SUPPLEMENTARY MATERIALS

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I. Supplementary Text: Detailed Methods

Data Sources

Data were from Medicare final action claims for the time period 2001-2012 (dialysis population) and 2004-2012 (non-ESRD population). Final action claims submitted for reimbursement include *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis codes, ICD-9 procedure codes, Diagnosis Related Groups (DRGs), dates of service, and beneficiary demographic details.

Non-ESRD Medicare Study Population and Design

We used an open cohort study of Medicare beneficiaries not on dialysis from January 1, 2005 through December 31, 2012, similar to what was done in the dialysis population. Individuals were included on the first day of the study period (January 1, 2005) and on a rolling basis at any point during each calendar year; the index date was defined as the first day of the month subsequent to the date on which they meet all the inclusion criteria: age at least 65 years and Medicare as their primary payer (Parts A and B) for at least six months.

Follow-up

Follow-up of the general Medicare not on dialysis population began on the index date and continued until the first occurrence of the following censoring events: (1) death or (2) loss of Medicare as primary payer. Administrative censoring occurred for all remaining eligible patients on December 31 2012.

Outcomes

Six primary outcomes (all-cause mortality, cardiovascular mortality, stroke, myocardial infarction (MI), and a cardiovascular composite ([first of death, stroke or MI], and red blood cell transfusion) and two secondary outcomes (heart failure and venous thromboembolism) were examined. The algorithms used to define outcomes are presented in **Supplementary Table S2**. The date of the hospital admission associated with each outcome was used to define the date of the outcome event. It is not uncommon for claims related to hospitalization events that bridge two calendar years (admission date in one year and discharge date in the subsequent) appear in the subsequent years' data. For example, approximately 20% of claims for hospitalization admissions that occur in December appear in subsequent year's data file. This under-reporting of claims could result in an underestimation of event rates in the preceding year. To minimize this, we included in our assessment of outcomes in each calendar year claims from the subsequent year. This was especially important in calendar year 2012, the last year in our study period.

Baseline Characteristics

Dialysis population

Baseline characteristics include age (18-44, 45-64, 65-74, 75-84, and ≥ 85 years), race (white, black, other), ethnicity (Hispanic/non-Hispanic), sex, ESRD primary cause (diabetes, hypertension, glomerulonephritis, other), modality (in-center hemodialysis, peritoneal dialysis), dialysis vintage (< 2, 2-< 5, ≥ 5 years), body mass index (< 18.5, 18.5-< 25.0, 25.0-30.0, > 30.0 kg/m^2), and comorbid conditions. All information except

modality and comorbid conditions was derived from the ESRD Medical Evidence Report. Modality was defined from dialysis claims. Age, vintage, and modality were defined for each cohort year on January 1 of the year or on the index date during the year. Comorbid conditions were defined during the baseline period for each calendar year using the diagnosis codes listed in **Supplementary Table S1**.

The baseline period was defined as the time from January 1 of the given calendar year (or from the index date) back to the earliest time Medicare claims data were available for that patient, or January 1, 2001. This approach enabled use of all available covariate information in defining comorbidity from claims and ensured that each patient had at least six months of claims history preceding his/her index date. We defined each comorbid condition using a multiple category variable that integrated both the timing and source of the claims information as follows: i) identified in the inpatient setting within six months of the index date, ii) identified in the outpatient setting within six months of the index date, iii) identified in the inpatient setting more than six months before the index date, iv) identified in the outpatient setting more than six months before the index date, v) identified on the ESRD Medical Evidence Form, which is completed at initiation of chronic dialysis, or vi) no evidence of the comorbidity within the claims history. If we identified claims for a comorbid condition in both the inpatient and outpatient setting within a given time period, we categorized the comorbid condition based on inpatient setting. Before 2010, there were nine fields available for identifying comorbid conditions based on Medicare claims; starting in 2010 the number of fields increased to 25, thereby increasing the probability of identifying patients with potential comorbid conditions. To

maintain consistency in the assessment of comorbidities over the study period, we only used the first nine claims for all years.

We defined the yearly percent of national influenza-like illness (ILI) outpatient visits using data downloaded from Centers for Disease Control and Prevention (http://www.cdc.gov/flu/weekly, accessed 11/10/2014). We averaged the weekly ILI percent to yearly ILI percent for each year. Because geographic variation exists for most of clinical events among ESRD patients, geographic area was considered in analyses. The geographic areas were defined as the ESRD Network based on patients' dialysis facilities.

Non-ESRD Medicare Population

Baseline characteristics include age (65-74, 75-84, and ≥ 85 years), sex, race (white, black, and other), ethnicity (Hispanic/non-Hispanic), and the equivalent set of co-morbid conditions that were evaluated in the dialysis population. All of these characteristics were defined during the six-month baseline period preceding the index date for individuals in each calendar year.

Statistical Analyses

We used descriptive statistics to characterize patients contributing patient-time to each calendar year. Anemia management parameters were described quarterly to allow for assessment of changes throughout the calendar year (dialysis population only). We calculated rates for all of our primary and secondary events as the total number of events

divided by the total follow-up time at risk during the calendar year of interest and expressed as per 100 patient-years. The 95% confidence interval (CI) was estimated using the Poisson distribution.

To account for secular trends in risks and benefits of anemia treatment with epoetin alfa, we used mixed-effects Poisson regression models with year as a random effect to fit a log linear trend line (a linear function of year) from 2005 through 2010, with adjustment for patient baseline characteristics. Specifically,

$$y \sim Poisson(\mu)$$

$$\log(\mu) = \log(t) + year \cdot \beta_1 + x \cdot \beta_2 + YEAR \cdot \gamma$$

$$\gamma \sim N(0, \sigma^2)$$

Where, *y* is number of events; *t* is the follow-up time; *year* is the continuous calendar year and β_1 is the yearly slope; *x* is the patient baseline characteristic vector and β_1 is the effect vector of *x*; *YEAR* is the categorical calendar year and treated as a random effect in the model, γ is the *YEAR* effect and following a normal distribution. We applied the resulting models to patients in 2011 and 2012 separately to calculate predicted rates in 2011 and 2012 and used bootstrapping to calculate confidence intervals around the predicted rates and the differences and ratios between observed and predicted rates for 2011 and 2012. The random *YEAR* in the model allowed a similar variation from the trend line in years 2005-2010 for the observed/expected comparison in 2011 and 2012. This analysis was done for all eight outcomes. Typically, 1,000 iterations are used when generating confidence intervals using bootstrapping, but owing to the large sample size (>200,000 patients per year) and the number of primary and secondary outcome events

under investigation, such an approach would require months of processing time. We chose 600 iterations after conducting an analysis comparing the widths of the confidence intervals based on bootstrapping using 200, 400, 600, 800, 1200, 1400 and 1600 iterations. The 95% CI's stabilized at 600 iterations.

II. Supplementary Table S1. International Classification of Diseases, Ninth Revision, Clinical Modification codes used to identify patient clinical characteristics

Characteristic	Code
Arrhythmia	427.9, 427.60, 426.x, 427.4, 37.94, 00.51
Atrial fibrillation	427.31, 427.3
Coronary artery disease/atherosclerosis	414.0x, 429.2x, 429.5x, 429.7x, 440.x, 412-414, 36.1x, 36.06, 36.07, 36.01, 36.02, 36.05, 0.66,
Cancer	140-172, 174-208, 230-231, 233
Cardiomyopathy	674.5, 425.x
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4x-425.9x, 428.x
Chronic obstructive pulmonary disease	491.x, 492.x, 494.x, 496.x, 510.x,
Cardiovascular disease	390.x-434.x, 436.x-448.x, 435
Diabetes	250.x, 357.2, 362.0x, 366.41
Gastrointestinal bleeding	531.x-534, 456.0-456.2, 530.7, 569.84, 569.85, 578
Hyperlipidemia/dyslipidemia	272.x
Hypertension	401.x-405.x, 437.2, 362.11
Left ventricular hypertrophy	402, 404, 425.1
Liver disease	571.x, 570, 572.1, 572.4, 573.1-573.3, V42.7
Myocardial infarction/acute coronary syndrome	410.x, 411.x
Pulmonary hypertension	416.0, 416.8
Peripheral vascular disease	440.20-440.24, 440.29, 440.30-440.32, 443.81, 443.9, 440.x-444.x, 447.x, 451.x-453.x, 557.x
Stroke	434.91,434.11,430, 431, 432.0-432.9,434.01, 433, 436, 437, 438
Transient ischemic attack	435.X
Valvular disease	394.x-397.x, 424.x, V43.3, 35.x
Other Cardiac	429.0, 429.1, 429.3, 429.6, 429.8, 429.9, 420-421, 423, 785.0-785.3, V42.2, V43.3

III. Supplementary Table S2. Codes and algorithms used to identify outcomes

Outcome	Code	Source and/or Algorithm	Sensitivity Analysis
All-cause death		Death and date of death derived from ESRD Death Notification	
Cardiovascular death	Cause of death code from form CMS-2746*: 23, 25, 26, 27, 28, 29, 30, 31, 32	Derived from the ESRD Death Notification	
Stroke	ICD-9-CM codes: 430, 431, 433.x1, 434 (excluding 434.x0), 436	Diagnosis code appears in any diagnosis field of an inpatient claim	*Sensitivity analysis 1*: Use only the first 3 diagnosis fields in inpatient claims *Sensitivity analysis 2*: Include CPT codes 70551, 70552, 70460, and 70450 in the same claim
Myocardial infarction	ICD-9-CM code 410	Diagnosis code appears in any diagnosis field of an inpatient claim	*Sensitivity analysis 1*: Use only the first 3 diagnosis fields in inpatient claims *Sensitivity analysis 2*: Require at least 3 hospital days and only diagnosis codes 410.x1
Composite endpoint†		Any event of death, myocardial infarction, or stroke	
Transfusion	1. ICD-9-CM procedure codes: 99.03-99.04 2. Value code: 37 3. HCPCS codes: P9010, P9011, P9016, P9021, P9022, P9038, P9039, and P9040 4. CPT code: 36430	Need one ICD-9-CM procedure code or value code in the inpatient and outpatient setting or a HCPCS code or CPT code from Part B physician/supplier claims. We can accurately capture the date of outpatient transfusions, but not the units transfused; thus we can count one transfusion event per day. We cannot always capture the date of inpatient transfusions, or the units transfused; thus only one transfusion event will be attributed during an inpatient stay.	
Heart failure	ICD-9-CM diagnosis code 428	Primary diagnosis code from claims for hospitalization, ER visit, or hospital observation stay	
Venous thromboembolism	ICD-9 diagnosis codes 415.x, 451.x, and 453.x	Diagnosis code appears in any diagnosis field from claims in the inpatient or outpatient setting	

*Centers for Medicare & Medicaid Death Notification.

†Composite endpoint describes rates of all-cause death, stroke, and myocardial infarction.

CPT, Current Procedural Terminology; ESRD, end-stage renal disease; HCPCS, Healthcare Common Procedure Coding System; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification.

IV. Supplementary Table S3. Trends in all baseline characteristics among patients on dialysis, 2005-2012

Variable	2005	2006	2007	2008	2009	2010	2011	2012
n	235,883	238,052	241,437	248,198	251,805	263,500	275,527	285,433
Dialysis modality, %								
In-center hemodialysis	92.2	92.3	92.7	92.8	92.9	92.8	92.5	92.0
Peritoneal dialysis	7.8	7.7	7.3	7.2	7.1	7.2	7.5	8.0
Mean age, yrs.	62.2	62.2	62.2	62.2	62.1	62.2	62.3	62.3
Mean age group, yrs.								
18-44	14.7	14.5	14.3	14.2	14.1	13.8	13.5	13.4
45-64	37.6	38.4	38.9	39.5	40.1	40.5	40.8	41.2
65-74	24.7	24.3	24.2	24.1	23.9	23.8	23.8	23.9
75-84	18.8	18.4	18.0	17.5	17.0	16.8	16.7	16.4
≥ 85	4.2	4.4	4.6	4.8	4.9	5.0	5.1	5.1
Mean dialysis duration, yrs	4.3	4.3	4.4	4.5	4.6	4.7	4.8	4.9
Mean dialysis duration group, yrs.								
< 2	37.7	36.9	36.3	35.3	34.1	33.5	33.0	32.1
2-< 5	34.7	34.8	34.6	34.7	35.0	34.8	34.4	34.4
≥ 5	27.6	28.3	29.1	29.9	30.9	31.7	32.5	33.6
Sex, %								
Female	46.7	46.4	46.2	45.9	45.8	45.8	45.7	45.7
Male	53.3	53.6	53.8	54.1	54.2	54.2	54.3	54.3
Race, %								
White	43.2	42.4	42.1	41.7	41.2	40.8	40.6	40.2
Black	38.2	38.7	38.7	38.6	38.6	38.8	38.8	38.6
Other	18.6	18.9	19.2	19.7	20.2	20.4	20.7	21.2
Ethnicity, %								
Hispanic	13.6	13.8	14.0	14.4	14.7	14.8	14.9	15.1
Non-Hispanic	86.4	86.2	86.0	85.6	85.3	85.2	85.1	84.9
ESRD cause, %								
Diabetes	43.1	43.4	43.7	43.9	44.1	44.3	44.3	44.4
Hypertension	29.2	29.2	29.1	29.1	29.0	29.2	29.4	29.5
Glomerulonephritis	11.7	11.3	11.0	10.7	10.4	10.1	9.8	9.7
Other	16.0	16.1	16.3	16.4	16.4	16.4	16.5	16.4
Mean BMI, kg/m^2	28.0	28.3	28.6	28.9	29.1	29.4	29.6	29.7
Mean BMI group, kg/m^2								
< 18.5	4.0	3.8	3.6	3.4	3.2	3.1	3.0	2.8
18.5-< 25	31.8	31.2	30.5	29.8	29.1	28.3	27.6	26.9
25-< 30	26.4	26.8	27.1	27.3	27.3	27.3	27.1	27.1
≥ 30	29.4	31.3	33.1	34.6	36.0	37.4	38.6	39.6
Missing	8.4	6.9	5.7	4.9	4.4	4.0	3.7	3.6
Renal Network, %								
Network 1	3.5	3.5	3.3	3.4	3.4	3.3	3.2	3.3
Network 2	6.0	5.9	5.7	5.6	5.5	5.0	5.3	5.4
Network 3	4.4	4.3	4.3	4.3	4.3	4.2	4.0	4.0
Network 4	4.3	4.1	4.1	4.0	3.9	3.9	3.9	3.9

Network 5	6.3	6.1	6.0	6.0	6.1	6.1	6.1	6.0
Network 6	11.0	11.2	11.3	11.1	11.0	11.1	11.0	10.9
Network 7	6.0	5.9	6.0	6.0	6.1	6.2	6.2	6.1
Network 8	6.0	6.3	6.4	6.4	6.3	6.3	6.4	6.3
Network 9	7.3	7.5	7.6	7.5	7.5	7.4	7.2	7.1
Network 10	4.0	4.1	4.1	4.2	4.1	4.1	4.2	4.2
Network 11	6.4	6.1	5.9	5.8	5.6	5.9	5.8	5.9
Network 12	4.0	4.0	3.9	3.9	3.8	3.8	3.8	3.8
Network 13	4.4	4.5	4.5	4.5	4.6	4.5	4.5	4.4
Network 14	9.9	10.1	10.3	10.5	10.6	10.7	10.8	10.7
Network 15	4.1	3.9	3.9	4.0	4.1	4.1	4.2	4.3
Network 16	2.4	2.5	2.5	2.5	2.6	2.6	2.7	2.7
Network 17	4.0	4.1	4.1	4.1	4.3	4.3	4.3	4.4
Network 18	5.9	6.1	6.1	6.2	6.3	6.4	6.5	6.6
Arrhythmia, %								
No	67.9	66.9	66.1	65.2	64.5	63.9	63.3	62.9
IP within 6 mo.	4.1	4.1	4.0	4.0	4.0	4.0	3.9	3.8
OP within 6 mo.	7.4	7.5	7.4	7.7	7.7	8.2	8.0	7.5
IP historical	9.8	10.1	10.6	10.8	11.0	11.0	11.2	11.5
OP historical	10.9	11.4	11.9	12.3	12.8	13.0	13.6	14.3
Atrial fibrillation, %								
No	75.4	74.6	74.0	73.3	73.0	72.5	71.7	70.9
IP within 6 mo.	7.4	7.8	7.9	7.4	6.9	7.1	7.4	7.5
OP within 6 mo.	5.3	5.5	5.7	6.5	7.0	7.4	8.0	8.5
IP historical	7.8	8.0	8.1	8.3	8.2	7.8	7.6	7.5
OP historical	4.0	4.2	4.3	4.5	4.9	5.1	5.3	5.6
CAD/atherosclerosis, %								
No	27.1	26.0	25.6	25.1	24.8	24.7	24.6	25.0
IP within 6 mo.	21.6	20.9	20.0	20.0	19.5	19.0	18.3	17.4
OP within 6 mo.	25.0	25.9	26.9	27.4	28.3	29.2	29.6	28.9
IP historical	14.5	14.9	15.0	14.7	14.3	13.9	13.7	13.8
OP historical	11.8	12.2	12.6	12.9	13.1	13.3	13.9	14.9
Cancer, %								
No	79.4	78.9	78.5	78.4	78.2	78.0	77.7	77.5
IP within 6 mo.	2.3	2.2	2.2	2.2	2.3	2.2	2.2	2.2
OP within 6 mo.	6.0	6.2	6.1	6.1	6.4	6.6	6.8	6.7
IP historical	3.5	3.7	3.7	3.8	3.8	3.9	3.9	4.0
OP historical	7.9	8.1	8.4	8.4	8.3	8.2	8.3	8.6
Medical Evidence	0.9	1.0	1.0	1.1	1.0	1.1	1.1	1.0
Cardiomyopathy, %								
No	74.3	73.4	72.8	72.3	71.9	71.9	71.6	71.6
IP within 6 mo.	5.1	5.3	5.3	5.4	5.2	5.1	5.1	4.9
OP within 6 mo.	4.8	5.0	5.1	5.1	5.3	5.6	5.6	5.6
IP historical	9.2	9.7	10.1	10.4	10.6	10.6	10.7	10.7
OP historical	6.7	6.7	6.8	6.9	6.9	6.9	7.0	7.1
CHF, %								
No	28.1	27.1	26.4	26.0	26.0	26.0	26.0	26.3
IP within 6 mo.	21.1	21.2	21.0	20.1	19.2	19.1	19.1	18.9
OP within 6 mo.	16.4	16.7	17.2	18.3	19.0	19.7	19.6	19.3
IP historical	21.7	22.2	22.5	22.6	22.6	21.7	21.6	21.6

OP historical	10.0	10.0	10.0	10.2	10.5	10.6	10.9	11.2
Medical Evidence	2.7	2.8	2.9	2.8	2.8	2.8	2.7	2.7
COPD, %								
No	60.9	59.3	57.9	57.1	56.5	55.8	55.1	54.6
IP within 6 mo.	9.4	9.7	9.8	9.0	8.1	8.2	8.1	7.9
OP within 6 mo.	8.4	8.7	9.4	10.4	11.6	12.2	12.7	13.0
IP historical	11.5	12.0	12.3	12.5	12.2	11.5	11.2	11.0
OP historical	9.1	9.5	9.9	10.3	11.0	11.6	12.2	12.9
Medical Evidence	0.6	0.7	0.7	0.7	0.7	0.7	0.7	0.7
CVD, %								
No	1.6	1.5	1.4	1.3	1.2	1.1	1.1	1.1
IP within 6 mo.	45.6	45.5	45.0	44.5	43.7	43.5	43.0	42.1
OP within 6 mo.	41.9	42.5	43.2	44.0	45.6	46.5	46.7	47.1
IP historical	8.2	8.0	7.9	7.8	7.3	6.7	7.0	7.3
OP historical	2.7	2.6	2.5	2.4	2.2	2.2	2.3	2.4
Diabetes, %								
No	25.8	23.9	22.3	20.7	19.7	18.7	18.0	17.5
IP within 6 mo.	25.3	24.9	24.2	24.3	23.8	23.9	23.6	23.1
OP within 6 mo.	35.2	37.1	38.9	40.2	41.2	42.1	43.1	43.1
IP historical	3.6	3.7	3.6	3.7	3.7	3.6	3.6	3.8
OP historical	9.7	10.0	10.5	10.7	11.2	11.2	11.4	12.2
Medical Evidence	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.4
GI bleeding, %								
No	68.0	67.5	67.4	67.3	67.2	67.5	67.3	66.9
IP within 6 mo.	5.2	5.0	4.8	4.7	4.5	4.5	4.6	4.6
OP within 6 mo.	4.4	4.2	4.1	4.0	4.0	4.0	3.9	4.2
IP historical	13.5	14.1	14.3	14.5	14.7	14.7	14.6	14.5
OP historical	8.9	9.2	9.4	9.4	9.5	9.5	9.7	9.8
Hyperlipidemia/ dyslipidemia, %								
No	29.4	25.4	21.9	19.4	17.4	15.6	14.0	13.3
IP within 6 mo.	8.6	8.5	8.3	9.4	10.0	10.2	10.2	10.0
OP within 6 mo.	33.9	37.1	41.4	42.7	44.6	47.4	48.5	46.1
IP historical	9.0	9.9	10.0	10.2	10.3	10.2	10.4	11.5
OP historical	19.1	19.1	18.4	18.3	17.7	16.7	16.9	19.1
Hypertension, %								
No	1.0	0.7	0.6	0.5	0.4	0.3	0.3	0.3
IP within 6 mo.	42.4	42.5	42.2	42.0	41.3	41.2	40.8	40.0
OP within 6 mo.	37.6	38.6	39.5	40.5	42.5	43.7	44.0	44.4
IP historical	13.3	12.8	12.6	12.2	11.4	10.5	10.6	10.7
OP historical	4.0	3.7	3.5	3.4	3.2	3.0	3.1	3.2
Medical Evidence	1.7	1.6	1.5	1.5	1.3	1.3	1.2	1.3
LV hypertrophy, %								
No	57.1	55.8	55.0	54.4	53.7	53.7	53.9	54.4
IP within 6 mo.	5.7	5.4	5.4	5.0	4.8	4.6	4.2	4.0
OP within 6 mo.	9.3	9.9	9.9	10.5	11.0	11.4	10.9	9.9
IP historical	14.4	14.8	15.0	15.1	15.0	14.6	14.6	14.6
OP historical	13.5	14.1	14.8	15.0	15.5	15.7	16.4	17.2
Liver disease, %								
No	76.2	75.8	75.8	75.7	75.8	76.0	75.3	74.9

IP within 6 mo.	1.4	1.4	1.4	1.4	1.4	1.5	1.5	1.6
OP within 6 mo.	9.8	9.3	8.6	8.7	8.5	8.2	8.6	7.5
IP historical	2.1	2.4	2.6	2.7	2.9	2.9	3.1	3.3
OP historical	10.6	11.0	11.5	11.5	11.5	11.5	11.5	12.7
MI/ACS, %								
No	70.1	69.8	69.9	69.8	69.8	70.1	70.2	70.1
IP within 6 mo.	5.7	5.4	5.2	5.2	5.0	5.0	4.8	4.8
OP within 6 mo.	3.2	3.1	3.0	2.9	2.9	2.9	2.9	2.8
IP historical	15.2	15.7	15.8	15.9	16.0	15.8	15.8	15.7
OP historical	5.9	6.0	6.1	6.2	6.2	6.2	6.3	6.5
Other cardiac, %								
No	25.6	24.7	24.2	23.8	23.4	23.6	23.4	23.2
IP within 6 mo.	16.1	15.7	15.4	14.6	13.9	13.4	12.9	12.5
OP within 6 mo.	19.6	20.1	20.3	21.1	21.8	22.5	22.9	22.7
IP historical	23.3	24.0	24.4	24.5	24.6	24.0	23.9	23.8
OP historical	15.4	15.5	15.7	15.9	16.3	16.5	17.0	17.7
Pulmonary hypertension, %								
No	89.1	88.2	87.3	86.0	84.6	83.2	81.7	80.3
IP within 6 mo.	1.4	1.4	1.4	1.8	2.0	2.2	2.4	2.7
OP within 6 mo.	1.6	1.8	2.0	2.3	2.7	3.0	3.2	3.4
IP historical	4.1	4.4	4.5	4.8	5.2	5.7	6.2	6.8
OP historical	3.8	4.2	4.7	5.1	5.5	5.9	6.4	6.8
PVD, %								
No	28.7	26.7	24.9	23.3	22.1	21.2	20.2	19.4
IP within 6 Months	14.1	14.0	13.5	13.2	13.0	12.7	12.1	11.2
OP within 6 Months	22.8	24.1	24.9	25.6	26.5	27.3	27.5	27.3
IP Historical	15.7	16.0	16.4	16.5	16.5	16.1	16.1	16.4
OP Historical	16.5	16.8	17.4	17.9	18.0	18.2	18.8	19.7
Medical Evidence	2.2	2.5	2.9	3.4	3.9	4.6	5.3	6.0
Stroke, %								
No	60.8	59.5	58.4	57.2	56.4	55.7	55.1	54.5
IP within 6 mo.	6.8	6.7	6.5	6.8	6.8	6.7	6.4	6.2
OP within 6 mo.	9.2	9.7	10.1	10.4	10.7	11.2	11.4	11.5
IP historical	12.3	12.8	13.2	13.4	13.5	13.6	13.7	13.9
OP historical	10.9	11.3	11.8	12.2	12.6	12.8	13.4	13.9
TIA, %								
No	81.4	80.6	80.0	79.5	79.2	78.9	78.4	77.9
IP within 6 mo.	1.6	1.6	1.5	1.5	1.5	1.5	1.4	1.4
OP within 6 mo.	2.0	2.0	2.0	2.0	1.9	2.0	2.0	2.0
IP historical	5.1	5.4	5.5	5.6	5.7	5.7	5.9	5.9
OP historical	5.2	5.4	5.6	5.7	5.9	5.8	6.0	6.2
Medical Evidence	4.6	5.0	5.4	5.6	5.8	6.1	6.4	6.6
Valvular disease, %								
No	53.0	51.2	49.8	48.6	48.1	48.2	47.9	47.4
IP within 6 mo.	9.6	9.7	9.8	9.0	8.2	7.8	7.7	7.5
OP within 6 mo.	8.2	8.5	8.9	9.6	10.3	10.8	10.8	11.0
IP historical	18.0	19.0	19.7	20.3	20.3	19.7	19.4	19.3
OP historical	11.1	11.6	11.8	12.4	13.1	13.5	14.1	14.8

Note: Clinical characteristics identified in the first nine diagnosis fields in each year and in the inpatient setting six months prior to the index date

ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; GI, gastrointestinal; IP, inpatient; OP, outpatient; LV, left ventricular; MI, myocardial infarction; PVD peripheral vascular disease; TIA transient ischemic attack.

V. Supplementary Table S4. Absolute and relative differences in all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, heart failure, and venous thromboembolism in 2011and 2012

Year	Observed	Predicted	Observed		Predicted		Difference*	Ratio*
			Lower Limit	Upper Limit	Lower Limit	Upper Limit		
All-cause death								
2011	19.53	19.07	19.34	19.72	18.59	19.46	0.47	1.02
2012	18.62	18.60	18.44	18.80	18.13	19.04	0.01	1.00
Cardiovascular death								
2011	7.83	7.69	7.71	7.95	7.40	7.98	0.140	1.018
2012	7.36	7.41	7.25	7.48	7.13	7.67	-0.045	0.994
Stroke								
2011	3.40	3.42	3.32	3.48	3.29	3.51	-0.02	1.00
2012	3.06	3.30	2.99	3.14	3.17	3.41	-0.24	0.93
Myocardial infarction								
2011	9.12	8.67	8.99	9.24	8.37	9.01	0.44	1.05
2012	8.44	8.73	8.31	8.56	8.37	9.06	-0.29	0.97
Composite endpoint								
2011	32.12	31.14	31.88	32.36	30.54	31.72	0.98	1.03
2012	30.17	30.57	29.94	30.40	29.99	31.20	-0.40	0.99
Heart failure								
2011	13.22	13.13	13.06	13.37	12.70	13.61	0.09	1.01
2012	11.75	12.53	11.61	11.90	12.03	13.02	-0.77	0.94
Venous thromboembolism								
2011	27.37	28.44	27.15	27.59	27.40	29.53	-1.07	0.96
2012	26.06	28.49	25.85	26.28	27.42	29.73	-2.43	0.91

*Observed to predicted

VI. Supplementary Table S5. Trends in baseline characteristics in the Medicare population without end-stage renal disease, 2005-2012

Variable	2005	2006	2007	2008	2009	2010	2011	2012
n	1,429,298	1,397,639	1,352,599	1,330,947	1,315,630	1,334,904	1,337,516	1,355,219
Mean age, yrs.	75.8	75.9	75.9	75.9	75.9	75.8	75.8	75.6
Mean age group, yrs.								
65-74	51.0	50.8	50.8	51.2	51.5	52.3	52.6	53.7
75-84	35.7	35.6	35.1	34.4	33.8	32.9	32.4	31.5
≥ 85	13.2	13.6	14.1	14.4	14.7	14.8	15.0	14.8
Sex, %								
Female	58.5	58.4	58.2	58.0	57.8	57.5	57.2	56.9
Male	41.5	41.6	41.8	42.0	42.2	42.5	42.8	43.1
Race, %								
White	87.4	87.4	87.5	87.4	87.2	86.9	86.6	86.4
Black	7.8	7.7	7.6	7.5	7.5	7.6	7.7	7.7
Other	4.8	4.8	5.0	5.1	5.3	5.5	5.7	6.0
Ethnicity, %								
Hispanic	1.8	1.8	1.7	1.7	1.7	1.7	1.8	1.7
Non-Hispanic	98.2	98.2	98.3	98.3	98.3	98.3	98.2	98.3
Arrhythmia, %								
No	80.5	78.9	77.5	76.5	75.6	75.2	74.8	74.8
IP within 6 mo.	1.0	1.0	1.0	1.0	1.0	0.9	0.9	0.8
OP within 6 mo.	3.8	3.8	3.8	3.8	3.9	4.0	4.0	3.9
IP historical	4.2	4.7	5.3	5.7	6.1	6.2	6.3	6.3
OP historical	10.5	11.5	12.4	12.9	13.4	13.7	14.0	14.2
Atrial fibrillation, %								
No	84.6	83.7	82.8	82.2	81.5	81.3	80.9	80.8
IP within 6 mo.	2.3	2.3	2.4	2.3	2.3	2.3	2.3	2.3
OP within 6 mo.	6.0	6.2	6.5	6.8	7.1	7.4	7.6	7.8
IP historical	3.3	3.6	3.9	4.0	4.1	4.0	4.0	3.9
OP historical	3.9	4.2	4.5	4.7	4.9	5.0	5.2	5.3
CAD/atherosclerosis, %								
No	55.7	53.8	52.1	51.1	50.2	50.2	50.1	50.9
IP within 6 mo.	4.7	4.5	4.5	4.4	4.3	4.0	3.9	3.6
OP within 6 mo.	18.3	18.4	18.7	19.1	19.5	19.5	19.4	19.0
IP historical	6.5	7.2	7.8	8.0	8.2	8.2	8.2	8.0
OP historical	14.9	16.1	16.9	17.4	17.9	18.1	18.4	18.5
Cancer, %								
No	79.2	78.0	76.8	75.9	75.1	74.8	74.4	74.3
IP within 6 mo.	1.2	1.2	1.2	1.2	1.2	1.1	1.1	1.1
OP within 6 mo.	8.9	9.0	9.2	9.5	9.7	9.7	9.7	9.7
IP historical	1.7	2.1	2.3	2.6	2.8	2.9	3.1	3.2
OP historical	8.9	9.7	10.3	10.8	11.2	11.5	11.7	11.8
Cardiomyopathy, %								
No	93.7	93.2	92.7	92.3	91.9	91.8	91.6	91.6
IP within 6 mo.	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

OP within 6 mo.	1.6	1.6	1.7	1.8	1.8	1.9	1.9	1.9
IP historical	1.4	1.5	1.7	1.8	1.9	1.9	2.0	2.0
OP historical	2.8	3.1	3.4	3.6	3.8	3.9	4.0	4.0
CHF, %								
No	77.3	76.3	75.3	74.7	74.2	74.3	74.3	74.8
IP within 6 mo.	3.0	2.9	2.8	2.7	2.7	2.6	2.5	2.4
OP within 6 mo.	6.8	6.7	6.7	6.8	6.9	6.9	6.8	6.6
IP historical	4.8	5.3	5.7	6.0	6.1	6.1	6.0	5.9
OP historical	8.2	8.8	9.4	9.8	10.1	10.2	10.3	10.3
COPD, %								
No	70.9	69.1	67.5	66.5	65.4	65.2	64.8	65.0
IP within 6 mo.	3.0	2.9	3.0	2.9	2.8	2.7	2.7	2.5
OP within 6 mo.	9.6	9.7	9.8	10.1	10.5	10.6	10.6	10.6
IP historical	5.0	5.6	6.2	6.5	6.7	6.7	6.7	6.6
OP historical	11.5	12.7	13.6	14.1	14.7	14.9	15.2	15.3
CVD, %								
No	16.3	15.0	14.0	13.5	13.0	13.5	13.5	14.1
IP within 6 mo.	10.2	10.1	10.2	10.1	10.0	9.7	9.7	9.3
OP within 6 mo.	54.3	54.9	55.7	56.6	57.4	57.6	57.7	57.5
IP historical	5.4	6.0	6.4	6.5	6.5	6.5	6.5	6.5
OP historical	13.8	14.0	13.8	13.3	13.1	12.7	12.6	12.6
Diabetes, %								
No	68.4	66.6	64.4	62.6	61.0	60.2	59.3	58.9
IP within 6 mo.	2.9	2.9	3.0	3.0	3.0	2.9	3.0	2.8
OP within 6 mo.	17.7	18.3	19.2	20.1	20.7	21.1	21.5	21.7
IP historical	1.5	1.7	1.9	2.0	2.1	2.2	2.3	2.3
OP historical	9.5	10.6	11.6	12.3	13.2	13.6	14.0	14.2
GI bleeding, %								
No	82.5	81.1	79.8	78.9	78.1	77.8	77.6	77.7
IP within 6 mo.	0.9	0.9	0.9	0.9	0.8	0.8	0.8	0.7
OP within 6 mo.	2.4	2.2	2.2	2.1	2.1	2.0	2.0	1.9
IP historical	3.9	4.4	4.9	5.2	5.4	5.5	5.5	5.5
OP historical	10.2	11.4	12.3	13.0	13.6	13.9	14.2	14.2
Hyperlipidemia/ dyslipidemia, %								
No	29.9	26.2	23.3	21.3	19.7	19.3	18.6	18.7
IP within 6 mo.	3.1	3.2	3.5	3.6	3.7	3.7	3.8	3.7
OP within 6 mo.	38.7	40.4	42.1	43.8	45.0	45.9	46.6	46.8
IP historical	3.8	4.6	5.3	5.8	6.4	6.7	7.0	7.2
OP historical	24.5	25.6	25.8	25.5	25.2	24.4	24.0	23.6
Hypertension, %								
No	24.1	22.1	20.5	19.5	18.7	18.8	18.6	19.1
IP within 6 mo.	7.5	7.5	7.6	7.6	7.6	7.3	7.4	7.1
OP within 6 mo.	46.2	47.3	48.4	49.7	50.9	51.5	52.0	51.9
IP historical	6.6	7.3	7.7	7.9	7.9	7.8	7.7	7.7
OP historical	15.6	15.9	15.8	15.3	15.0	14.5	14.4	14.2
LV hypertrophy, %								
No	84.1	82.8	81.7	80.8	80.1	79.9	79.7	79.9
IP within 6 mo.	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.3
OP within 6 mo.	4.6	4.6	4.5	4.5	4.5	4.4	4.3	4.2

IP historical	2.1	2.3	2.5	2.6	2.7	2.7	2.7	2.7
OP historical	8.8	9.9	10.9	11.6	12.2	12.5	12.8	12.9
Liver disease, %								
No	96.0	95.4	94.8	94.2	93.6	93.1	92.6	92.1
IP within 6 mo.	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
OP within 6 mo.	0.8	0.8	0.9	0.9	1.0	1.0	1.1	1.1
IP historical	0.5	0.6	0.7	0.8	0.9	0.9	1.0	1.0
OP historical	2.6	3.0	3.5	3.9	4.4	4.8	5.2	5.5
MI/ACS, %								
No	86.8	85.8	84.9	84.5	84.0	84.0	84.0	84.3
IP within 6 mo.	1.3	1.2	1.1	1.0	1.0	0.9	0.9	0.8
OP within 6 mo.	1.2	1.1	1.0	1.0	1.0	1.0	1.0	0.9
IP historical	6.7	7.5	8.1	8.5	8.8	8.9	8.9	8.8
OP historical	4.1	4.5	4.8	5.0	5.1	5.2	5.2	5.2
Other cardiac, %								
No	57.7	54.9	52.5	50.9	49.6	49.4	48.9	49.2
IP within 6 mo.	2.8	2.8	2.7	2.6	2.5	2.3	2.3	2.1
OP within 6 mo.	10.9	11.0	11.2	11.5	11.8	11.9	12.0	11.9
IP historical	8.6	9.5	10.4	11.0	11.4	11.4	11.5	11.4
OP historical	20.1	21.8	23.2	24.0	24.7	24.9	25.3	25.4
Pulmonary hypertension, %								
No	96.8	96.3	95.8	95.3	94.8	94.3	93.9	93.6
IP within 6 mo.	0.2	0.3	0.3	0.3	0.4	0.4	0.4	0.4
OP within 6 mo.	0.5	0.5	0.6	0.7	0.8	0.9	0.9	0.9
IP historical	0.9	1.1	1.2	1.3	1.5	1.6	1.7	1.8
OP historical	1.5	1.8	2.1	2.4	2.6	2.9	3.1	3.3
PVD, %								
No	69.4	66.9	64.6	62.8	61.2	60.5	59.7	59.7
IP within 6 Months	1.7	1.7	1.7	1.7	1.7	1.6	1.5	1.5
OP within 6 Months	9.8	10.2	10.6	11.0	11.5	11.7	11.9	11.7
IP Historical	4.5	5.1	5.6	5.9	6.2	6.3	6.4	6.3
OP Historical	14.5	16.0	17.5	18.6	19.4	19.9	20.5	20.8
Stroke, %								
No	75.4	73.3	71.2	69.6	68.2	67.5	66.8	66.7
IP within 6 mo.	1.8	1.8	1.8	1.8	1.8	1.7	1.7	1.6
OP within 6 mo.	6.3	6.4	6.7	6.9	7.2	7.2	7.3	7.2
IP historical	5.3	6.0	6.7	7.1	7.5	7.7	7.8	7.8
OP historical	11.1	12.4	13.6	14.6	15.4	15.9	16.4	16.7
TIA, %								
No	89.3	88.4	87.6	87.0	86.5	86.4	86.3	86.4
IP within 6 mo.	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.4
OP within 6 mo.	1.6	1.6	1.5	1.5	1.5	1.4	1.4	1.3
IP historical	2.7	3.0	3.3	3.4	3.6	3.7	3.8	3.8
OP historical	5.9	6.6	7.2	7.6	7.9	8.0	8.1	8.0
Valvular disease, %								
No	76.2	74.0	71.8	70.1	68.8	68.3	67.7	67.7
IP within 6 mo.	1.9	1.9	1.9	1.8	1.7	1.6	1.5	1.5
OP within 6 mo.	5.4	5.6	6.0	6.3	6.6	6.6	6.8	6.8
IP historical	5.9	6.7	7.4	8.0	8.3	8.3	8.3	8.2

OP historical	10.5	11.7	12.9	13.8	14.7	15.2	15.6	15.8

Note: Clinical characteristics identified in the first nine diagnosis fields in each year and in the inpatient setting six months prior to the index date.

ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; GI, gastrointestinal; IP, inpatient; OP, outpatient; LV, left ventricular; MI, myocardial infarction; PVD peripheral vascular disease; TIA transient ischemic attack.

VII. Supplementary Figure S1. Trends in rates of stroke and myocardial infarction in the dialysis and non-ESRD Medicare populations, 2005-2012.