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ORIGINAL ARTICLE

Efficacy of Antiplatelet Agent Usage for Primary and Secondary Prevention in Dialysis Patients: a Nationwide Data Survey and Propensity Analysis

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Abstract

Background Although cardiovascular (CV) disease is the leading cause of mortality and morbidity in dialysis patients, there is little evidence to guide the use of antiplatelet agents in dialysis patients.

Method A nationwide database (Registry for Catastrophic Illnesses) for Taiwan, which has data from nearly all patients who received dialysis therapy from 1995 to 2008, was used. This is a population-based cohort study with time to event analyses to estimate the relation between antiplatelet agent use and outcomes. Hazard ratios were calculated to evaluate the effect of antiplatelet agent use on the risk of major CV events and mortality. Baseline characteristics were matched by propensity score (PS).

Results A total of 71,835 were included, and 10,595 (14.7%) patients received an anti-platelet agent. The median value of follow-up days was 61.6 months. After PS-based matching, 9598 patients who used an antiplatelet agent and 23,794 non-users were included in the analysis. After PS matching, there was no difference between patients using an antiplatelet agent or not in CV events ($p = 0.672$) and total mortality ($p = 0.529$). A subgroup analysis of different usage periods of antiplatelet agents indicated that CV events and total mortality were similar in those who used antiplatelet agents for short or long durations. In subgroup analysis, there was also no difference between patients with a different modality of dialysis (hemodialysis or peritoneal dialysis), different antiplatelet agents (aspirin, clopidogrel, and/or ticlopidine) or patients with/without previous cardiovascular disease in CV events and total mortality.

Conclusions Antiplatelet agent usage does not reduce CV events and total mortality in dialysis patients.

Keywords Antiplatelet · Aspirin · Clopidogrel · Ticlopidine · Dialysis · Propensity score

Introduction

Cardiovascular (CV) disease is the leading cause of mortality and morbidity in patients with chronic kidney disease or end-stage renal disease (ESRD) [1]. Patients in dialysis have a poorer outcome after acute coronary syndrome (ACS) compared with patients with normal renal function [2]. However, even though antiplatelet therapy is effective in preventing CV events in high CV risk patients [3], in contrast to other CV risk factors, the data on antiplatelet therapy for dialysis patients is rare [3, 4]. Unfortunately, there is little evidence to guide the use of aspirin or other antiplatelet agents in dialysis patients [5].

To date, there have been no randomized controlled trials that have specifically evaluated the effects of antiplatelet therapy on the primary or secondary prevention of atherosclerotic

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events in dialysis patients [6]. A meta-analysis derived from 14 small studies on antiplatelet therapy for maintenance of access patency among 2632 hemodialysis patients demonstrated a 41% reduction in the relative risk of serious vascular events [3]. In contrast to this, in another study (DMMS Wave 2) which included 3374 dialysis patients with or without coronary artery disease (CAD) failed to show the benefit of aspirin for CV event prevention [7]. However, in another large observational study with 28,320 randomly selected hemodialysis patients, aspirin was associated with decreased risk of stroke in all patients and increased risk of myocardial infarction (MI) and cardiac events [8].

Antiplatelet agents other than aspirin, such as thienopyridines (ticlopidine or clopidogrel), have an equal or better effect preventing CV events in high CV risk patients and a lower rate of gastrointestinal bleeding [9, 10]. These characteristics make them a better choice for dialysis patients. They are also commonly used as antiplatelet agents instead of aspirin in dialysis patients [11]. However, clopidogrel was associated with a higher mortality than aspirin in a retrospective cohort study that enrolled 41,425 hemodialysis patients [12].

The worldwide number of patients with ESRD who are undergoing dialysis has grown significantly in recent decades. In particular, the current incidence and prevalence of ESRD are extremely high in Taiwan [13]. Thus, we performed a nationwide, population-based study of a large cohort of dialysis patients from Taiwan, with the use of propensity score matching to reduce selection bias and confounding effects, to examine the effect of the use of an antiplatelet agent on major clinical endpoints and to compare the effects among different antiplatelet agents.

Methods

Data Sources, Study Population and Outcomes, Comorbidities, and Propensity Score (PS)–Based Matching

Data Sources

The Taiwan National Health Insurance (NHI) program was implemented in March 1995, and > 99% of the total population of Taiwan are currently enrolled in this program [13]. In 1996, the Bureau of NHI (BNHI) contracted with 97% of the hospitals and clinics throughout Taiwan [14]. The National Health Research Institute (NHRI) cooperates with the BNHI to establish an NHI research database for research. The BNHI performs expert reviews on a random sample of every 50–100 ambulatory, and inpatient claims on a quarterly basis to ensure the accuracy of the claims files, with false diagnoses possibly leading to severe penalties from the BNHI [15]. Data for age, gender, use of medications, and diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; www.icd9data.com/2007) were retrieved for the analyses performed in this study.

Study Population and Outcomes

For the current study, we used the Registry for Catastrophic Illness database from the NHRI. This database encompasses almost all patients who received renal replacement therapy from 1995 to 2008 in Taiwan (with a total population of about 23 million people). Following a review of ambulatory and inpatient claims data, we included ESRD subjects undergoing hemodialysis or peritoneal dialysis, older than 18 years, and without a history of CV events and antiplatelet therapy in 1997 and 1998. The exclusion criteria were as follows: patients had CV events defined as ACS (including Q wave or non-Q wave myocardial infarction and unstable angina; ICD-9-CM codes 410.X, 411.1), coronary intervention (including percutaneous coronary intervention and coronary artery bypass grafting; ICD-9-CM codes 36.0X, 36.1X) or previous stroke (e.g., ischemic stroke, hemorrhagic stroke, or transient ischemic accident; ICD-9-CM codes 430.X-432.X, 435.X, 434.X) within 90 days after or before dialysis therapy; patients receiving antiplatelet before dialysis therapy; patients who used more than one antiplatelet agent. The patient flow diagram is shown in Figure 1. The date of inclusion was the date dialysis therapy was started. The patients were followed from the date of inclusion to 2009. The median value of the follow-up days was 61.6 months. The main variables of interest were the use of an antiplatelet agent, which were identified from prescription claims data. We collected information about the prescribed drugs, including dosage and dates of prescriptions, supply days, and a total number of dispensed pills by review of the outpatient pharmacy prescription database, which is part of the claims database. By searching the outpatient pharmacy prescription database, we retrieved the codes and collected information on the prescription of other prescribed medications including statin, warfarin, betablockers, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), calcium channel blockers (CCBs), oral hypoglycemic agents, and insulin. A total of 71,835 subjects were included in the final analyses. The clinical outcomes were death, new-onset ACS (including unstable angina, Q wave or non-Q wave myocardial infarction), coronary intervention (including percutaneous coronary intervention and coronary artery bypass grafting), and ischemic stroke. We also followed the major bleeding events which included intracranial hemorrhage (ICH; ICD-9-CM codes 430.X-432.X) and hospitalized due to gastrointestinal bleeding (ICD-9-CM codes 456.X, 530.X, 562.X, 569.X, 578.X).

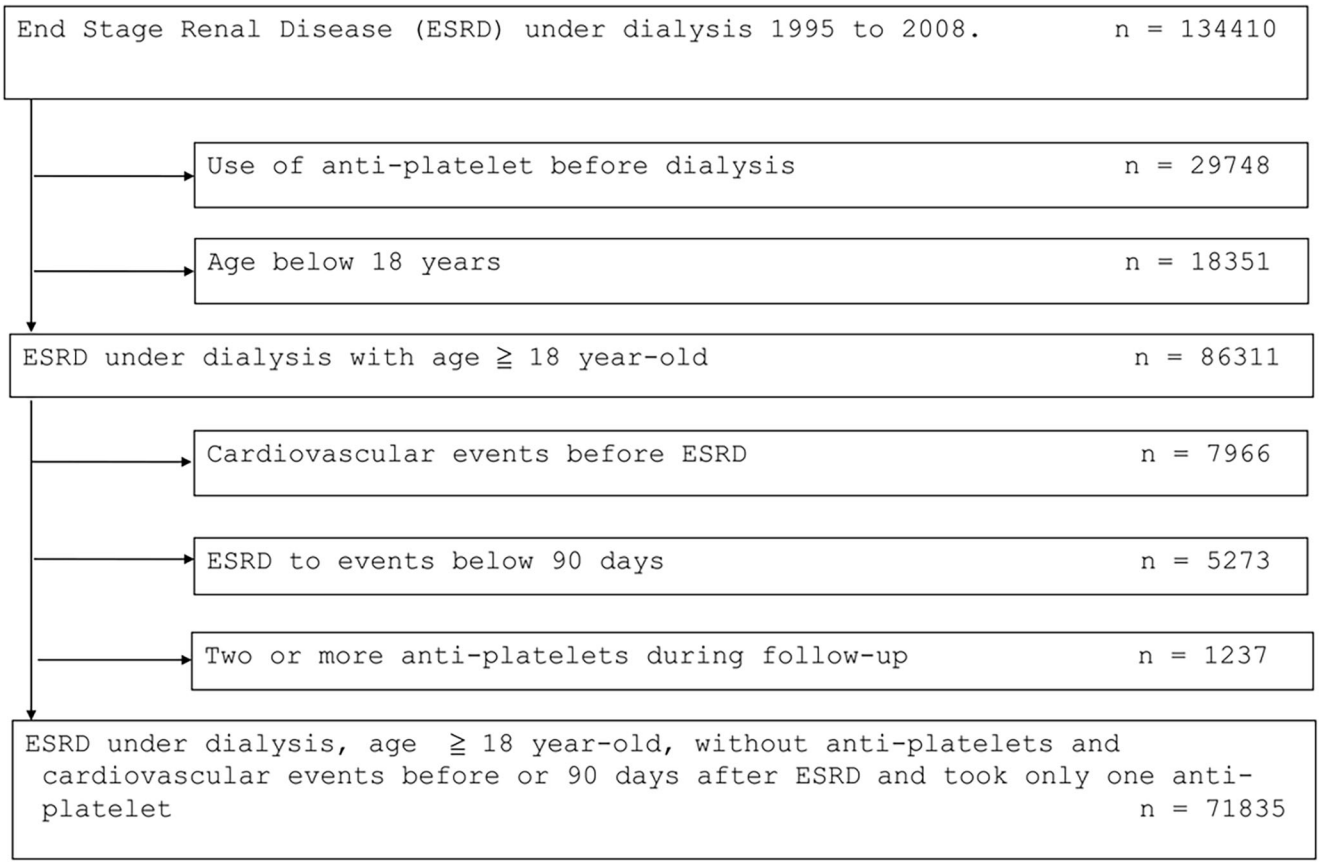

Fig. 1 The designed patient flow diagram

Comorbidities

The presence of comorbidity was defined by diagnosis at hospital discharge or by review of the clinical record, after the index use of an antiplatelet agent. We searched the database for the presence of diabetes mellitus (DM; ICD-9-CM codes 250.X, 249.X), hyperlipidemia (ICD-9-CM codes 272.X), hypertension (HTN; ICD-9-CM codes 401.X-405.X), CAD(ICD-9-CM codes 411.X-414.X, V17.3, V81.0), congestive heart failure (CHF; ICD-9-CM codes 428.0–428.3, 428.9), peripheral arterial disease (PAD; ICD-9-CM codes 250.7, 443.X, 444.2), and atrial fibrillation (AF; ICD-9-CM codes 427.31, 427.3).

Propensity Score–Based Matching

Propensity score (PS) matching is a statistical method used to account for observed covariates in the comparison of two treatment groups. In the present study, the PS was the conditional probability for the use of an antiplatelet agent (binary dependent variable) under a set of measurements [16]. Clinical risk factors, such as age, gender, HTN, DM, CHF, other comorbidities, and medication usage (except antiplatelet agent) were added into a non-parsimonious multivariable logistic regression model to predict the preference for use of an antiplatelet agent. The predicted probability derived from the logistic equation was used as the PS for each patient. Subjects using and not using an antiplatelet agent were pooled together and sorted according to their PS in ascending order. Patients without appropriate matches within the acceptable rank range were excluded from further analysis. Since the patient population in the control group is far greater than that in the antiplatelet group, a well-matched 3:1 cohort was chosen. The covariate coefficients (odds ratio) and goodness of fit estimated by Cox and Snell R square were listed in Table 1. The acceptable rank range for matching was 0.05.

Statistical Analysis

For analysis of the baseline characteristics of users and nonusers of an antiplatelet agent, categorical covariates were compared with the chi-square test. For estimation of the risk associated with duration of an antiplatelet agent use and development of CV events and mortality, Cox's proportional hazard models (with adjustment for age, gender, risk factors [hypertension (HTN), diabetes mellitus

Table 1 Results of the logistic regression model used for propensity matching. The rank range chosen for propensity matching is 0.05. The goodness of fit estimated by Cox and Snell *R* square is 0.077

	Odds ratio	95% C.I. of odds ratio	*P*
Age	1.013	1.011–1.014	< 0.001
Gender	1.009	0.966–1.054	0.685
Hemodialysis	0.942	0.881–1.006	0.076
HTN	0.963	0.913–1.016	0.165
DM	0.998	0.951–1.046	0.923
Hyperlipidemia	1.022	0.972–1.074	0.393
CAD	0.992	0.944–1.043	0.760
PAD	1.017	0.964–1.073	0.542
CHF	1.215	1.157–1.275	< 0.001
AF	1.056	0.955–1.168	0.289
Warfarin	2.029	1.869–2.201	< 0.001
Beta-blocker	1.835	1.745–1.930	< 0.001
CCB	1.812	1.713–1.917	< 0.001
ACEI/ARB	1.519	1.444–1.598	< 0.001
OHA	1.325	1.259–1.395	< 0.001
Insulin	1.356	1.276–1.441	< 0.001
Statin	1.514	1.438–1.594	0.001
Constant	0.029	0.065	0.001

HTN, hypertension; *DM*, diabetes mellitus; *CAD*, coronary artery disease; *PAD*, peripheral artery disease; *CHF*, congestive heart failure; *AF*, atrial fibrillation; *CCB*, calcium channel blocker; *ACEI*, angiotensin-converting enzymes inhibitor; *ARB*, angiotensin receptor blocker; *OHA*, oral hypoglycemia agents

(DM), hyperlipidemia], comorbidities [coronary artery disease (CAD), peripheral artery disease (PAD), congestive heart failure (CHF), atrial fibrillation (AF)] and medications in the model were used. Subjects who did not use an antiplatelet agent were defined as the reference group and were compared with patients who used an antiplatelet agent for different durations. The study subjects were divided into tertiles according to the total duration of an antiplatelet agent use. The event-free survival time was defined as the time from the day of enrollment to the occurrence of an event. If an event did not occur, the case was classified as censored at the end of the study. Subgroup analyses were used to determine if the results remained for subgroups with different age, gender, cardiovascular disease (CVD; CVD = CAD + PAD) incidence, or use of other medications. Kaplan-Meier curves were plotted to show the event-free survival of users and non-users of an antiplatelet agent. To compare the effects between the usages of an antiplatelet agent, we used Cox's proportional hazard models to adjust for possible confounding factors. Subjects who did not use an antiplatelet agent served as the reference group and were compared with patients who used an antiplatelet agent after PS matching by use of a logistic regression model. All analyses were performed with SPSS 15.0 for Windows 7 (SPSS Inc. Chicago, IL, USA). A 2-tailed *p* value of less than 0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

The designed patient flow diagram is shown in Fig. 1. Table 2 summarizes the basic demographic and clinical characteristics of the patients. A total of 71,835 patients (34,269 men) were included in the final analyses, and the median follow-up period was 61.6 months. An antiplatelet agent was prescribed to 10,595 (14.7%), among whom 7440 patients received aspirin, 1607 patients received clopidogrel, and 1548 patients received ticlopidine. Compared with the control group, subjects receiving an antiplatelet agent were older (59.9 ± 13.2 vs. 59.6 ± 15.0 years, $p = 0.003$) and more likely to have CHF (30.0% vs. 22.0%, $p < 0.001$). Patients using an antiplatelet agent were also more likely to receive a concomitant medication, including warfarin (9.3% vs. 3.8%, $p < 0.001$), a betablocker (58.3% vs. 30.6%, $p < 0.001$), a calcium channel blockers (CCB, 74.9% vs.46.7%, $p < 0.001$), an angiotensin-converting enzyme inhibitor (ACEI)/ARB (angiotensin II receptor blocker) agent (57.3% vs. 30.9%, $p < 0.001$), an oral hypoglycemic agent (OHA; 33.1% vs.16.4%, $p < 0.001$), insulin (19.2% vs. 9.1%, $p = 0.005$), or a statin (26.9% vs.25.4%, $p = 0.005$).

During the study period, there were a higher number of CV events in patients receiving an antiplatelet agent (12.7% vs.12.0%, $p < 0.001$), which was due to the higher incidence of an acute coronary syndrome (6.4% vs.4.7%, $p < 0.001$) and coronary intervention (7.2% vs.4.5%, $p < 0.001$). The overall mortality was lower in patients receiving an antiplatelet agent (28.1% vs. 29.8%, $p < 0.001$).

The PS-based matching process identified 9598 patients who used an antiplatelet agent and 28,794 patients who did not (Table 2). As expected from the matching of these two groups, they exhibited little difference in sex, co-morbidities, medication usage, and other clinical variables (Table 2). However, there was still a significant difference in age, usage of warfarin, CCB, insulin, and statins. No subject was lost to follow-up in either group.

After PS matching, there were no differences between patients using an antiplatelet agent or not in CV events (user 12.9% vs. non-user 12.8%, $p = 0.672$), mortality (user 29.4% vs. non-user 29.1%, $p = 0.529$), intracranial hemorrhage (user 4.0% vs. non-user 4.0%, $p = 0.893$), and gastrointestinal bleeding (user 19.7% vs. non-user 19.7%, $p = 0.900$). The Kaplan-Meier curves of dialysis patients for

Table 2 Basic characteristics of the study subjects before and after propensity matching

	Control ($N = 61,240$)	Antiplat ($N = 10,595$)	P	Control ($N = 28,794$)	Antiplat ($N = 9598$)	P
Baseline characteristics						
Age	59.6 ± 15.0	59.9 ± 13.2	0.003	59.4 ± 14.5	59.9 ± 13.3	< 0.001
Gender, F	52.3	52.3	0.493	52.1	52.6	0.457
Hemodialysis	87.0	86.4	0.089	86.5	86.5	0.958
Comorbidities						
HTN	71.8	71.1	0.129	71.1	71.3	0.630
DM	37.8	37.6	0.736	37.4	37.7	0.679
Hyperlipidemia	29.9	30.2	0.513	29.6	30.0	0.402
CAD	31.7	31.4	0.519	31.1	31.7	0.263
PAD	22.3	22.3	0.930	22.1	22.4	0.523
CHF	22.0	30.2	< 0.001	27.9	28.9	0.056
AF	4.8	5.0	0.463	4.7	5.0	0.203
Medications						
Warfarin	3.8	9.3	< 0.001	6.7	7.7	0.001
Beta-blocker	30.6	58.3	< 0.001	55.0	54.7	0.611
CCB	46.7	74.9	< 0.001	76.4	72.5	< 0.001
ACEI/ARB	30.9	57.3	< 0.001	54.5	53.9	0.332
OHA	16.4	33.1	<0.001	28.9	29.7	0.150
Insulin	9.1	19.2	< 0.001	15.5	16.8	0.005
Statin	14.9	29.7	< 0.001	25.4	26.9	0.005
Outcomes						
CV events	12.0	12.7	< 0001	12.8	12.9	0.672
Acute coronary syndrome	4.7	6.4	< 0.001	3.6	3.3	0.170
Coronary intervention	4.5	7.2	< 0.001	3.3	3.4	0.635
Ischemic stroke/TIA	5.1	5.2	0.478	5.8	6.2	0.189
Mortality	29.8	28.1	< 0.001	29.1	29.4	0.529
Bleeding						
ICH	4.2	2.2	< 0.001	4.0	4.0	0.893
GI bleeding	19.0	24.0	< 0.001	19.7	19.7	0.900

HTN, hypertension; *DM*, diabetes mellitus; *CAD*, coronary artery disease; *PAD*, peripheral artery disease; *CHF*, congestive heart failure; *AF*, atrial fibrillation; *CCB*, calcium channel blocker; *ACEI*, angiotensin-converting enzymes inhibitor; *ARB*, angiotensin receptor blocker; *OHA*, oral hypoglycemia agents; *TIA*, transient ischemic accident; *ICH*, intracranial hemorrhage; *GI*, gastrointestinal

the risk of all-cause mortality and cardiovascular events are shown in Fig. 2.

Effect of Duration of Antiplatelet Agent Usage

Table 3 shows the HRs for different clinical outcomes in PS-matched patients who took an anti-platelet agent for three different durations (≤ 76 days, 77–236 days, ≥ 236 days). The model was adjusted for age, gender, risk factors (HTN, DM, and hyperlipidemia), comorbidities (CAD, PAD, CHF, and AF), and medications.

Subgroup analysis including different antiplatelet agents (aspirin, clopidogrel, and ticlopidine) did not reveal differences among subgroups.

The results indicated that CV events, total mortality, and bleeding events were similar in those who used antiplatelet agents for short or long durations. (p all > 0.05).

Subgroup Analysis

Table 4 showed the effect of an antiplatelet agent in different subgroups. These results indicate that the neutral effect of antiplatelet agent usage on the number of CV events and total mortality remained robust in all subgroups after PS matching and Cox regression adjustment. Of note, there was no difference between patients with (secondary prevention) or without (primary prevention) previous cardiovascular disease in CV events and total mortality. In the comparison of different antiplatelet agents, there was also no difference among aspirin,

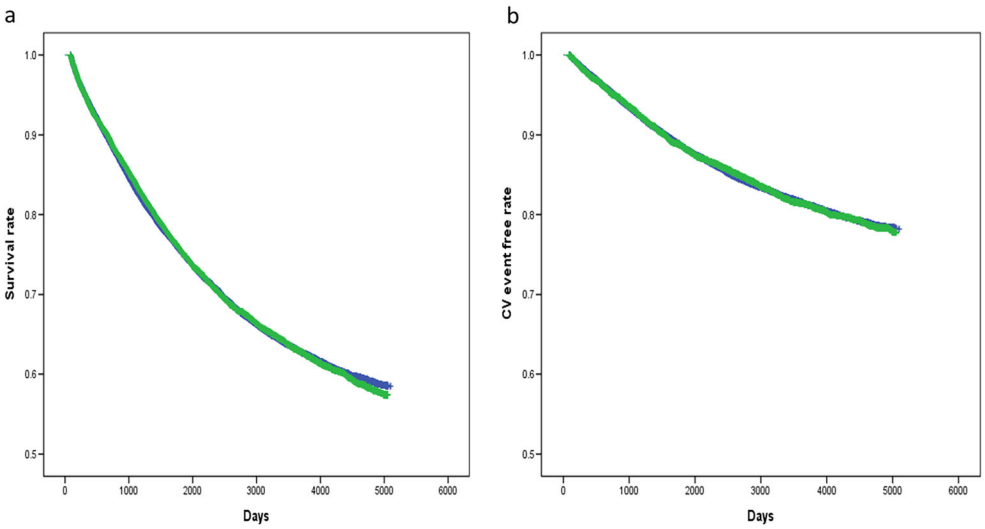

Fig. 2 Kaplan-Meier curves of dialysis patients for the risk of all-cause mortality (**a**) and cardiovascular events (**b**), according to the prescription of an antiplatelet agent after propensity matching methods. The blue line indicates patients not taking an antiplatelet agent; the green line indicates patients taking an antiplatelet agent. Both *p* value are > 0.05 by log-rank test

clopidogrel, and ticlopidine in CV events and total mortality. As to different modalities of dialysis (hemodialysis or peritoneal dialysis), CV events, and total mortality revealed no significant difference.

Discussion

There is little evidence in the literature to guide the use of aspirin or other antiplatelet agents in dialysis patients, especially as a means of primary prevention. There are no randomized controlled trials in dialysis patients to evaluate the safety and efficacy of antiplatelet agents for primary or secondary prevention of atherosclerotic events. However, since ESRD patients are among the highest-risk groups for atherosclerotic events, it might be reasonable to use aspirin or other antiplatelet agents in dialysis patients without contraindications for antiplatelet therapy. In the recommendation from the K/DOQI Clinical Practice Guidelines, aspirin is recommended for secondary prevention [6]. For primary prevention, aspirin is reported to be possibly effective for the primary prevention of atherosclerotic disease in dialysis patients with low bleeding risk but should be used with careful monitoring for bleeding complications [6]. In the guideline from Canadian Cardiovascular Society, antiplatelet therapy should be considered for secondary prevention in patients with CKD (class IIa, level C) and for primary prevention in patients with ESRD and a low risk of bleeding (class IIb, level C) [5]. In the subgroup analysis of the current study, we found that there is no benefit of antiplatelet agents for CV events and overall mortality in both primary and secondary prevention.

Regarding the benefit of antiplatelet agents for CV event prevention, the data from previous studies have produced conflicting results [3, 7, 8]. Moreover, there was also no reported mortality data for these patients. Since the impaired hemostatic status may hinder the use of antiplatelet agents in ESRD patients [5], it is important to also consider the survival benefit in the evaluation of the benefits in antiplatelet therapy. For this reason, we added total mortality and major bleeding as the important outcome measures in this study. However, we also did not see a survival benefit and bleeding hazards in antiplatelet users in this study.

Table 3 Hazard ratios of antiplatelet vs. control and tertiles of antiplatelet treatment period vs. control for different outcomes after propensity matching

	Overall antiplatelet (*N* = 9598) vs. C (*N* = 28,794)	T1 vs. C ≦ 76 days (*N* = 3222)	T2 vs. C 77–236 days (*N* = 3179)	T3 vs. C > 236 days (*N* = 3197)	*P*
CV event	0.99 (0.93–1.06)	1.00 (0.90–1.11)	0.99 (0.89–1.09)	0.63 (0.57–0.69)	0.992
ACS	0.89 (0.79–1.01)	0.92 (0.75–1.12)	0.97 (0.80–1.18)	0.80 (0.65–0.99)	0.180
Ischemic stroke	1.05 (0.95–1.15)	1.07 (0.93–1.24)	0.99 (0.85–1.16)	1.07 (0.93–1.24)	0.653
Mortality	1.00 (0.96–1.04)	1.01 (0.95–1.08)	1.01 (0.94–1.08)	0.98 (0.91–1.05)	0.863
Hemorrhagic stroke	1.00 (0.89–1.13)	1.08 (0.91–1.29)	0.84 (0.69–1.02)	1.08 (0.91–1.29)	0.167
GI bleeding	0.99 (0.94–1.04)	0.98 (0.90–1.06)	0.96 (0.88–1.04)	1.03 (0.95–1.12)	0.590

Model adjusted for age, gender, risk factors (HTN, DM, hyperlipidemia), comorbidities (CAD, PAD, CHF, AF), and medications

Table 4 Hazard ratios of antiplatelet vs. control for cardiovascular event and mortality in different subgroups after propensity matching

	Number	CV event	*P*	Mortality	*P*
Age, years					
< 65	22,989	0.962 (0.89–1.05)	0.363	1.03 (0.97–1.08)	0.360
≧ 65	15,403	1.04 (0.94–1.15)	0.501	0.96 (0.89–1.02)	0.189
Gender					
Men	18,344	0.99 (0.90–1.09)	0.836	1.01 (0.95–1.08)	0.703
Women	20,048	0.99 (0.90–1.09)	0.834	0.99 (0.93–1.05)	0.666
HTN					
Yes	27,308	1.00 (0.93–1.07)	0.976	1.01 (0.96–1.06)	0.688
No	11,084	0.93 (0.77–1.11)	0.422	0.97 (0.89–1.05)	0.439
DM					
Yes	14,387	0.95 (0.87–1.03)	0.230	0.98 (0.92–1.04)	0.456
No	24,005	1.05 (0.95–1.16)	0.321	1.02 (0.96–1.08)	0.586
CVD					
Yes	16,767	0.97 (0.90–1.05)	0.465	0.99 (0.93–1.05)	0.733
No	21,625	1.03 (0.91–1.17)	0.625	1.01 (0.95–1.07)	0.845
CHF					
Yes	10,819	0.99 (0.88–1.12)	0.858	0.98 (0.91–1.06)	0.635
No	27,573	0.99 (0.92–1.07)	0.844	1.00 (0.96–1.06)	0.827
ACEI/ARB					
Yes	20,868	0.97 (0.89–1.06)	0.473	1.00 (0.95–1.06)	0.962
No	17,524	1.02 (0.93–1.12)	0.695	0.99 (0.93–1.06)	0.796
Statin					
Yes	9906	1.03 (0.91–1.17)	0.601	1.04 (0.96–1.13)	0.390
No	28,486	0.98 (0.91–1.05)	0.561	0.99 (0.94–1.04)	0.564
Type of antiplatelet					
Aspirin	6747	0.98 (0.91–1.05)	0.575	1.00 (0.95–1.05)	0.871
Clopidogrel	1431	0.97 (0.83–1.12)	0.653	0.97 (0.88–1.07)	0.592
Ticlopidine	1420	1.09 (0.95–1.26)	0.233	1.044 (0.95–1.15)	0.388
Type of dialysis					
HD	34,481	0.992 (0.929–1.060)	0.820	0.996 (0.953–1.041)	0.866
PD	3911	0.919 (0.725–1.163)	0.481	0.951 (0.812–1.114)	0.533

HD, hemodialysis; *PD*, peritoneal dialysis

Model adjusted for age, gender, risk factors (HTN, DM, hyperlipidemia), comorbidities (CAD, PAD, CHF, AF), and medications

In the DMMS Wave 2 study, which found that aspirin was not associated with the incidence of further CV events, the use of aspirin was associated with pre-existing CAD. The benefit of aspirin might be hindered in an unadjusted analysis [7]. In our study, we provided the PS-based analysis to avoid this shortcoming. Our data clearly showed the neutral effect of antiplatelet agents for CV events and overall mortality without this bias.

Another large observational study from The Dialysis Outcomes and Practice Patterns Study (DOPPS) I and II showed that aspirin prescription was found to have no effect on all-cause mortality, but was associated with a statistically significant 18% lower risk of stroke in all patients and an 11% lower risk in dialysis patients with previous stroke [8]. In contrast, aspirin prescription was associated with an increased risk of CV events (RR, 1.08; $p < 0.01$) and MI (RR, 1.21; $p < 0.01$) in all patients. The study used Cox models and propensity scoring for baseline characteristics and comorbidity adjustments. However, the follow-up time was short (median 1.91 years), and only the baseline measurement of aspirin prescription was used in association with the outcome due to the relatively low frequency of medication data collection in DOPPS II. In contrast, our study not only provided the result from a longer period of follow-up (median 61.6 months) but also from a large population of dialysis patients with a different status of pre-existing CV disease status. Using subgroups analysis, we could evaluate not only the effect of both primary and

secondary prevention but also the effect of different antiplatelet agents.

The prescription rate of antiplatelet agents (mainly aspirin) is low in previous studies [7, 8, 11] and is due to the many factors that hinder the prescription of antiplatelet agents in dialysis patients. In DOPPS I (1996 to 2001), the aspirin prescription rate was low and varied widely, from 7.9% in Japan to 35.6% in the UK (average 19.3%). And even though the aspirin prescription rate increased from DOPPS I to DOPPS II (2002–2004) [8], such as in Japan where the prevalence of aspirin prescription almost doubled to 14.2% in DOPPS II, the rate of aspirin prescription still remained low. Only one-third of patients with CVD or diabetes were prescribed aspirin. For primary prevention, the prescription rate of aspirin is 9.6% for patients without CVD or diabetes in DOPPS I and increased insignificantly in DOPPS II. The prescription rate in our study of antiplatelet agents was around 14.7%, which seems to be similar to other Asian countries. Our study also reflects a real-world prescription situation of antiplatelet agents in ESRD patients.

We also compared the effect of three different antiplatelet agents (aspirin, clopidogrel, and ticlopidine) in subgroup analysis. The antiplatelet effect of clopidogrel is inadequate in dialysis patients. In a previous study, 82.4% of hemodialysis patients were poor responders to clopidogrel, as evaluated by the VerifyNow point-of-care P2Y12 assay [17]. Furthermore, another recent study showed that hemodialysis impairs clopidogrel responsiveness in patients with ESRD, resulting in an increase of 6.5% of clopidogrel low responders [18]. In contrast, aspirin responsiveness is not impaired by hemodialysis. In light of the available evidence, aspirin should be the drug of choice in antiplatelet agents in ESRD. In one previous study including 1936 dialysis patients experiencing a first ischemic stroke between 1998 and 2006, aspirin but not clopidogrel was associated with a favorable outcome as assessed by death or readmission to hospital for stroke [19]. In another recent study, both aspirin and clopidogrel usage were associated with higher mortality in hemodialysis patients [12]. In the current study, there was no significant difference among aspirin, clopidogrel, and ticlopidine. Further research is needed to clarify this issue.

Moreover, although our study revealed that the usage of antiplatelet was not associated with decreased CV events or increased bleeding risk in dialysis patients, we should keep in mind the "innate limitation" in big data analysis without detailed information. For example, if someone suffered from bleeding, which further caused CV events, the reduction of CV events by antiplatelet therapy might be masked. In addition, CV events in our study did not include heart failure and arrhythmia, which might also underestimate the benefit of antiplatelet therapy.

Strengths and Limitations

The main strengths of this study are that it was a population-based, nation-wide study that captured all validated dialysis cases in Taiwan and followed them for a long period. All comorbidities and medications were carefully recorded under the national health insurance policy. The results of our propensity analysis, in which known confounding factors were matched, indicate the neutral effect of long-term antiplatelet agents in protecting dialysis patients from mortality and CV events. However, a prospective trial with randomization is the best way to confirm our results.

Our study had several limitations. First, we relied exclusively on the claims data from the national insurance system, so there may have been a bias in disease classification. Second, despite PS matching, there were differences in age and medication (Warfarin, CCB, insulin, and statin) between groups, which might have influenced the result. Moreover, selection bias might still exist. Although we controlled for the most important risk factors in PS-base matching, they were only the known variables. Some unknown factors that may have been unequally distributed in the antiplatelet use group and the control group might have affected the observed differences in the outcome analysis. Third, we did not have access to detailed blood test data, and as a result, some uncorrected potentially confounding factors were not taken into consideration in this study. Fourth, this study was designed to evaluate single antiplatelet agent effect. The effect of dual antiplatelet use was difficult to access due to different duration of each antiplatelet agent use, and we cannot therefore elaborate on the effects of dual antiplatelet agents. Fifth, our available NHI research database was limited to 2008. New data might be needed for further analysis.

Conclusions

In dialysis patients, usage of an antiplatelet agent was neither associated with CV event decrease nor bleeding risk increase.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in the current study were conducted in accordance with the ethical standards of the institutional

and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The data of this study was obtained from the Taiwan National Health Insurance research database. Informed consent from individual patients was not required.

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