for Medicare and Medicaid Services, Kinney R. 2005 Annual Report: ESRD Clinical Performance Measures Project. Am J Kidney Dis. 2006;48:S1–106.

73. Pisoni RL. Erythropoietin therapy in Europe: Results from the DOPPS. Contrib Nephrol. 2002;137:396–402.

74. Macdougall IC, Roberts DE, Coles GA, et al**.** Clinical pharmacokinetics of epoetin (recombinant human erythropoietin). Clin Pharmacokinet. 1991;20(2):99–113.

75. Macdougall IC, Padhi D, Jang G. Pharmacology of darbepoetin alfa. Nephrol Dial Transplant. 2007;22 Suppl 4:iv2-iv9.

76. Brookhart MA, Schneeweiss S, Avorn J, et al**.** Comparative mortality risk of anemia management practices in incident hemodialysis patients. JAMA. 2010;303(9):857–864.

77. Obrador GT, Roberts T, St Peter WL, et al. Trends in anemia at initiation of dialysis in the United States. Kidney Int. 2001;60:1875–1884.

78. Hariharan S, Yang H. Introduction. Am J Kidney Dis. 2006; 47(4 Suppl 2):S1.

79. Harnett JD, Kent GM, Foley RN, et al. Cardiac function and hematocrit level. Am J Kidney Dis. 1995;25:S3–7.

80. Zehnder C, Zuber M, Sulzer M, et al. Influence of long-term amelioration of anemia and blood pressure control on left ventricular hypertrophy in hemodialyzed patients. Nephron 1992;61:21–25.

81. Benz RL, Pressman MR, Hovick ET, et al. A preliminary study of the effects of correction of anemia with recombinant human erythropoietin therapy on sleep, sleep disorders, and daytime sleepiness in hemodialysis patients (The SLEEPO study). Am J Kidney Dis. 1999;34:1089–1095.

82. Pickett JL, Theberge DC, Brown WS, et al. Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis. 1999;33:1122–1130.

83. Nissenson AR, Swan SK, Lindberg JS, et al. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. Am J Kidney Dis. 2002;40:110–118.

84. Vanrenterghem Y, Bárány P, Mann JF, et al. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. Kidney Int. 2002;62:2167–2175.

85. Tolman C, Richardson D, Bartlett C, Will E. Structured conversion from thrice weekly to weekly erythropoietic regimens using a computerized decision-support system: a randomized clinical study. J Am Soc Nephrol. 2005;16:1463–1470.

86. Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. J Am Soc Nephrol. 1999;10:610–619.

87. Xia H, Ebben J, Ma JZ, Collins AJ. Hematocrit levels and hospitalization risks in hemodialysis patients. J Am Soc Nephrol. 1999;10:1309–1316.

88. Ofsthun N, Labrecque J, Lacson E, et al. The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients. Kidney Int. 2003;63:1908–1914.

89. Li S, Collins AJ. Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients. Kidney Int. 2004;65:626–633.

90. Li S, Foley RN, Collins AJ. Anemia, hospitalization, and mortality in patients receiving peritoneal dialysis in the United States. Kidney Int. 2004; 65:1864–1969.

91. Locatelli F, Pisoni RL, Combe C, et al. Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2004;19:121–132.

92. Pisoni RL, Bragg-Gresham JL, Young EW, et al. Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2004;44:94–111.

93. Lu WX, Jones-Burton C, Zhan M, et al. Survival benefit of recombinant human erythropoietin administration prior to onset of end-stage renal disease: variations across surrogates for quality of care and time. Nephron Clin Pract. 2005;101:c79–c86.

94. Robinson BM, Joffe MM, Berns JS, et al. Anemia and mortality in hemodialysis patients: accounting for morbidity and treatment variables updated over time. Kidney Int. 2005;68:2323–2330.

95. Wolfe RA, Hulbert-Shearon TE, Ashby VB, et al. Improvements in dialysis patient mortality are associated with improvements in urea reduction ratio and hematocrit, 1999 to 2002. Am J Kidney Dis. 2005;45:127–135.

96. Regidor DL, Kopple JD, Kovesdy CP, et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol. 2006;17:1181–1191.

97. Gilbertson DT, Ebben JP, Foley RN, et al. Hemoglobin level variability: associations with mortality. Clin J Am Soc Nephrol. 2008;3:133–138.

98. Messana JM, Chuang CC, Turenne M, et al. Association of quarterly average achieved hematocrit with mortality in dialysis patients: a time-dependent comorbidity-adjusted model. Am J Kidney Dis. 2009;53:503–512.

99. Strippoli GF, Craig JC, Manno C, Schena FP. Hemoglobin targets for the anemia of chronic kidney disease: a meta-analysis of randomized, controlled trials. J Am Soc Nephrol. 2004;15:3154–3165.

100. Volkova N, Arab L. Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. Am J Kidney Dis. 2006;47:24–36.

101. Parfrey PS. Target hemoglobin level for EPO therapy in CKD. Am J Kidney Dis. 2006; 47:171.

102. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 2007;369:381–388.

103. Clement FM, Klarenbach S, Tonelli M, et al. The impact of selecting a high hemoglobin target level on health-related quality of life for patients with chronic kidney disease: a systematic review and meta-analysis. Arch Intern Med. 2009;169:1104–1112.

104. Palmer SC, Navaneethan SD, Craig JC, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. Ann Intern Med. 2010;153:23–33.

105. Johansen KL, Finkelstein FO, Revicki DA, et al. Systematic review and meta-analysis of exercise tolerance and physical functioning in dialysis patients treated with erythropoiesis-stimulating agents. Am J Kidney Dis. 2010;55:535–548.

106. Gandra SR, Finkelstein FO, Bennett AV, et al. Impact of erythropoiesis-stimulating agents on energy and physical function in nondialysis CKD patients with anemia: a systematic review. Am J Kidney Dis. 2010;55:519–534.

107. Lewis EF, Pfeffer MA, Feng A, et al. Darbepoetin alfa impact on health status in diabetes patients with kidney disease: a randomized trial. Clin J Am Soc Nephrol 2011;6:845–855.

108. The rise and fall of a billion-dollar drug. Washingpost. http://www.washingtonpost.com/wp-srv/business/amgen-anemia-drugs/index.html. [Accessed May 17, 2015]

109. KDOQI. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis. 2007;50:471–530.

110. McFarlane PA, Pisoni RL, Eichleay MA, et al**.** International trends in erythropoietin use and hemoglobin levels in hemodialysis patients. Kidney Int. 2010;78(2):215–223.

111. Collins AJ. ESRD payment policy changes: the new "bundled" dialysis prospective payment system (PPS) in the United States, National Kidney Foundation Spring Clinical Meeting Presentation 2012; 2012.

112. Robinson BM, et al. The impact of bundling on clinical practice: Changes in practice pattern & laboratory values, National Kidney Foundation Spring Clinical Meeting Presentation 2012; 2012.

113. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. On the relative safety of parenteral iron formulations. Nephrol Dial Transplant. 2004;19(6):1571–1575.

114. Agarwal R, Vasavada N, Sachs NG, et al. Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease. Kidney Int. 2004;65:2279–2289.

115. Brewster UC. Intravenous iron therapy in end-stage renal disease. Semin Dial. 2006;19:285–290.

116. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int. 2002;62(5):1524–1538.

117. Maynor L, Brophy DF. Risk of infection with intravenous iron therapy. Ann Pharmacother 2007;41:1476–1480.

118. Duncan R, Gaspar R. Nanomedicine(s) under the microscope. Mol Pharm. 2011;8:2101–2141.

119. Charytan DM, Pai AB, Chan CT, et al. Considerations and challenges in defining optimal iron utilization in hemodialysis. J Am Soc Nephrol. 2015;26(6):1328–1347.

120. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine. JAMA 1980;243:1726–1731.

121. Rampton D, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. Haematologica 2014;99:1671–1676.

122. Michael B, Coyne DW, Fishbane S, et al; Ferrlecit Publication Committee: Sodium ferric gluconate complex in hemodialysis patients: Adverse reactions compared to placebo and iron dextran. Kidney Int. 2002;61:1830–1839.

123. Aronoff GR, Bennett WM, Blumenthal S, et al; United States Iron Sucrose (Venofer) Clinical Trials Group: Iron sucrose in hemodialysis patients: Safety of replacement and maintenance regimens. Kidney Int. 2004;66:1193–1198.

124. Moniem KA, Bhandari S. Tolerability and efficacy of parenteral iron therapy in haemodialysis patients: a comparison of preparations. Transfus Altern Transfus Med. 2007;1:1–7.

125. Sav T, Tokgoz B, Sipahioglu MH. Is there a difference between allergic potencies of the iron sucrose and low molecular weight iron dextran? Ren Fail. 2007;29:423–426.

126. Wysowski DK, Swartz L, Borders-Hemphill BV, et al. Use of parenteral iron products and serious anaphylactic-type reactions. Am J Hematol. 2010;85:650–654.

127. Vecchio LD, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. Clin Kidney J. 2016;9:260–267.

128. Wang C, Graham DJ, Kane RC, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. JAMA 2015;314:2062–2068.

129. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001833.jsp&mid=WC0b01ac058004d5c1 [Accessed 15 December 2016]

130. FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol). US Food and Drug Administration, Drug Safety Communications. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM440336.pdf. [Accessed 11 May 2015]

131. Bishu K, Agarwal R. Acute injury with intravenous iron and concerns regarding long-term safety. J Am Soc Nephrol. 2006;1 (Suppl 1):S19–S23.

132. Stadler N, Lindner RA, Davies MJ. Direct detection and quantification of transition metal ions in human atherosclerotic plaques: evidence for the presence of elevated levels of iron and copper. Arterioscler Thromb Vasc Biol 2004;24:949–954.

133. Zager RA, Johnson AC, Hanson SY, et al. Parenteral iron formulations: A comparative toxicologic analysis and mechanisms of cell injury. Am J Kidney Dis. 2002;40:90–103.

134. Toblli JE, Cao G, Oliveri L, et al. Assessment of the extent of oxidative stress induced by intravenous ferumoxytol, ferric carboxymaltose, iron sucrose and iron dextran in a nonclinical model. Arzneimittelforschung. 2011;61:399–410.

135. Lim CS, Vaziri ND. The effects of iron dextran on the oxidative stress in cardiovascular tissues of rats with chronic renal failure. Kidney Int. 2004;65:1802–1809.

136. Sullivan JL. Do hemochromatosis mutations protect against iron-mediated atherogenesis? Circ Cardiovasc Genet. 2009; 2:652–657.

137. Li JJ, Meng X, Si HP, et al. Hepcidin destabilizes atherosclerotic plaque via overactivating macrophages after erythrophagocytosis. Arterioscler Thromb Vasc Biol. 2012;32:1158–1166.

138. Kautz L, Gabayan V, Wang X, et al. Testing the iron hypothesis in a mouse model of atherosclerosis. Cell Rep. 2013;5:1436–1442.

139. Reis KA, Guz G, Ozdemir H, et al. Intravenous iron therapy as a possible risk factor for atherosclerosis in end-stage renal disease. Int Heart J. 2005;46:255–264.

140. Drueke T, Witko-Sarsat V, Massy Z, et al. Iron therapy, advanced oxidation protein products, and carotid artery intima-media thickness in end-stage renal disease. Circulation. 2002;106:2212–2217.

141. van derWeerd NC, Grooteman MP, Bots ML, et al. Hepcidin-25 is related to cardiovascular events in chronic haemodialysis patients. Nephrol Dial Transplant. 2013; 28:3062–3071.

142. Himmelfarb, J. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. Semin. Dial. 2009;22:636–643.

143. Susantitaphong P, Alqahtani F, Jaber BL. Efficacy and safety of intravenous iron therapy for functional iron deficiency anemia in hemodialysis patients: A meta-analysis. Am J Nephrol. 2014;39:130–141.

144. Kalantar-Zadeh K, Regidor DL, McAllister CJ, et al. Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol. 2005;16:3070–3080.

145. Bailie GR, Larkina M, Goodkin DA, et al. Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality. Kidney Int. 2015;87:162–168.

146. Kuo KL, Hung SC, Lin YP, et al. Intravenous ferric chloride hexahydrate supplementation induced endothelial dysfunction and increased cardiovascular risk among hemodialysis patients. PLoS ONE. 2012;7:e50295.

147. Feldman HI, Joffe M, Robinson B, et al. Administration of parenteral iron and mortality among hemodialysis patients. J Am Soc Nephrol. 2004;15:1623–1632.

148. Gupta A, Zhuo J, Zha J, et al. Effect of different intravenous iron preparations on lymphocyte intracellular reactive oxygen species generation and subpopulation survival. BMC Nephrol. 2010;11:16.

149. Parkkinen J, von Bonsdorff L, Peltonen S, et al. Catalytically active iron and bacterial growth in serum of haemodialysis patients after i.v. iron-saccharate administration. Nephrol Dial Transplant. 2000;15:1827–1834.

150. Barton PA, Pai MP, Depczynski J, et al. Non-transferrin bound iron is associated with enhanced Staphylococcus aureus growth in hemodialysis patients receiving intravenous iron sucrose. Am J Nephrol. 2006;26:304–309.

151. Anker SD. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361:2436–2448.

152. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int. 2015;88:905–914.

153. Macdougall IC, Bock AH, Carrera F, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. Nephrol Dial Transplant. 2014;29:2075–2084.

154. Fishbane S. Review of issues relating to iron and infection. Am J Kidney Dis. 1999;34(4 Suppl 2): S47–S52.

155. Besarab A, Frinak S, Yee J. An indistinct balance: the safety and efficacy of parenteral iron therapy. J Am Soc Nephrol 1999;10(9):2029–2043.

156. Eschbach JW, Adamson JW. Iron overload in renal faiure patients: changes since the introduction of erythropoietin therapy. Kidney Int Suppl. 1999;69:S35–S43.

157. Ishida JH, Johansen KL. Iron and infection in hemodialysis patients. Sem Dial. 2014;27(1):26–36.

158. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ. 2013;347:f4822.

159. Sirken G, Raja R, Rizkala AR. Association of different intravenous iron preparations with risk of bacteremia in maintenance hemodialysis patients. Clin Nephrol. 2006;66:348–356.

160. Diskin CJ, Stokes TJ, Dansby LM, et al. Is systemic heparin a risk factor for catheter-related sepsis in dialysis patients? An evaluation of various biofilm and traditional risk factors. Nephron Clin Pract. 2007;107:c128–c132.

161. Kuragano T, Matsumura O, Matsuda A, et al. Association between hemoglobin variability, serumferritin levels, and adverse events/mortality in maintenance hemodialysis patients. Kidney Int. 2014;86:845–854.

162. Zitt E, Sturm G, Kronenberg F, et al. Iron Supplementation and Mortality in Incident Dialysis Patients: An Observational Study. PLoS ONE. 2014;9(12):e114144.

163. Robins JM, Hernán M. Estimation of the causal effects of time varying exposures. In *Longitudinal Data Analysis*. Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G (eds). Chapman and Hall/CRC Press: New York, NY, 2008;553–599.

164. European AIDS Clinical Society. Guidelines: clinical management and treatment of HIV infected adults in Europe. 2009. http://www.europeanaidsclinicalsociety.org/guidelinespdf/1_Treatment_of_HIV_Infected_Adults.pdf [Accessed 17 November 2016]

165. World Health Organization. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. 2009. http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf [Accessed 17 November 2016]

166. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. 2008. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf [Accessed 17 November 2016]

167. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2016;39(Suppl 1):S1–S119.

168. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(Suppl 2):S1–S45.

169. Robins JM. Information recovery and bias adjustment in proportional hazards regression analysis of randomized trials using surrogate markers. In Proceedings of the Biopharmaceutical Section, American Statistical Association 24–33. American Statistical Association, Alexandria, VA. 1993.

170. Robins JM, Rotnitzky A, Zhao LP. Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. J Amer Statist Assoc. 1995;90:106–121.

171. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–560.

172. Satten GA, Datta S. The Kaplan-Meier estimator as an inverse-probability-of-censoring weighted average. Am Stat. 2001; 55(3): 207–210.

173. Hernán MA, Lanoy E, Costagliola D, Robins JM. Comparison of dynamic treatment regimes via inverse probability weighting. Basic Clin Pharmacol Toxicol. 2006;98:37–242.

174. van der Lann MJ, Petersen ML. Causal effect models for realistic individualized treatment and intention to treat rules. Int J Biostat. 2007;3(1):Article 3.

175. Robins J, Orellana L, Rotnitzky A. Estimation and extrapolation of optimal treatment and testing strategies. Stat Med. 2008;27:4678–4721.

176. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes, Part I: Main content. Int J Biostat. 2010;6:Article 8.

177. Cain LE, Robins JM, Lanoy E, et al. When to start treatment? A systematic approach to the com- parison of dynamic regimes using observational data. Int J Biostat. 2010;6(2):Article18.

178. Cain LE, Logan R, Robins JM, et al. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: An observational study. Ann Intern Med. 2010;154:509–515.

179. Cotton CA, Heagerty PJ. A data augmentation method for estimating the causal effect of adherence to treatment regimens targeting control of an intermediate measure. Stat Biosci. 2011;3:28–44.

180. Cotton CA, Heagerty PJ. Evaluating epoetin dosing strategies using observational longitudinal data. Ann Appl Stat. 2014;8(4);2356–2377.

181. Shortreed SM, Moodie EEM. Estimating the optimal dynamic antipsychotic treatment regime: Evidence from the sequential multiple-assignment randomized clinical antipsychotic trials of intervention and effectiveness schizophrenia study. J R Stat Soc Ser C Appl Stat. 2012;61:577–599.

182. Robins JM. A new approach to causal inference in mortality studies with a sustained exposure period: application to the healthy worker survivor effect. Mathematical Modelling. 1986;7:1393–1512. [Errata (1987) in Computers and Mathematics with Applications 14,917–921. Addendum (1987) in Computers and Mathematics with Applications 14,923–945. Errata 1987 to addendum in Computers and Mathematics with Applications 18,477.].

183. Robins JM, Hernán MA, Siebert U. Effects of multiple interventions. In: Ezzati, M.; Lopez, AD.; Rodgers, A.; Murray, CJL., editors. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. Geneva: World Health Organization; 2004.

184. Taubman SL, Robins JM, Mittleman MA, Hernán MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. Int J Epidemiol. 2009;38(6):1599–1611.

185. Young J, Cain L, Robins JM, et al. Comparative effectiveness of dynamic treatment regimes: An application of the parametric g-formula. Stat Biosci. 2011;3:119–143.

186. The Kidney Care Council. http://kidneycarecouncil.org/the-kidney-care-council-members-davita-inc/. [Accessed Feb 05, 2014]

187. Manley HJ, Drayer DK, McClaran M, Bend W, Muther RS. Drug record discrepancies in an outpatient electronic medical record: frequency, type, and potential impact on patient care at a hemodialysis center. Pharmacotherapy. 2003;23(2):231–9.

188. United States Renal Data Systems. 2014 Researcher's Guide to the USRDS Database. 2014. http://www.usrds.org/research.aspx [Accessed Feb 05, 2014]

189. Foley RN, Collins AJ. The USRDS: What you needed to know about what it can and can't tell us about ESRD. Clin J Am Soc Nephrol. 2013;8:845–851.

190. Vardi M, Yeh RW, Herzog CA, et al. Strategies for postmarketing surveillance of drugs and devices in patients with ESRD undergoing dialysis. Clin J Am Soc Nephrol. 2013;8:2213–2220.

191. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Assoc. 1958;53:457–481.

192. Cole SR, Hernán MA. Constructing Inverse Probability Weights for Marginal Structural Models. Am J Epidemiol. 2008;168(6):656–664.

193. Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed. 2004;75(1):45–49.

194. Young JG, Tchetgen Tchetgen EJ. Simulating from a known Cox MSM using standard parametric models for the g-formula. Stat in Med. 2014;33:1001–1014.

195. Murphy SA. An experimental design for the development of adaptive treatment strategies. Stat Med 2005;24(10):1455–1481.

196. Lavori PW, Dawson R. Dynamic treatment regimes: practical design considerations. Clin Trials 2004;1(1):9–20.

197. Besarab A, Kaiser JW, Frinak S. A study of parenteral iron regimens in hemodialysis patients. Am J Kidney Dis. 1999;34(1):21–28.

198. Murphy SA, van der Laan MJ, Robins JM; CPPRG. Marginal mean models for dynamic regimes. J Am Stat Assoc. 2001;96(456):1410–1423.

199. Krishnan M, Wilfehrt HM, Lacson E, Jr. In data we trust: the role and utility of dialysis provider databases in the policy process. Clin J Am Soc Nephrol. 2012;7(11):1891–1896.

200. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2016.

201. Breiman L, Friedman JH, Stone CJ, et al. Classification and Regression Trees. CRC Press, 1984.

202. Breiman L. Random forests. Mach Learn. 2001;45:5–32.

203. Brookhart MA. Counterpoint: the treatment decision design. Am J Epidemiol. 2015;182(10):840–845.

204. U.S. DOPPS Practice Pattern Monitor, August 2014. http://www.dopps.org/DPM [Accessed 19 November 2014]