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Original Article

Correlates and outcomes of warfarin initiation in kidney transplant recipients newly diagnosed with atrial fibrillation

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ABSTRACT

In the kidney transplant population with atrial fibrillation (AF), evidence regarding the effectiveness and safety of warfarin treatment is lacking. We used fee-for-service Medicare claims to identify kidney transplant recipients with newly diagnosed AF from the United States Renal Data System. Warfarin use within 30 days of AF diagnosis was ascertained from Medicare Part D prescription claims (2007–11) or using a validated algorithm (1997–2011). The study end points were (i) the composite of death, stroke or gastrointestinal bleed, (ii) death and (iii) death-censored graft failure. Warfarin user and non-user groups were balanced using inverse probability of treatment weighting and hazard ratios were (HRs) estimated using Cox regression. Among 718 subjects with an indication for anticoagulation, 24% initiated warfarin treatment within 30 days of AF diagnosis. Age was the only independent correlate of warfarin use [odds ratio = 1.02 per year; 95% confidence interval (95% CI) 1.01–1.04]. In the larger cohort of 6492 patients with AF, warfarin use [(23.5%) versus non-use (76.5%)] was associated with small and non-significant reductions in the composite of death, stroke or gastrointestinal bleed (HR = 0.92; 95% CI 0.83–1.02), death (HR = 0.92; 95% CI 0.82–1.02) and death-censored graft failure (HR = 0.90; 95% CI 0.76–1.08). Our study suggests the need for clinical trials of warfarin use in the kidney transplant population with AF.

Keywords: anticoagulation, arrhythmia, end-stage renal disease, outcomes, risk assessment

INTRODUCTION

Kidney transplantation is the preferred treatment for patients with end-stage renal disease (ESRD) [1, 2]. Atrial fibrillation (AF) occurs in over 7% of patients by 3-years post-kidney transplant and is associated with reduced graft and patient survival [3]. In the general population with AF, randomized trials and observational studies have shown that anticoagulation significantly reduces the risk of ischemic stroke, an effect that outweighs a small associated increase in bleeding risk [4, 5]. Oral anticoagulation is therefore recommended in all patients with AF who have more than one stroke risk factor and no contraindication to therapy [6, 7]. In the ESRD population on hemodialysis, a number of retrospective studies have suggested that anti-coagulation for AF is associated with an increased risk of bleeding but no reduction in risk of ischemic stroke [8, 9]. However, the efficacy and safety of anti-coagulation for AF in the ESRD population with a functioning kidney transplant, another population at high cardiovascular risk, has yet to be determined.

The goal of this study was (i) to describe the prevalence and correlates of warfarin use in a recent era (2007–11) using prescription claims from Medicare Part D, (ii) to derive and validate an algorithm for the identification of warfarin use from non-prescription (Medicare Parts A and B) claims and (iii) to apply this algorithm to a broader cohort (1997–2011) to examine the association of warfarin use (versus non-use) with death, ischemic and hemorrhagic stroke, gastrointestinal bleed

and graft survival, in kidney transplant recipients with newly diagnosed AF.

MATERIALS AND METHODS

Description of US Renal Data System and Medicare

The United States Renal Data System (USRDS) is a national patient registry and contains demographic, clinical, treatment and survival data on almost all ESRD patients. The USRDS also contains detailed health-care claims and billing information for those subjects covered by the federal health insurer, Medicare [10].

The Medicare program was introduced in 1965 and currently provides health insurance coverage for almost one fifth of the US population [11, 12]. Individuals older than 65 and those with certain disabilities are eligible to enroll in the program. In the 1972 Amendments to the Social Security Act, Medicare was additionally mandated to cover all eligible patients with ESRD even if they were younger than 65. Therefore, patient registration with the USRDS is mandatory at the time of first ESRD diagnosis.

Medicare consists of several 'Parts:' Medicare Part A covers inpatient hospital care and is free for most individuals who have paid sufficient Medicare taxes during their working life. Medicare Part B covers doctors' services and outpatient care and requires payment of a monthly premium. Medicare Part D was introduced in 2006 and covers the cost of prescription drugs [13]. Medicare Part D is optional and requires payment of a monthly premium. In 2010, Medicare Part D covered drug costs up to $2800 per year. Beyond this coverage limit, individuals had to pay out-of-pocket for drugs up to a catastrophic coverage limit of $4550 per year after which drug costs were again covered by the plan. This coverage gap between $2800 and $4500 is commonly referred to as the 'doughnut-hole'. Prescriptions filled and paid for out-of-pocket by individuals while in the coverage gap may fail to appear in Part D claims data. Therefore, for this study, we required that subjects with Medicare Part D were additionally covered by a low-income subsidy, a means-tested federally administered financial aid program that eliminates the prescription drug coverage gap.

Study population: Medicare Part A and Part B cohort

We identified all adult patients (≥18 years) with a functioning kidney transplant in the USRDS between January 1997 and December 2011. We identified AF using the International Classification of Diseases (9th revision; ICD-9) code 427.31. An ICD-9 claims-based definition of AF has been previously validated with a sensitivity of 94%, specificity of 99% and positive predictive value of 97% [14, 15]. Such a claims-based approach has been used to identify Medicare patients for the National Registry of Atrial Fibrillation [16] and other claims-based research studies of AF [17–19]. We defined newly diagnosed AF using two methods: (i) any inpatient AF diagnosis claim; (ii) one outpatient AF diagnosis claim followed by a second outpatient AF claim within 30 days (but not on the same day). Patients were required to survive at least 30 days from the first AF diagnosis. Patients with any previous AF diagnoses were excluded. The index date was defined as Day 30 after hospital discharge or Day 30 after first outpatient AF diagnosis, respectively. Inclusion was restricted to individuals with uninterrupted Medicare Part A and B coverage (per payor history file) for 1 year prior to and 30 days after AF diagnosis.

Study population: Medicare Part D cohort

We also created a cohort of patients for whom Medicare Part D prescription claims data were available (July 2007–December 2011) using the same conditions as the Medicare Part A and B cohort with the additional requirement that subjects have Medicare Part D coverage with a low-income subsidy for 6 months prior to AF diagnosis and until at least 30 days following AF diagnosis. We required low-income subsidy status to ensure observation of all outpatient medication claims, as these patients do not have a prescription benefit coverage gap.

Warfarin use

The exposure of interest was new initiation of warfarin treatment either within 30 days of discharge following an inpatient AF diagnosis or within 30 days of a first outpatient AF diagnosis. In the Medicare Part D cohort, we excluded patients with any warfarin prescription in the 6 months or any ICD-9 code V58.61 [long-term (current) use of anti-coagulants] in the year prior to AF diagnosis. We defined new warfarin users as patients who filled a first prescription for warfarin within 30 days of the first AF claim.

Next, we used the 2007–2010 era Medicare Part D cohort ($n = 558$) to develop a laboratory/diagnosis claims-based algorithm for new warfarin exposure following AF diagnosis. We then tested the algorithm in an external cohort of subjects with Medicare Part D coverage that were diagnosed with AF in the year 2011.

Finally, we identified warfarin users/non-users in the Medicare Part A and B cohort (1997–2011) using the algorithm. Patients were considered to have been previously exposed to warfarin and were excluded if they had any V58.61 code or ≥2 prothrombin time claims in 12 months prior to AF diagnosis.

Patient characteristics

We ascertained the following characteristics from the USRDS patient, treatment history and transplant files: recipient age, sex, race (white, black, other), cause of ESRD, body mass index (BMI), time since transplant, time since first ESRD diagnosis, patient blood type, transplant type (living, standard deceased, expanded criteria deceased, donation after cardiac death), donor age and sex, HLA mismatch, panel reactive antibody and cold ischemia time.

We additionally identified the following comorbidities using the appropriate ICD-9 codes (see Supplementary data, Technical Appendix and Table 1): diabetes, cancer, coronary artery disease, cerebrovascular disease, alcohol dependence, peripheral arterial disease (PAD), hypertension, valvular heart disease, heart failure, chronic pulmonary disease and prior solid organ transplant (heart, lung, liver, pancreas). Comorbidities were

ascertained in the 365-day period prior to the date of AF diagnosis and were established by at least one inpatient or two outpatient claims not on the same day. We quantified health-care utilization in the year prior to AF diagnosis by determining whether the patient was in a skilled nursing facility, the number of days spent in hospital and the number of non-nephrology outpatient visits. We also included outpatient (versus inpatient) AF diagnosis, inpatient length of stay, inpatient discharge to home, hospital admission and duration of stay in the 30 days following AF diagnosis, census division and year of transplant as covariates [19, 20].

Outcomes

Our outcomes of interest were (i) the composite of death from any cause, stroke, or gastrointestinal bleed, (ii) death from any cause and (iii) death-censored graft failure. Death was determined from the USRDS patient file. Ischemic stroke was defined by an inpatient primary ICD-9 diagnosis code of 433.×1, 434.×1, 436 or 437.1 or by stroke as cause of death (fatal stroke subtype not specified in USRDS). Hemorrhagic stroke was defined as an inpatient primary ICD-9 diagnosis code of 430–432. Gastrointestinal bleeding was defined using a previously validated claims-based algorithm [20, 21] or by gastrointestinal bleeding as cause of death. Death-censored graft failure was identified from the USRDS patient files and defined as need for dialysis or re-transplant. For the outcome of death, patients were censored at 3-year post-AF diagnosis or end of study, 31 December 2011. For all other outcomes, patients were censored at 3-year post-AF diagnosis, end of study or loss of Medicare Parts A and B coverage.

Statistical analysis

We used multivariate logistic regression to characterize factors associated with warfarin use. Variables selected for the regression model included demographic characteristics: age, sex and race; components of the $CHADS_2$ score: heart failure, hypertension, stroke/TIA, diabetes mellitus, other factors known to affect stroke risk: valve disease, coronary and PAD (components of the newer CHA_2DS_2VASc score); risk factors for bleeding on warfarin: history of gastrointestinal bleed, intracranial hemorrhage, alcohol dependence and liver disease [6, 7, 22, 23]. We report odds ratios and corresponding 95% confidence intervals (CI).

In the Medicare Part A and B cohort, we categorized patients as new warfarin users or non-users. Categorical variables were expressed as percentages and continuous variables as medians and interquartile range. Differences between the two groups were assessed using standardized differences; any value <10 indicates good and <5 excellent balance between exposure groups [24].

Propensity scores to estimate the probability of receiving warfarin treatment were calculated using a multivariate logistic regression model that included all variables in Table 2 with the exception of those with missing data (BMI and all transplant-related variables; balance was still achieved even for these variables). In order to reduce selection bias between the warfarin user and non-user groups, we applied an inverse probability of treatment (IPT)-weighting (IPTW) approach using stabilized weights [25]. Stabilized weights are the inverse of the propensity of a patient receiving the treatment that they actually received (propensity score) multiplied by a constant [26]. This constant is defined separately for those exposed and unexposed as the average of the propensity scores within each group. Stabilization does not affect the point estimate but decreases the variability of the IPTW weights by reducing the influence of those patients with extreme weights. If stabilized weights were too large, they were truncated and reset to the value 10 (0.1). Final weights were computed as the product of the stabilized and trimmed weight for treatment. If necessary, final weights were also trimmed.

Unadjusted incidence rates, defined as the number of events over person-time observed, were calculated for each outcome. We used robust weighted multivariate Cox proportional hazards models to calculate the hazard ratio (HR) and 95% CI for each outcome.

As a sensitivity analysis, we performed Cox survival analysis for the three study end points in the Medicare Part D

Table 1. Distribution and odds ratios for established stroke and bleeding risk factors associated with warfarin use using the Medicare Part D cohort (2007–11)

Risk factors[a]	Warfarin non-users (n = 546)	Warfarin users (n = 172)	Std. diff. (%)	Adjusted odds ratio (95% confidence interval) for warfarin use (versus non-use)
Age (years)[b]	58 (49–67)	61 (53–68)	25.6	1.02 (1.01–1.04)[c]
Female (%)	45.6	44.8	1.7	0.88 (0.62–1.25)
White race (%)	62.8	57.6	10.7	1.0 (referent)
Black race (%)	29.1	31.4	4.9	1.24 (0.84–1.84)
Other race (%)	8.1	11.0	10.2	1.37 (0.75–2.49)
Heart failure (%)	36.4	42.4	12.3	1.24 (0.86–1.79)
Coronary artery disease (%)	31.3	33.1	3.9	0.98 (0.79–2.10)
Cerebrovascular disease (%)	13.9	16.9	8.1	1.29 (0.79–2.10)
Peripheral arterial disease (%)	22.5	21.5	2.4	0.87 (0.56–1.34)
Hypertension (%)	97.8	96.5	7.8	0.48 (0.17–1.35)
Diabetes mellitus (%)	66.3	68	3.7	1.01 (0.69–1.49)
Valvular disease (%)	26.9	26.7	0.4	0.94 (0.63–1.41)
Liver disease (%)	16.3	10.5	17.2	0.58 (0.33–1.00)
Gastrointestinal bleeding (%)	3.5	2.9	3.3	0.81 (0.29–2.26)

[a]Alcohol dependence and cerebral hemorrhage excluded from analysis because of too few events. US Federal Research regulations preclude publication of cell sizes <10.
[b]Median (interquartile range).
[c]Per year.

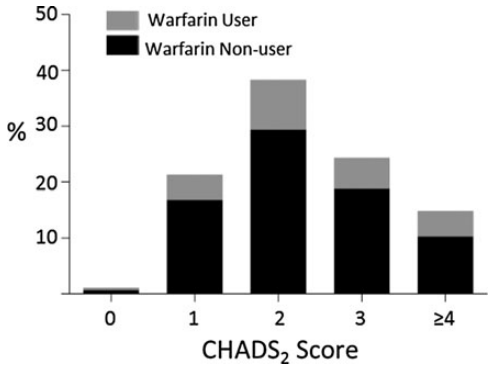

FIGURE 1: CHADS2 score and warfarin use in 718 patients in the Medicare Part D cohort with new-onset AF.

cohort using an IPTW approach identical to the main analysis (Supplementary data, Technical Appendix).

Analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA) and Stata MP, version 12 (Stata Corporation, College Station, TX, USA). The Institutional Review Board of Stanford University approved the study.

RESULTS

From all transplant recipients with Medicare Parts A, B and D coverage (2007–11), we identified 718 patients with newly diagnosed AF of whom 172 (24%) patients filled a prescription for warfarin within 30 days of AF diagnosis. Selected stroke and bleeding risk factors of patients who initiated warfarin versus those who did not are shown in Table 1. Warfarin users differed from non-users at baseline in terms of age and race, and in the prevalence of heart failure and liver disease. However, in multivariate logistic regression analysis, age was the only significant correlate of warfarin use (Table 1). We also stratified warfarin use by $CHADS_2$ score category and found that 24.6 and 30.8% of patients with scores ≥2 and ≥4, respectively, received warfarin (Figure 1).

In the Medicare Part D cohort 2007–10 ($n = 558$), we developed an optimum claims-based algorithm using a prescription-based definition of new warfarin use as our gold-standard. Among several candidate algorithms (not shown herein), we found that ≥1 claim with the ICD-9 code V58.61 and/or ≥2 claims for Current Procedural Terminology (CPT) code 86510 (prothrombin time) within 30 days of AF diagnosis had positive predictive and negative predictive values of 84% (95% CI 75–90%) and 90% (95% CI 87–93%), respectively, for warfarin use. We next validated this claims-based algorithm in a fully separate cohort of Medicare Part D eligible subjects who were diagnosed with AF in 2011 ($n = 197$). We found that the claims-based algorithm had a PPV of 93% (95% CI 81–98%) and an NPV of 94% (95% CI 89–97%) for new warfarin use (as identified through prescription claims).

Using the Medicare Part A and B cohort (1997–2011), we identified 6492 eligible kidney transplant recipients with a first diagnosis of AF. We used our claims-based algorithm to identify 1527 (23.5%) likely new warfarin users and 4965 (76.5%) non-users (Figure 2). Table 2 shows baseline unadjusted and

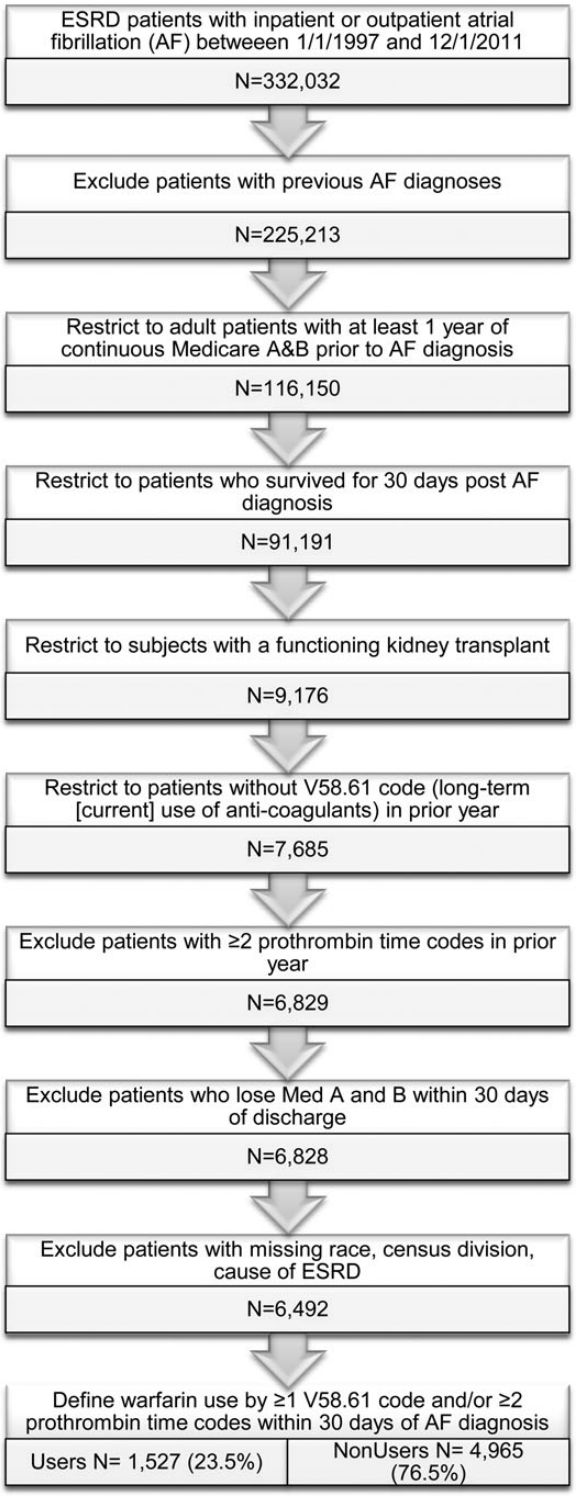

FIGURE 2: Details of the Medicare Part A and B cohort assembly.

IPT-weighted patient characteristics of warfarin users and non-users; IPT-weighting balanced all observed characteristics between groups.

During follow-up, 34.6% of warfarin users and 36.8% of non-users reached the composite end point of death, stroke or gastrointestinal bleed; 30.1% of warfarin users and 33.1% of non-users died and death-censored graft failure occurred in 12.8% of warfarin users and 14.2% of non-users. Table 3

Table 2. Baseline characteristics of the Medicare A and B Cohort (1997–2011)

	Unadjusted cohort			Inverse probability of treatment-weighted cohort		
	Warfarin non-users (n = 4965)	Warfarin users (n = 1527)	Std. diff. (%)	Warfarin non-users (n = 4965)	Warfarin users (n = 1527)	Std. diff. (%)
Age (years)	63 (54–69)	66 (58–71)	22.2	64 (55–70)	64 (55–69)	1.5
Female (%)	37	30.5	13.8	35.5	35.6	0.1
Race (%)						
White	74.1	79.7	13.2	75.4	75.6	0.4
Black	21.3	15.8	14.2	20.1	20.0	0.2
Other	4.5	4.5	0.3	4.5	4.4	0.4
Body mass index (kg/m^2)						
<20	2.5	1.6	6.1	2.4	1.9	3.6
20–25	36.6	31.9	9.8	36.3	33.4	6.1
25–30	34.7	37.3	5.5	35.1	35.3	0.4
>30	26.2	29.1	6.4	26.2	29.4	7.3
Missing	25.0	27.6	5.8	25.1	27.2	4.8
Time since ESRD (years)	2 (1–5)	2 (1–4)	5.4	2 (1–5)	2 (1–5)	0.8
Time since Transplant (years)	6 (3–10)	6 (3–11)	9.8	6 (3–10)	6 (3–10)	2.1
Cause of ESRD						
Diabetes	28.7	24.4	9.8	27.6	26.9	1.5
Glomerular disease	24.2	29	11.0	25.4	26.0	1.3
Hypertension	23.3	21.8	3.6	22.9	22.6	0.9
Other	23.8	24.8	2.3	24.1	24.6	1.1
Health-care utilization						
Hospital days	10 (4–18)	7 (3–15)	22.6	9 (4–18)	9 (4–18)	0.4
Skilled nursing facility stay (%)	8.8	5.0	15.1	7.9	7.9	0.2
Non-nephrology clinic visits	18 (10–29)	18 (10–29)	0.8	18 (10–29)	19 (10–29)	3.3
Comorbidities						
Heart failure	39.7	41.2	3.1	40.0	39.7	0.7
Coronary artery disease	36.2	32.2	8.4	35.2	35.5	0.5
Cerebrovascular disease	12.6	12.5	0.4	12.7	13.3	1.8
Peripheral arterial disease	21.5	17.7	9.5	20.6	21.3	1.7
Hypertension	94.9	91.4	13.8	94.6	92.7	7.8
Diabetes mellitus	56.6	53.3	6.6	55.7	55.2	1.0
Chronic obstructive lung disease	21.9	17.6	10.7	20.9	21.2	0.7
Smoking	5.9	3.8	9.8	5.4	5.3	0.3
Cancer	11.0	9.6	4.8	10.7	11.5	2.7
Alcohol dependence	1.5	1.0	4.3	1.4	1.0	3.8
Cerebral bleed	0.7	0.5	2.8	0.6	0.6	0.4
Peptic ulcer disease	3.1	1.6	10.3	2.9	2.0	5.7
Valvular disease	28.4	31.6	7.1	29.3	30.4	2.6
Arrhythmia	17.9	15.8	5.4	17.4	17.1	0.8
Liver disease	10.2	6.7	12.8	9.4	10.0	2.0
Gastrointestinal bleeding	3.7	1.5	13.9	3.2	2.7	3.1
Previous solid organ transplant						
Liver	1.2	1.0	2.5	1.2	1.1	0.8
Lung	0.2	0.2	0.3	0.2	0.4	3.3
Heart	0.7	0.3	5.3	0.7	0.3	5.5
Pancreas	2.2	1.6	4.6	2.1	1.9	1.2
Patient blood type						
A	38.5	41.2	5.5	38.5	40.8	4.8
B	12.1	10.4	5.5	12.0	11.0	3.4
AB	4.1	4.4	1.5	4.1	4.5	2.2
O	45.3	44.1	2.5	45.4	43.7	3.4
Missing	7.7	8.6	3.1	7.9	8.2	1.1
Panel-reactive antibody (%)						
0–20	71.6	73.7	4.6	72.2	72.4	0.3
20–80	20.9	19.8	2.8	20.5	20.4	0.2
>80	7.4	6.5	3.5	7.3	7.2	0.2
Missing	21.5	21	1.2	21.6	20.2	3.5
Donor age (years)	37 (23–50)	37 (23–50)	0.1	38 (23–50)	37 (23–49)	5.3
Missing	10.3	11	2.4	10.4	10.8	1.2
Female donor (%)	44.8	43.9	1.9	44.8	43.1	3.4
Missing	5.6	6.6	4.1	5.8	6.5	3.2

Continued

Table 2. Continued

	Unadjusted cohort			Inverse probability of treatment-weighted cohort		
	Warfarin non-users (n = 4965)	Warfarin users (n = 1527)	Std. diff. (%)	Warfarin non-users (n = 4965)	Warfarin users (n = 1527)	Std. diff. (%)
Donor type						
Living	26.9	28	2.4	27.5	25.8	3.7
Standard deceased	58.6	58.3	0.6	58.0	61.1	6.3
Expanded criteria	11.8	10.9	2.7	11.9	10.3	4.8
Donation after cardiac death	2.6	2.7	0.6	2.6	2.7	0.5
Missing	8.7	9.5	2.7	8.8	9.2	1.4
HLA mismatch						
0	11.8	13.2	4.3	11.9	12.7	2.4
1–3	39.6	40.4	1.6	39.9	38.2	3.5
3–6	48.6	46.4	4.5	48.3	49.2	1.8
Missing	10.2	10.7	1.6	10.3	10.3	0.1
Cold ischemia time (h)						
<10	31.5	32.6	2.4	31.7	30.7	2.1
10–23	41.0	41.9	1.7	41.0	41.8	1.7
>23	27.5	25.6	4.5	27.3	27.5	0.3
Missing	19.1	18.8	0.8	19.5	18.1	3.4
AF diagnosed as outpatient (%)	14.0	27.5	33.7	17.2	17.2	0.1
Length of inpatient stay (days)	6 (3–11)	5 (1–10)	17.1	6 (3–11)	6 (3–11)	0.7
Discharged home after hospitalization	77.9	68.6	21.1	75.7	75.5	0.5
Hospitalized within 30 days of inpatient AF discharge or first outpatient AF diagnosis	24.7	24.0	1.7	24.7	25.2	1.3

Table 3. Number of events, follow-up time, incidence rates and hazard ratios for all study outcomes based on an inverse probability of treatment-weighted population of ∼24% warfarin users and 76% non-users using Medicare Part A and B cohort of 6492 patients

	Treatment group	Number of events	Follow-up time (years)		Incidence rate (per 1000 person-years)	Hazard ratio (95% CI)[a]
			Mean ± SD	Median		
Composite of death, stroke or gastrointestinal bleed	Warfarin-user	545	1.87 ± 1.12	2.08	191.5	0.92 (0.83–1.02)
	Non-user	1890	1.82 ± 1.11	1.92	209.2	1.0 (referent)
Death	Warfarin-user	474	2.05 ± 1.08	2.58	152.2	0.92 (0.82–1.03)
	Non-user	1645	2.00 ± 1.10	2.46	165.6	1.0 (referent)
Death-censored graft failure	Warfarin-user	201	1.91 ± 1.11	2.20	69.3	0.90 (0.76–1.08)
	Non-user	703	1.84 ± 1.13	2.03	76.8	1.0 (referent)
Ischemic stroke	Warfarin-user	55	1.91 ± 1.10	2.19	18.8	1.24 (0.86–1.78)
	Non-user	142	1.87 ± 1.11	2.06	15.3	1.0 (referent)
Hemorrhagic stroke	Warfarin-user	13	1.95 ± 1.09	2.29	4.3	0.95 (0.51–1.75)
	Non-user	43	1.89 ± 1.10	2.12	4.6	1.0 (referent)
Gastrointestinal bleed	Warfarin-user	68	1.91 ± 1.11	2.23	23.4	0.86 (0.63–1.17)
	Non-user	250	1.85 ± 1.11	2.00	27.3	1.0 (referent)

[a]Hazard ratio calculated from an unadjusted weighted robust Cox proportional hazards model where weights were computed from a logistic regression model predicting warfarin use using all variables in Table 1 except BMI and transplant-related variables. Composite = death, stroke or gastrointestinal bleeding.

shows the incidence rates for the three main outcomes as well as the less common outcomes of ischemic stroke, hemorrhagic stroke and gastrointestinal bleed.

Figure 3 shows the results of the Cox survival analysis for the three study outcomes in the IPTW adjusted groups. Warfarin use was associated with non-significant differences in the composite of death, stroke or gastrointestinal bleeding (HR 0.92; 95% CI 0.83–1.02), death (HR 0.92; 95% CI 0.82–1.03) and death-censored graft failure (HR 0.90; 95% CI 0.76–1.08).

HRs from models applied to the Medicare Part D cohort were similar to that of the main cohort, albeit with wider CIs given the relatively small sample size (Supplementary Table S2).

DISCUSSION

In a contemporary cohort of US kidney transplant recipients with newly diagnosed AF, warfarin use was associated with a small non-significant reduction in the composite outcome of death, stroke or gastrointestinal bleed. Data available in non-dialysis chronic kidney disease patients with AF suggest an advantage for standard warfarin therapy in terms of stroke prevention and mortality [27, 28]. Our findings are perhaps more akin to previous studies in the hemodialysis population that have failed to show a definite benefit associated with warfarin use [8, 9].

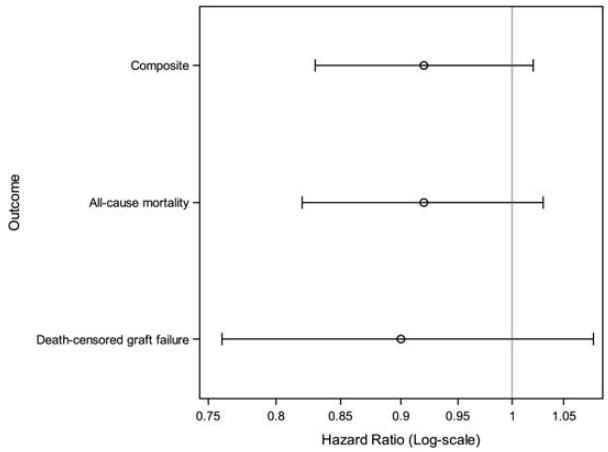

FIGURE 3: Hazard ratios for the main study outcomes based on an IPTW sample of the Medicare Part A and B cohort.

Our work also highlights that kidney transplant recipients with AF are less likely to receive warfarin than has been reported in the general population [9, 29]. Guidelines suggest that individuals with AF and a $CHADS_2$ score ≥2, in the absence of a contraindication, be treated with warfarin [6, 7]. However, just 24.6 and 30.8% of our study subjects with a $CHADS_2$ score ≥2 and ≥4, respectively, received warfarin treatment following a diagnosis of AF. Physicians' unwillingness to anticoagulate kidney transplant patients with AF may reflect the lack of available evidence for warfarin therapy in this unique population, as well as some 'spill-over' concern about increased bleeding risk from studies in the hemodialysis population [8, 9]. Interestingly, age was the only correlate of warfarin use whereas several established stroke and bleeding risk factors were not associated with use of oral anticoagulation. Unfortunately, we do not have data on transplant function, a factor that undoubtedly may influence the decision to initiate warfarin in a kidney transplant patient with AF. Additionally, our claims-based data cannot distinguish between a transient episode of AF (perhaps related to surgery or intercurrent illness) and sustained AF which could also potentially influence the decision to treat with warfarin.

We also examined death-censored graft failure as an outcome. AF is associated with the development of ESRD in the non-transplant population [30, 31], perhaps as a consequence of chronic renal microemboli. The effect of warfarin use on kidney function in chronic kidney disease patients with AF is conflicting. A small retrospective study demonstrated an association between warfarin use and preservation of kidney function in elderly Taiwanese patients with in chronic kidney disease and AF [32]. Other studies have highlighted the potentially deleterious effect of supra-therapeutic INRs on kidney function (so-called warfarin nephropathy) [33, 34]. While we found no association between warfarin use and death-censored graft failure, there was a non-significant trend toward reduced graft failure in the warfarin-treated group.

Confounding by indication represents the greatest threat to the validity of retrospective comparative outcomes studies such as ours. In order to mitigate such confounding, we derived propensity scores for the probability of warfarin use and used the scores to adjust our study groups by IPTW. Using this method, we achieved an excellent balance between the warfarin-treated and non-treated groups in terms of observed baseline characteristics. However, as with all non-randomized analyses, we cannot rule out residual confounding by unobserved variables.

We developed a promising claims-based algorithm developed from a sub-population of our cohort to identify new warfarin use following AF diagnosis. Algorithms utilizing various permutations of prescription claims, the V-code 58.61 and the CPT code 86510 have previously been successfully employed by other research groups [17, 23, 35–37]. Our algorithm gave positive predictive and negative predictive values of 84 and 93% and 90 and 94%, respectively, for warfarin use in inception and external validation cohorts, respectively, meaning that 7–16% of the warfarin-user group and 6–10% of the non-user group were misclassified, an effect that would tend to diminish any treatment-related outcome differences between the groups. We ascertained warfarin use at baseline only (immediately following AF diagnosis) after which there may have been significant unobserved treatment crossover between groups (widespread in warfarin users in the general population [29]), we therefore restricted follow-up to 3-year post-AF diagnosis. The sensitivity and specificity of our algorithm for identifying warfarin use was 62 and 97%, respectively, we therefore limited our discussion of the prevalence and correlates of warfarin use to the cohort of subjects for whom we had warfarin (Medicare Part D) prescription data. We have no information regarding aspirin use which is available over the counter, and an appropriate treatment alternative in individuals at low stroke risk or with contraindications to warfarin [6, 7]. We also have no information on other behaviors that may affect bleeding risk, such as smoking, over-the-counter non-steroid anti-inflammatory drugs (NSAIDs), or histamine-2 receptor antagonist use. It is possible that patients receiving oral anticoagulation are advised to avoid behaviors that put them at increased bleeding risk (smoking, NSAID use) or receive more gastroprotective medications for that indication. The event rates for the individual outcomes of ischemic stroke, hemorrhagic stroke and gastrointestinal bleeding were low. Consequently, the CIs for these events were wide and require caution in interpreting the point estimates of their respective HRs. Finally, our study cohort predates the widespread use of new generation oral anticoagulants.

In summary, in this retrospective analysis of kidney transplant recipients with newly diagnosed AF, we found that anticoagulation with warfarin was associated with a small non-significant reduction in the composite of death, stroke or GI bleeding, death and death-censored graft failure. Rates of warfarin use for AF in the transplant population are below that of the general population. Our data support the need for clinical trials of warfarin in the kidney transplant population with AF.

MANDATORY DISCLAIMERS

Data reported herein were supplied by the United States Renal Data System (USRDS). Interpretation and reporting of these data are the responsibility of the authors and in no way should

be seen as official policy or interpretation of the US government. The content and opinions expressed are solely the responsibility of the authors and do not necessarily represent the views or policies of the Department of Veterans Affairs.

SUPPLEMENTARY MATERIAL

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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