Anticoagulant and Antiplatelet Usage Associates with Mortality among Hemodialysis Patients

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ABSTRACT

Many prescribe anticoagulants and antiplatelet medications to prevent thromboembolic events and access thrombosis in dialysis patients despite limited evidence of their efficacy in this population. This retrospective cohort study examined whether use of warfarin, clopidogrel, and/or aspirin affected survival in 41,425 incident hemodialysis patients during 5 yr of follow-up. The prescription frequencies for warfarin, clopidogrel, and aspirin were 8.3, 10.0, and 30.4%, respectively, during the first 90 d of initiating chronic hemodialysis. Compared with the 24,740 patients receiving none of these medications, Cox proportional hazards analysis suggested that exposure to these medications was associated with increased risk for mortality (warfarin hazard ratio [HR] 1.27 [95% confidence interval (CI) 1.18 to 1.37]; clopidogrel HR 1.24 [95% CI 1.13 to 1.35]; and aspirin HR 1.06 [95% CI 1.01 to 1.11]). The increased mortality associated with warfarin or clopidogrel use remained in stratified analyses. A covariate- and propensity-adjusted time-varying analysis, which accounted for longitudinal changes in prescription, produced similar results. In addition, matching for treatment facility and attending physician revealed similar associations between prescription and mortality. We conclude that warfarin, aspirin, or clopidogrel prescription is associated with higher mortality among hemodialysis patients. Given the possibility of confounding by indication, randomized trials are needed to determine definitively the risk and benefit of these medications.

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Anticoagulation and antiplatelet therapies are indicated for the treatment and prevention of thrombosis or embolism in the general population, in which prospective, randomized trials have demonstrated good efficacy.[1–5] Although no similar studies have been performed in the ESRD population, warfarin, clopidogrel, and aspirin are nevertheless commonly used among these patients when the prevalence of access thrombosis and cardiovascular disease is high.[6] Approximately 30% of dialysis patients are reported to take aspirin[7]; other studies showed a center-specific prevalence of warfarin use to be as high as 25%,[8] even though few if any studies support the benefits of such therapy for patients with ESRD.[9,10] Studies conducted to date have demonstrated no benefit of warfarin on preventing thrombosis in hemodialysis access,[11–14] and the Dialysis Access Consortium trial concluded clopidogrel did not reduce the early failure of new fistulas.[15] No studies have examined the efficacy of anticoagulation or antiplatelet therapy in atrial fibrillation or the prevention of thromboembolism in the ESRD population.[10]

Despite the sparse literature on the efficacy of anticoagulation and antiplatelet use in patients with ESRD, a number of small studies have indicated prescription of such medications may confer harm. Elliott *et al.*[16] concluded that warfarin doubled the

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risk for major bleeding through a systemic review of 28 publications addressing anticoagulation in the ESRD population. In another study of 255 dialysis patients,[17] warfarin was found to increase significantly the risk for bleeding up to four times and aspirin was found to increase the risk by five times. Analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS) patients with ESRD suggested that aspirin could be associated with an increased risk for cardiovascular events and with no decrease in overall mortality.[7] These studies highlight the possibility that anticoagulation and antiplatelet drugs may have a different risk profile in the ESRD population, and their use, singly or in combination, may be contraindicated in a setting where the patients are already anticoagulated with heparin at every treatment and have well-known intrinsic platelet dysfunction when on dialysis[18,19]; therefore, the evidence remains limited as to how warfarin, clopidogrel, and aspirin prescription affect survival in the general dialysis population.

Recently, implementation of automated text-matching software has allowed the accurate identification of oral prescription and documented over-the-counter medications from text fields in the electronic medical records at Fresenius Medical Care North America. This has allowed the integration of pharmacotherapy information with existing laboratory, patient encounter, and demographic data at the individual patient level to answer novel questions about disease management. We sought to determine the prevalence of warfarin, aspirin, and clopidogrel use and establish their contribution to survival in a diverse population of incident hemodialysis patients at Fresenius Medical Care North America.

RESULTS

Baseline Characteristics

In an incident hemodialysis population at the time of the study of 41,425 patients, 8.3% received warfarin, 10.0% received clopidogrel, and 30.4% received aspirin within 90 d of initiating dialysis; 8.1% patients were on at least two of these drugs, and 59.7% were on none. Baseline patient characteristics are summarized in Table 1. Patients on multidrug therapy were older and had increased comorbidity, particularly in cardiovascular disease. As expected, warfarin users had higher international normalization rate (INR) levels and more INR laboratory draws. As well, warfarin users had a higher prevalence of atrial fibrillation and digoxin use (Table 1). There was no clinically relevant difference in heparin administration among the groups.

Among warfarin users, 21.7% had coexistent atrial fibrillation; 0.2% had a diagnosis of hypercoagulable state; 8.5% had a history of arterial thrombosis, pulmonary embolism, or deep vein thrombosis; and 1.5% had a prosthetic mechanical valve. A total of 69.6% of patients on warfarin had no identifiable comorbidity that is considered a standard indication for anticoagulation therapy documented but were presumably on the drug for the prevention of access thrombosis.

Crude and Adjusted Survival Rates

Kaplan-Meier analysis showed significant survival differences between patients (Figure 1). In the full multivariable analysis, warfarin prescription was associated with a 27% ($P < 0.001$) increase in mortality, clopidogrel with a 24% ($P = 0.0002$) increase in mortality, and aspirin with a 6% ($P = 0.02$) increase in mortality when compared with patients receiving none of these medications (Table 2). Prescription of multiple drugs was associated with a 22% ($P < 0.0001$) increase in mortality. No statistically significant interaction was found among warfarin, clopidogrel, and aspirin on survival. Dosage of heparin was found to increase survival minimally (0.992 hazard ratio [HR] per 1000 units; 95% confidence interval [CI] 0.986 to 0.998). Addition of propensity scoring to the model did not significantly change the results (Table 2).

Significantly higher crude mortality and hospitalization rates from bleeding (Table 3) were associated with warfarin or clopidogrel use (*versus* nonuse). The rates of bleeding between patients on aspirin and no medication were statistically and clinically no different. In the covariate and propensity score–adjusted analysis (Table 3), the risk for death or hospitalization from bleeding was also increased when patients were on warfarin or clopidogrel.

Stratified, Time-Varying, and Matched Analyses

Stratified analysis (Figure 2) showed persistent increases in mortality associated with warfarin (35 of 36 strata) or clopidogrel (33 of 36 strata) use. Increased mortality with medication use remained regardless of whether patients underwent dialysis with a fistula, graft, or catheter (Figure 2). Subgroups of patients with a history of myocardial infarction, stroke, or coronary artery disease demonstrated trends of benefiting from aspirin therapy, despite an overall association of increased mortality with its use.

Results from the covariate- and propensity-adjusted time-varying analysis, which accounted for longitudinal changes in patient drug prescription, were consistent with the primary findings ($n = 34{,}254$): Warfarin (HR 1.31; 95% CI 1.21 to 1.42), clopidogrel (HR 1.25; 95% CI 1.15 to 1.36), aspirin (HR 1.04; 95% CI 0.98 to 1.09), and mutlidrug therapy (HR 1.34; 95% CI 1.25 to 1.43).

When matched for facility and attending nephrologist and adjusting once again for the same covariates other than facility, the results remained consistent with the primary findings for risk for death with warfarin (HR 1.21; 95% CI 1.10 to 1.34; $n = 4924$), clopidogrel (HR 1.13; 95% CI 1.03 to 1.24; $n = 5898$), and aspirin (HR 1.04; 95% CI 0.98 to 1.10; $n = 15{,}982$).

DISCUSSION

This retrospective study suggests that commonly prescribed oral anticoagulation or antiplatelet drugs such as warfarin, clopidogrel, and aspirin were also frequently prescribed among a large, national cohort of incident long-term hemodialysis pa-

Table 1. Baseline patient characteristics by drug therapy[a]

Characteristic	Warfarin	Clopidogrel	Aspirin	≥2 Drugs	None	*P*
n	2369	1624	9332	3360	24,740	
Age (yr)	67.40 (0.300)	67.40 (0.300)	65.60 (0.100)	67.50 (0.200)	59.50 (0.100)	<0.0001
Gender (% male)	54.70 (1.000)	48.00 (1.000)	54.40 (0.500)	57.10 (0.900)	52.60 (0.300)	<0.0001
Race (%)						
Caucasian	73.20 (0.900)	65.40 (1.200)	62.30 (0.500)	73.20 (0.800)	52.70 (0.300)	<0.0001
African American	20.30 (0.800)	25.10 (1.100)	28.40 (0.500)	19.10 (0.700)	35.30 (0.300)	
other	6.50 (0.500)	9.50 (0.700)	9.20 (0.300)	7.60 (0.500)	12.00 (0.200)	
Cause of ESRD (%)						
diabetes	39.30 (1.000)	54.60 (1.200)	53.30 (0.500)	54.50 (0.900)	41.10 (0.300)	<0.0001
hypertension	33.40 (1.000)	29.80 (1.100)	31.00 (0.500)	29.60 (0.800)	35.00 (0.300)	
glomerulonephritis	7.60 (0.500)	3.90 (0.400)	4.20 (0.200)	2.90 (0.300)	7.80 (0.200)	
other	19.60 (0.800)	11.80 (0.800)	11.50 (0.300)	13.10 (0.600)	16.10 (0.200)	
BMI (kg/m^2)	29.10 (0.200)	28.10 (0.200)	28.90 (0.100)	28.90 (0.200)	28.20 (0.100)	<0.0001
Albumin (g/dl)	3.52 (0.010)	3.54 (0.010)	3.56 (0.004)	3.54 (0.010)	3.55 (0.003)	0.0020
Hemoglobin (g/dl)	11.50 (0.020)	11.70 (0.030)	11.70 (0.010)	11.60 (0.020)	11.50 (0.010)	<0.0001
Calcium (mg/dl)	8.80 (0.010)	8.70 (0.020)	8.80 (0.010)	8.70 (0.010)	8.70 (0.004)	<0.0001
Phosphorus (mg/dl)	4.73 (0.030)	4.78 (0.030)	4.91 (0.010)	4.73 (0.020)	5.10 (0.010)	<0.0001
PTH (pg/ml)	414.00 (7.000)	432.00 (8.000)	432.00 (3.000)	397.00 (5.000)	484.0 (2.000)	<0.0001
Bicarbonate (mEq/L)	23.50 (0.10)	23.30 (0.100)	23.30 (0.030)	23.50 (0.050)	22.90 (0.020)	<0.0001
Creatinine (mg/dl)	5.90 (0.050)	5.80 (0.050)	6.30 (0.020)	5.70 (0.040)	7.20 (0.020)	<0.0001
Ferritin (ng/ml)	358.00 (7.000)	345.00 (8.000)	319.00 (3.000)	333.00 (5.000)	345.00 (2.000)	<0.0001
WBC count (1000 cells/mm^3)	8.07 (0.050)	8.02 (0.060)	8.03 (0.020)	8.14 (0.040)	7.88 (0.020)	<0.0001
INR	2.23 (0.020)	1.26 (0.050)	1.41 (0.030)	2.10 (0.030)	1.57 (0.030)	<0.0001
INR orders (labs per 90 d)	5.21 (0.050)	0.10 (0.010)	0.08 (0.040)	1.51 (0.020)	0.10 (0.002)	<0.0001
eKt/V with Kru	1.34 (0.010)	1.36 (0.010)	1.35 (0.004)	1.36 (0.010)	1.31 (0.002)	<0.0001
Dialysate calcium (mEq/L)	2.58 (0.010)	2.61 (0.010)	2.57 (0.003)	2.57 (0.005)	2.59 (0.002)	<0.0001
Pre-HD SBP (mmHg)	140.40 (0.500)	149.10 (0.500)	150.50 (0.200)	145.70 (0.400)	150.90 (0.100)	<0.0001
Pre-HD DBP (mmHg)	71.40 (0.300)	74.30 (0.300)	75.60 (0.100)	72.80 (0.200)	79.10 (0.100)	<0.0001
Heparin (1000 IU/session)	4.30 (0.070)	4.57 (0.080)	4.76 (0.030)	4.45 (0.050)	4.63 (0.020)	<0.0001
SMR in facilities	1.01 (0.009)	1.04 (0.010)	0.99 (0.004)	1.00 (0.007)	1.05 (0.003)	<0.0001
Access (%)						
fistula	17.10 (0.800)	17.60 (1.000)	22.10 (0.400)	17.90 (0.700)	21.00 (0.300)	<0.0001
graft	16.90 (0.800)	23.00 (1.000)	19.90 (0.400)	17.90 (0.700)	16.50 (0.200)	
catheter	60.20 (1.000)	53.50 (1.000)	52.30 (0.500)	58.40 (0.900)	55.30 (0.300)	
unknown	5.80 (0.500)	5.80 (0.600)	5.80 (0.200)	5.80 (0.400)	7.20 (0.200)	
Atrial fibrillation (%)	21.40 (0.800)	2.60 (0.400)	3.30 (0.200)	10.00 (0.500)	1.90 (0.100)	<0.0001
CAD (%)	24.20 (0.900)	26.50 (1.100)	24.70 (0.400)	39.90 (0.800)	10.40 (0.200)	<0.0001
Myocardial infarction (%)	7.30 (0.500)	8.80 (0.700)	7.70 (0.300)	14.60 (0.600)	3.00 (0.100)	<0.0001
Stroke (%)	7.90 (0.600)	10.90 (0.800)	6.00 (0.200)	11.50 (0.600)	3.00 (0.100)	<0.0001
HTN (%)	68.20 (1.000)	68.60 (1.000)	71.70 (0.500)	71.10 (0.800)	68.10 (0.300)	<0.0001
CHF (%)	33.70 (1.000)	29.10 (1.100)	27.10 (0.500)	35.20 (0.800)	19.30 (0.300)	<0.0001
Charlson comorbidity index	4.69 (0.040)	4.99 (0.050)	4.85 (0.020)	5.24 (0.030)	4.35 (0.010)	<0.0001
Digoxin use (%)	18.30 (0.800)	6.70 (0.600)	5.90 (0.200)	9.40 (0.500)	2.50 (0.100)	<0.0001

[a]Data are mean (SE). BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; DBP diastolic BP; eKt/V, equilibrated Kt/V; HD, hemodialysis; HTN, hypertension; Kru, residual renal function; PTH, parathyroid hormone; SBP systolic BP; WBC, white blood cell.

tients. Furthermore, exposure to these medications was associated with significantly higher mortality when compared with nonexposure. These findings remained significant with adjustment for multiple confounders and correction for confounding by indication, and in stratified, time-varying, or matched models. The adjusted excess mortality rate associated with warfarin, clopidogrel, or aspirin use in our study cohort was estimated to be three deaths per 100 patient-years.

Mechanism of action of warfarin is to inhibit vitamin K epoxide reductase enzyme, which in turn inhibits the production of clotting factors VII, IX, II, and X and results in disruption of the extrinsic coagulation cascade.[20] Warfarin can also theoretically increase cardiovascular death through the inhibition of Matrix Gla protein and Gas-6 to accelerate vascular calcification.[21] Clopidogrel reversibly blocks adenosine diphosphate and aspirin inactivates the cyclooxygenase enzyme, which inhibit platelet function. These drugs work in series to interrupt the coagulation process and promote dissolution of clots for the primary treatment or prophylaxis of embolic or occlusive vascular disease; however, an increased

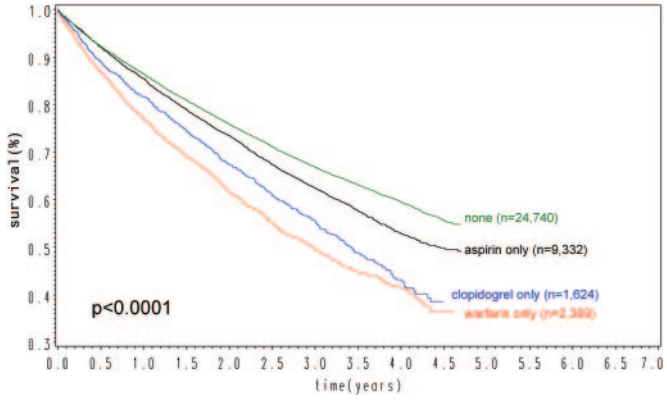

Figure 1. Kaplan-Meier analysis of survival by drug therapy. Log rank test among four groups was $P < 0.0001$. Pair-wise log rank test: Warfarin *versus* none ($P < 0.0001$), clopidogrel *versus* none ($P < 0.0001$), aspirin *versus* none ($P < 0.0001$).

propensity to bleed places dialysis patients at risk for further morbidity and mortality from hemorrhage. We found warfarin or clopidogrel users were at least 39% more likely to die or be hospitalized for major bleeding when compared with patients on no antiplatelet or anticoagulation therapy. This increased risk for bleeding with the use of these medications is often highlighted in dialysis patients because they have an additional acquired defect of platelet dysfunction and altered platelet–vessel wall interaction secondary to uremia.[18,19]

Studies of patients with ESRD that have examined the relationship between survival with anticoagulation and antiplatelet use compared with patients not taking any such medications are limited. This remains an important question because mortality amalgamates the net efficacy and harm of intervention into a single measure. Furthermore, previous studies on anticoagulation and antiplatelet therapy for patients with ESRD limited their focus to a single drug in a small population, limiting their generalizability to dialysis patients across the United States.

In terms of specific medications, this retrospective study documented a significant association of increased mortality with warfarin prescription, which suggests that the risks of such medications outweigh the theoretical benefit of these drugs in most patients with ESRD. The trend persisted in subgroups of patients who are assumed to benefit most from anticoagulation, namely those with a history of coronary artery disease, myocardial infarction, or atrial fibrillation, as well as those at high risk for thrombosis.

The study also found that 69.6% of patients on warfarin did not have an associated comorbid condition documented in the clinical system for which warfarin therapy is indicated. Although we recognize the likelihood of comorbidity underreporting and our inability to track who was on warfarin for prophylaxis of access thrombosis, the large number of patients on warfarin but with no documented indication is suggestive that a reasonable number of patients are likely prescribed these drugs for access thrombosis prophylaxis. Studies to date have

Table 2. Multivariable Cox regression models for mortality HRs by drug therapy[a]

Parameter	*n*	Warfarin	Clopidogrel	Aspirin	≥2 Drugs[b]
Unadjusted	41,425	1.73 (1.62 to 1.85)	1.50 (1.39 to 1.62)	1.17 (1.12 to 1.22)	1.54 (1.46 to 1.64)
Adjusted					
model 1: age, gender, race, Charlson comorbidity index	41,305	1.37 (1.28 to 1.46)	1.16 (1.07 to 1.25)	0.96 (0.92 to 1.00)	1.16 (1.09 to 1.23)
model 2: model 1 + entry period	41,305	1.37 (1.28 to 1.46)	1.16 (1.07 to 1.26)	0.96 (0.92 to 1.00)	1.16 (1.10 to 1.23)
model 3: model 2 + dialysis access	41,305	1.35 (1.26 to 1.44)	1.16 (1.07 to 1.25)	0.97 (0.93 to 1.01)	1.15 (1.08 to 1.22)
model 4: model 3 + stratification for SMR	41,305	1.38 (1.29 to 1.47)	1.15 (1.06 to 1.25)	1.00 (0.96 to 1.04)	1.17 (1.10 to 1.24)
model 5: model 4 + BMI	41,154	1.39 (1.30 to 1.48)	1.15 (1.06 to 1.25)	1.01 (0.96 to 1.05)	1.18 (1.11 to 1.25)
model 6: model 5 + cardioprotective medications	41.154	1.33 (1.24 to 1.43)	1.20 (1.11 to 1.31)	1.05 (1.01 to 1.10)	1.24 (1.17 to 1.32)
model 7: model 6 + heparin dosage[c]	41,154	1.33 (1.24 to 1.42)	1.22 (1.11 to 1.31)	1.05 (1.01 to 1.10)	1.24 (1.17 to 1.32)
model 8: model 7 + baseline laboratory values	34,461	1.27 (1.18 to 1.37)	1.24 (1.13 to 1.35)	1.06 (1.01 to 1.11)	1.22 (1.14 to 1.31)
model 9: model 8 + propensity score[c]	34,461	1.28 (1.16 to 1.40)	1.23 (1.10 to 1.38)	1.06 (1.00 to 1.13)	1.22 (1.12 to 1.34)

[a]Reference group is no drug. Variable eliminated ($P > 0.20$) from regression: Bicarbonate.
[b]Mortality HRs by different drug combinations: Aspirin + clopidogrel (HR 1.18; 95% CI 1.07 to 1.30), aspirin + warfarin (HR 1.33; 95% CI 1.16 to 1.52), clopidogrel + warfarin (HR 1.38; 95% CI 1.03 to 1.86), aspirin + clopidogrel + warfarin (HR 1.34; 95% CI 0.99 to 1.83).
[c]Mortality HR for heparin 0.99 (95% CI 0.990 to 0.998) per 1000 U of heparin administered.

Table 3. Mortality and hospitalization from bleeding[a]

Parameter	*n*	Warfarin		Clopidogrel		Aspirin		≥2 Drugs		None
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	
Crude mortality rate	41,425	0.21 (0.08 to 0.55)	0.0400	0.30 (0.12 to 0.77)	0.0020	0.10 (0.05 to 0.22)	0.9500	0.11 (0.04 to 0.31)	0.8400	0.10 (0.08 to 0.13; ref)
Crude hospitalization rate	41,425	2.93 (2.28 to 3.73)	0.0002	2.52 (1.91 to 3.34)	0.0800	2.13 (1.80 to 2.52)	0.6400	2.24 (2.11 to 3.27)	0.0030	2.07 (1.94 to 2.19; ref)
Adjusted HR for mortality[b]	34,200	1.77 (0.82 to 3.82)		2.74 (1.26 to 6.00)		0.90 (0.51 to 1.59)		0.90 (0.38 to 2.14)[c]		1.00 (ref)
Adjusted HR for hospitalization[b]	34,200	1.46 (1.18 to 1.81)		1.39 (1.08 to 1.80)		1.05 (0.91 to 1.20)		1.27 (1.03 to 1.55)[d]		1.00 (ref)

[a]Rates reported as incidence density in events per 100 patient years (95% CI, *P* value in comparison with none).
[b]Adjusted for age, race, gender, Charlson comorbidity index, entry date, dialysis access, cardiovascular drug use, BMI, baseline laboratory values (hemoglobin, albumin, calcium, phosphorus, PTH, creatinine, WBC count, and ferritin), dialysate calcium, heparin dosage, and propensity score with stratification for the facility SMR.
[c]Mortality HRs by different drug combinations: Aspirin + clopidogrel (HR 0.84; 95% CI 0.29 to 2.37); warfarin + clopidogrel and/or aspirin (HR 1.05; 95% CI 0.25 to 4.41); patients who received aspirin + warfarin, clopidogrel + warfarin, or aspirin + clopidogrel + warfarin were pooled together (*i.e.*, warfarin + clopidogrel and/or aspirin) because two of the groups had no deaths from bleeding.
[d]Hospitalization HRs by different drug combinations: Aspirin + clopidogrel (HR 1.11; 95% CI 0.87 to 1.43); aspirin + warfarin (HR 1.57; 95% CI 1.13 to 2.20); clopidogrel + warfarin (HR 2.19; 95% CI 1.03 to 4.66), aspirin + clopidogrel + warfarin (HR 1.13; 95% CI 0.36 to 3.53).

not been able to demonstrate a significant association between warfarin and decreased risk for access thrombosis.[11–14] The results seem to apply to patients with grafts, fistulas, and catheters as suggested by the stratified analysis. Furthermore, increased mortality associated with catheter use may be partially attributed to locking with heparin or tissue plasminogen activator,[22] which can leak or accidentally be pushed into the patient's circulation. Although the stratified analyses identified a possible survival benefit with warfarin in patients with a history of stroke, further studies are necessary to validate this finding given the effect was statistically insignificant ($P = 0.38$).

No studies in the dialysis population have examined the outcomes associated with the long-term use of clopidogrel, which is used for the treatment of stroke and acute coronary syndrome and has been evaluated for its use in preventing fistula thrombosis. With respect to access, a recent National Institutes of Health–sponsored randomized trial showed clopidogrel use after fistula creation did not increase its likelihood to become suitable for dialysis.[15] Furthermore, another randomized trial of 200 patients with grafts was stopped early when patients receiving both aspirin and clopidogrel had more bleeding than those on placebo. There was no significant benefit of active treatment in the prevention of thrombosis.[23] We found clopidogrel prescription was associated with a 24% increased risk for mortality.

With respect to aspirin use, a small but significant increase in mortality was seen and fully adjusted HRs were statistically no different from the result reported in the DOPPS study[7] for patients with ESRD; however, the finding was not consistently demonstrated in subsequent sensitivity analyses. Further study is required before more definitive conclusions can be drawn about aspirin's role in the prevention of cardiovascular disease in ESRD.

As reported in other studies,[7,8] the prescription of warfarin, clopidogrel, and aspirin was found to be common in this large and diverse dialysis population. The only other comparable study of similar size and diversity focused on aspirin, in which the prevalence was 31.3%[7] and was close to the 30.4% found in our study.

The main limitations of this study are associated with its retrospective and observational design. First, use of electronic data confers the potential of underreporting and information bias from misclassification. Our study found 4% of patients not on warfarin had at least one INR value in the first 90 d of dialysis, which could represent unidentified warfarin prescription, patients with concurrent coagulopathy from liver disease, or desire to get a baseline value at the start of dialysis. Conversely, 30% of warfarin users had no INR monitoring, which could represent patients who sought warfarin monitoring from an outside clinic, misclassification, or the use of low-dosage warfarin. Although the collection of covariates and outcome parameters into the clinical data system undergoes quality assurance/control auditing processes,[24,25] an external validation of the information was not feasible given the large

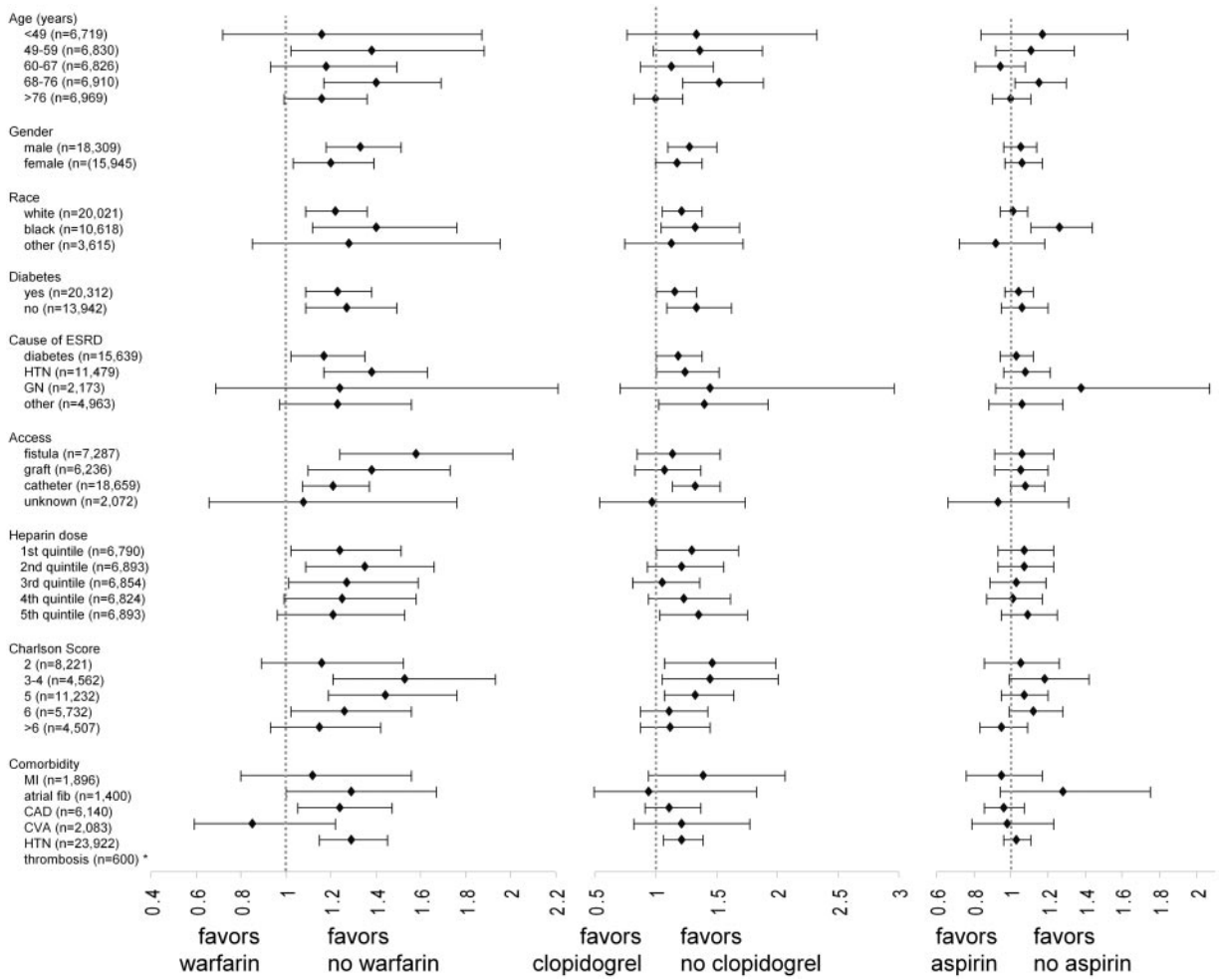

Figure 2. Mortality HRs by different drug therapy, stratified according to the characteristics of the patient. *Mortality HRs in patients with a history of thrombosis ($n = 600$): HR for warfarin (*versus* no warfarin) 1.28 (95% CI 0.81 to 2.04); HR for clopidogrel (*versus* no clopidogrel) 0.78 (95% CI 0.41 to 1.48); HR for aspirin (*versus* no aspirin) 1.39 (95% CI 0.75 to 2.59). All models are adjusted for age, race, gender, Charlson comorbidity index, entry date, dialysis access, cardiovascular drug use, body mass index, baseline laboratory values (hemoglobin, albumin, calcium, phosphorus, parathyroid hormone, creatinine, white blood cell count, and ferritin), dialysate calcium, heparin dosage, and propensity score with stratification for the facility SMR.

size and geographic diversity of the patient cohort. Overall, baseline characteristics by study group seemed reasonably consistent with patterns seen in clinical practice and other epidemiologic studies,[26] which supports internal validity. The database is primarily a clinical database that facilitates day-to-day health care delivery, with the focus on ensuring that data are entered accurately for patient care. Second, even with propensity scoring, the possibility of confounding by indication cannot be excluded without blinding and randomization. Propensity scoring was used to adjust for selection effects reflected in the 34 comorbid, demographic, or laboratory variables used in the model but not for those attributed to unmeasured factors. Third, we highlight that 16.8% of patients were excluded from the final adjusted model (models 8 and 9 in Table 2) because of missing covariate data, which could result in selection bias. Fourth, we did not examine the contribution of the daily dosage of warfarin, clopidogrel, and aspirin to our results. Finally, our analysis focused on the effects of anticoagulation and antiplatelet administration in the general ESRD population. As a next step, we recommend a more detailed investigation by indication for drug prescription to develop and validate practice recommendations that can be more relevant to an individual's clinical status.

This study has some strengths. We had access to an extensive clinical database that integrates a wide array of demographic, clinical, laboratory, pharmacologic, and patient encounter data that has been used to distill meaningful clinical conclusions in the past.[25,27–29] The patients in our study were representative of patients seen in routine clinical practice, because we drew from a national population and few patients were excluded from the analysis. Furthermore, inclusion of patients from a large number of clinics (1303 clinics in total) likely minimized bias.[30] In addition, the results for warfarin and clopidogrel withstood several sensitivity analyses that in-

corporated propensity scoring, time-varying modeling, stratification, and matching. Increased mortality remained regardless of physician, facility, demographics, access, comorbidity, or propensity for treatment.

In conclusion, our study found a clinically and statistically significant association between warfarin or clopidogrel prescription and mortality in a large population of incident hemodialysis patients. Formal testing of this hypothesis through randomized trials would be a reasonable next step. Until then, these drugs should be generally avoided for access prophylaxis and other indications for which the evidence for efficacy is sparse.

CONCISE METHODS

Study Cohort and Data Collection

We initiated the start of follow-up of patient outcomes from the time the patient started dialysis. We included all patients who were admitted to a Fresenius Medical Care clinic between January 1, 2003, and December 31, 2004, and initiated long-term hemodialysis for the first time within the previous 31 d. The entire study cohort was followed to December 31, 2007. Patients with <3 mo of follow-up ($n = 7400$) were excluded from the study.

All study data were prospectively entered into a central electronic database. The Clinical Quality Group and Data Entry Error Reduction Task Force at Fresenius mandates protocols and audits incoming information to ensure demographic, laboratory, and mortality data are accurately documented for clinical care and Medicare billing. In addition, clinical data are initially decoupled from identification fields before being uploaded into the data warehouse tables. The assignment of encrypted patient identification numbers permits the analysis of health care information in an anonymous manner. Oral medication records tracked all active prescriptions and over-the-counter medications prescribed by any physician from whom the patient had sought medical care in a wide range of health care settings. Patients are instructed to bring their medication bottles to clinic once per month, on admission, or after hospitalization so nurses can update the medication record for accuracy. Registered nurses are responsible for recording hospital discharge diagnosis and comorbidity data from obtained copies of discharge summaries and physician progress notes. All blood samples collected are uniformly processed and shipped by Spectra East (Rockland, NJ), a good clinical practice–accredited central laboratory. The INR assay used incorporates heparin adsorbent to remove heparin from the plasma of blood samples before anticoagulation testing (Inotech Biosystems Int., Rockville, MD). In the past 10 yr, multiple high-quality publications have resulted from the analysis of clinical data from the same Fresenius repository of electronic data we used in the study.[25,27–29]

Identification and Classification of Oral and Over-the-Counter Medications

All outpatient medications were entered in free text fields in the electronic medical records. We developed a computer algorithm using PERL[31] to parse these free text fields to identify specific anticoagulation, antiplatelet, and cardiovascular drugs against the current list of all trade and generic drug names approved by the Food and Drug Administration.[32] The algorithm used "fuzzy string matching"[33] to ensure drug entries with lexical and spelling errors would be identified. Such software is currently used in spell-checking software to match unrecognized words against a dictionary to make suggestions for misspelled words. The technology's accuracy was previously validated on live medical records.[34]

To validate the accuracy of the fuzzy string matching algorithm in the Fresenius database, we randomly selected 10,000 drug entries from the study cohort and used the PERL script to identify possible anticoagulation, antiplatelet, or cardiovascular drugs from this list. A blinded physician also manually reviewed the same 10,000 drug entries. The algorithm had a negative predictive value of >99.9% and a positive predictive value of 16% (sensitivity 99.8%; specificity 51.6%).

For the actual study, the algorithm was used to identify a subset of electronic drug entries that matched or approximately matched an anticoagulation, antiplatelet, or cardiovascular drug approved by the Food and Drug Administration. Drug entries ruled in by the algorithm were then reviewed by a physician blinded to patient and outcomes to ensure the accurate classification of the drug entry before it was used in the final analysis.

We also examined the concurrent relationship between INR and warfarin drug entries to validate whether patients classified as warfarin users in the clinical database were taking the drug. Seventy percent of warfarin users had at least one INR checked in the first 90 d of dialysis, whereas 96% of patients not on warfarin had no INR monitoring. A 1-mg increase in daily warfarin dosage recorded in the clinical records was significantly associated with a corresponding 0.28 increase in INR ($R^2 = 0.31$, $P < 0.0001$), consistent with a dosage-response relationship between a patient's warfarin status documented in the clinical system and his or her actual degree of anticoagulation.

Outcomes, Drug Exposure, and Baseline Characteristics

The primary outcome of the intention-to-treat analysis was mortality. Death and hospitalization from bleeding was the secondary outcome.

Warfarin, clopidogrel, and aspirin exposure at baseline was defined as any use within the first 90 d of the study. The process for extracting these oral and over-the-counter medication prescription information from the clinical data system was described already. We categorized patients into one of eight groups representing all possible prescription combinations for clopidogrel, aspirin, and warfarin during the first 90 d of dialysis (none as the reference group).

Standard baseline demographic, laboratory, cardioprotective medication use, and comorbidity characteristics were collected during the first 90 d of study enrollment. Race was categorized as Caucasian, African-American, or other. Dialysis access was categorized as graft, fistula, catheter, or unknown used on the 90th day after the start of hemodialysis. Heparin dosage was defined as the average total units of heparin administered per dialysis session and

did not include units used for catheter locking. Cardioprotective medication use was determined and validated with the same procedure used for warfarin, clopidogrel, and aspirin. We used information documented in the electronic database under hospital discharge diagnoses, renal diagnosis, cause of death, and medical history to identify the presence of hypertension, previous stroke, coronary artery disease, thrombosis (pulmonary embolism, deep vein thrombosis, hypercoagulable state, or arterial clot), diabetes, congestive heart failure, atrial fibrillation, bleeding, and other comorbidities. Baseline comorbidity was quantified using the Charlson comorbidity index,[35] an instrument that can be accurately implemented with patient information abstracted from medical records and *International Classification of Diseases, Ninth Revision* coding[36–41] and has been validated as a predictor of mortality in the dialysis populations.[42,43] The index scores morbidity through the presence or absence of 19 possible chronic conditions in an individual patient recorded in the first 90 d of dialysis. Study entry date was defined as days after January 1, 2003. The facility standardized mortality ratio (SMR) was defined as the facility-specific, case mix–adjusted mortality rate relative to all Fresenius dialysis centers throughout the United States on January 1, 2003.[44] SMR was stratified for in the Cox models to diminish between-center variations in survival that were not accounted for in the other measured covariates.

To account for the potential for confounding by indication and selection effects, we implemented propensity score–based risk adjustment for multiple groups.[45,46] To quantify the degree of possible bias, we used multinomial logistic regression to model the probability for prescription to all eight possible combinations of clopidogrel, aspirin, and warfarin a patient could receive (none as the reference group, clopidogrel only, aspirin only, warfarin only, or in any combination) as a function of the laboratory and demographic variables used in the primary analysis and 19 comorbid diagnoses (stroke, myocardial infarction, atrial fibrillation, hypertension, peptic ulcer disease, AIDS, peripheral vascular disease, coronary artery disease, dementia, chronic obstructive pulmonary disease, hemiplegia, diabetes, cancer, liver disease, arterial clot, deep vein thrombosis, mechanical heart valve, pulmonary embolism, and hypercoagulable state). We incorporated these propensity scores as covariates into the Cox regression models.

Four-way ANOVA and χ^2 statistics were used to compare continuous and categorical values, respectively. Continuous variables were expressed as mean (SE). Categorical variables were expressed as percentage (SE). Incidence rates with 95% CIs for INR orders, death from bleeding, and hospitalization from bleeding were calculated using Poisson regression.

Statistical Analysis

The Kaplan-Meier method was initially used to examine crude survival in the entire cohort between patients on only warfarin, clopidogrel, aspirin, and no drug therapy. *P* values were determined using the log-rank test. We followed this with a Cox regression analysis using backward variable selection with variable exit criteria set at $P < 0.2$ to adjust progressively for confounders such as age, race, gender, Charlson comorbidity index, entry date, dialysis access, cardiovascular drug use, body mass index, baseline laboratory values (hemoglobin, albumin, calcium, phosphorus, parathyroid hormone, creatinine, bicarbonate, white blood cell count, and ferritin), dialysate calcium, propensity score, and heparin dosage with stratification for the facility SMR. Diabetic status was a component of the Charlson comorbidity score (+3 points). The analysis used available cases when covariates were missing, whereas interaction effects were tested in separate models through the inclusion of cross-product terms between warfarin, clopidogrel, and aspirin. Covariate- and propensity score–adjusted HRs for mortality and hospitalization from bleeding with drug use were also calculated in the same way. We also performed a stratified analysis, with adjustment for baseline covariates and propensity score, for a number of variables (age, gender, race, diabetic status, cause of ESRD, access, Charlson score, individual comorbidities, and heparin dosage) to examine more closely how baseline differences were associated with the outcome of mortality.

The primary analysis was intention to treat, which assumed patients remained on the same medications prescribed in the first 90 d of dialysis throughout the follow-up period. To account for the possibility that patients could add, stop, or switch a medication after the first 90 d of dialysis, we performed a secondary analysis in which drug exposure (warfarin, clopidogrel, aspirin, or multidrug *versus* none) was modeled as time-varying variable (monthly changing). For this analysis, the same baseline covariates and propensity scores used in the primary analysis and measured during the first 90 d of dialysis were entered into the Cox model.

Finally, to account for the possibility of residual and nonlinear confounding inherent to the treating clinic or physician that could not be completely adjusted for with the facility SMR, we performed a 1:1 matched analysis using a "greedy nearest available" matching algorithm.[47,48] For example, we performed a sensitivity analysis to determine the survival associated with warfarin use *versus* nonuse using Cox regression, after matching to ensure patients in the two groups were from the same facility and under the care of the same nephrologist. Like in the primary analysis, we adjusted for age, race, gender, Charlson comorbidity index, entry date, dialysis access, cardiovascular drug use, body mass index, baseline laboratory values (hemoglobin, albumin, calcium, phosphorus, parathyroid hormone, creatinine, bicarbonate, white blood cell count, and ferritin), dialysate calcium, propensity score, heparin dosage, clopidogrel use, and aspirin use. Logistic regression was used to estimate the propensity score for warfarin as a function of clopidogrel use; aspirin use; and the same demographic, laboratory, and comorbidity variables used in the multinomial propensity model mentioned already. The analysis was then repeated in a similar manner with clopidogrel and then aspirin as the predictor variable.

All statistical analysis was done using SAS 9.0 (SAS Institute, Cary, NC). The study had no external funding.

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DISCLOSURES

None.

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