



Effect of Prior Antiplatelet Therapy on Major Adverse Cardiac Events in Patients Diagnosed with Infective Endocarditis: Population-Based Retrospective Cohort Study

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Background: Infective endocarditis (IE) occurs with an incidence of about 3–10 per 100,000 person-years globally. Those with infective endocarditis complicated embolic events have worse outcomes. However, whether antiplatelet therapy could prevent the development of ischemic stroke and myocardial infarction remained unknown. **Materials and Methods:** We conducted a retrospective cohort study using Taiwan National Health Insurance Research Database to access the effect of prior antiplatelet therapy on major adverse cardiac events in patients diagnosed with infective endocarditis. **Results:** The clinical characteristics and the risk of subsequent major adverse cardiac events in 901 patients with infective endocarditis with prior antiplatelet therapy and a matched cohort without antiplatelet therapy were retrospectively analyzed. The majority (63%) of the patients with prior antiplatelet therapy were male and 568 (57.7%) had a high (≥ 3) Charlson Comorbidity Index score. There was no significant difference in the risk of myocardial infarction, ischemic stroke, and major bleeding between the two groups. The tests of interaction showed the risk of myocardial infarction was contingent on heart failure. **Conclusions:** Prior antiplatelet therapy did not prevent the cerebral and myocardial infarction in those with infective endocarditis. Neither did them increase the risk of major bleeding in patients with infective endocarditis.

Key words: Antiplatelet therapy, embolism, infective endocarditis, major adverse cardiac events

INTRODUCTION

Infective endocarditis (IE) is an uncommon but lethal disease with an incidence of 30–100 episodes per million person-years and mortality of 15%–30%.^{1–3} Embolism events, the most dreadful complications, were observed in 20%–50% of IE patients.^{4,5} Those embolic events included myocardial infarction in 1.5% patients and 47.4% involved central nerve system with up to 65% of central nerve system embolic events leading to ischemic stroke.^{6–8}

Patients suffering from embolic events had much higher mortality rate.^{9,10} Since antiplatelet therapy was widely

used to prevent the recurrence of cerebral and myocardial infarction,^{11,12} their use in patients with IE had been assessed in many studies.^{13–16} However, most studies did not observe the beneficial effect of antiplatelet therapy; instead, the increasing risk of bleeding was the major concern.^{4,5,16,17} Nowadays, antiplatelet therapy is not recommended as adjunctive therapy for prevention of embolism in IE patients. However, a retrospective study demonstrated that the risk of symptomatic emboli associated with IE was reduced in patients received continuous daily antiplatelet before the onset of IE.¹⁴

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Therefore, this population-based, observational, retrospective cohort study included patients who received antiplatelet therapy before hospitalization to delineate the association between prior antiplatelet therapy and subsequent risk of ischemic stroke and myocardial infarction as well as the risk of major bleeding in patients with IE.

MATERIALS AND METHODS

Data source

We retrieved data from the Taiwan National Health Insurance Research Database (NHIRD), a nationwide, anonymized secondary database, released by Taiwan National Health Insurance Administration, Ministry of Health and Welfare, for research purposes. This database collected data from the NHI system including demographic data, detailed orders, and diagnosis coding etc., The diagnosis of disease was coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM).¹⁸ The study was exempt from full review by the Institutional Review Board of Taipei City Hospital (TCHIRB-1030603-W) because the data set comprised deidentified secondary data.

Study design

This nationwide population-based, retrospective cohort study was conducted to evaluate the effect of prior antiplatelet therapy on major adverse cardiac events in patients diagnosed with infective endocarditis. The data were extracted from Taiwan NHIRD. Adults who were admitted to hospitals for the treatment under the diagnosis of IE (ICD-9-CM code 421.0, 421.1, and 421.9) between January 2000 and December 2009 were enrolled. These codes were shown to be a reliable substitute for chart-based IE diagnosis on the basis of the revised Duke criteria.^{19,20} Patients were excluded if their age were <20 years or had a history of IE before this hospitalization. Eligible patients were divided into two cohorts based on the use of antiplatelet agents before hospitalization. The treatment cohort consisted of adults (aged ≥ 20 years) who had received at least one dose of any of the antiplatelet agent (aspirin, clopidogrel, or ticlopidine) within 3 months before the time of hospitalization for IE. One comparison cohort patient was matched to one treated cohort patient with a similar propensity score based on nearest-neighbor matching without replacement using calipers of a width equal to 0.1 standard deviation (SD) of the logit of the propensity score. The important variables included in the propensity score were based on the previous studies^{21,22} as shown in Table 1.

The outcomes of interest were the risk of major adverse cardiovascular events (MACE), including ischemic stroke (ICD-9-CM code 433.x, 434.x, or 436), myocardial

infarction (ICD-9-CM code 410.x), and major bleeding. Major bleeding was defined as intracranial hemorrhage, upper gastrointestinal bleeding, hematuria, hemoptysis, and pulmonary hemorrhage (ICD-9-CM code 430.x-432.x, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 578.0, 578.1, 578.9, 599.7, 786.3, and 770.3 516.1). All subjects were followed up until discharge or mortality during hospitalization.

Statistical analysis

Descriptive statistics were used to characterize the baseline characteristics of the study cohorts. Baseline characteristics of the two groups were compared by the use of the Pearson Chi-square test for categorical variables and the independent *t*-test for parametric continuous variables. The SQL Server 2012 (Microsoft Corp, Redmond, WA, USA) was used for data linkage, processing, and sampling. Propensity scores were calculated with SAS version 9.3 (SAS Institute, Cary, NC, USA). All other statistical analyses were conducted with STATA statistical software (version 12.0; StataCorp, College Station, TX, USA). *P* < 0.05 was considered statistically significant.

RESULTS

There were 901 patients in the treatment cohort and the same number in the comparison cohort. The mean (SD) age of the treatment and comparison cohort were 60.9 (16.5) years and 60.4 (17.2) years, respectively. Most of these patients were male (63% and 61.9% in the treatment and control group, respectively) and had Charlson Comorbidity Index scores ≥ 3 (57.7% and 56%, respectively). There was no significant statistical difference in traditional risk factors of cardiovascular disease and concomitant medications between these two groups. The detailed characteristics are shown in Table 1.

During the follow-up period, after the adjustment for several confounding factors, such as sex, age, hypertension, heart failure, dyslipidemia, hemodialysis, and statin usage, the adjusted hazard ratios (HRs) for the risk of subsequent MACEs during hospitalization for IE in treatment cohort did not attain statistical significance; 1.18 (95% confidence interval [CI], 0.53–2.66) for myocardial infarction and 1.29 (95% CI, 0.87–1.91) for ischemic stroke [Table 2]. For major bleeding, the risk was not significant, 1.26 (95% CI, 0.9–1.77). Tests of interaction were performed for sex, age, hypertension, heart failure, dyslipidemia, hemodialysis, and statin usage. None of these were statistically significant for the risk of ischemic stroke [Table 3], but the risk of myocardial infarction was contingent on heart failure [Table 4].

Table 1: Demographic and clinical characteristics of patients

Characteristic	Antiplatelet		<i>P</i>
	Treatment cohort ^a	Comparison cohort	
Number of patients	901	901	
Mean age (SD), years	60.9 (16.5)	60.4 (17.2)	0.502
Male	568	558	0.627
Monthly income			
Dependent	235	236	0.995
NT\$0-19,100	226	222	
NT\$19,100-42,000	397	401	
>NT\$42,000	43	42	
Urbanization level ^b			
1	463	484	0.639
2	351	338	
3	80	75	
4 (rural)	7	4	
CCI score ^c			
0	106	101	0.408
1	126	152	
2	149	143	
≥3	520	505	
Concomitant medications			
Statin	57	50	0.485
Warfarin	124	150	0.088
Alpha blocker	40	38	0.817
Beta blocker	166	179	0.436
Calcium channel blocker	264	271	0.718
Diuretics	149	148	0.949
ACEI or ARB	285	294	0.650
Other antihypertensive drugs	28	28	>0.99
Antihyperglycemic drugs	159	145	0.378
Dipyridamole	75	85	0.408
Nitrate	169	170	0.952
Proton-pump inhibitor	55	48	0.477
NSAID	470	474	0.850
Steroid	158	170	0.464
Risk factors for cardiovascular disease			
Hypertension	621	634	0.505
Diabetes	346	325	0.306
Coronary artery disease	539	533	0.773
Heart failure	411	410	0.962
Dyslipidemia	313	297	0.426
End-stage renal disease	97	98	0.940

Contd...

Table 1: Contd...

Characteristic	Antiplatelet		
	Treatment cohort ^a	Comparison cohort	<i>P</i>
Chronic renal disease	265	262	0.877

^aPrescription termination date (date of dispensation + day supply) overlaps with the index date or prescription termination date of 1-90 days before the index date. ^bUrbanization levels in Taiwan are divided into four strata according to the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas, and Level 4 designates the least urbanized areas. ^cCCI score is used to determine the overall systemic health. With each increased level of CCI score, there are stepwise increases in the cumulative mortality. SD=Standard deviation; ACEI=Angiotensin converting enzyme inhibitors; ARB=Angiotensin II receptor blockers; NSAID=Nonsteroidal anti-inflammatory drug; CCI=Charlson comorbidity index

Table 2: Crude and adjusted odds ratio for the risk of major adverse cardiac events from infective endocarditis with oral antiplatelet drug use

	Number of events	Number of patients	OR (95% CI)	
			Crude	<i>P</i>
Myocardial infarction				
Anti-platelet nonuser	11	901	1 (reference)	0.681
Antiplatelet use ^a	13	901	1.18 (0.53-2.66)	
Ischemic stroke				
Antiplatelet nonuser	48	901	1 (reference)	0.200
Antiplatelet use ^a	61	901	1.29 (0.87-1.91)	
Major bleeding				
Antiplatelet nonuser	67	901	1 (reference)	0.173
Antiplatelet use ^a	83	901	1.26 (0.90-1.77)	

^aUsing any antiplatelet within 90 days before the index date. OR=Odds ratio; CI=Confidence interval

DISCUSSION

The present study demonstrated that prior antiplatelet therapy did not prevent the cerebral and myocardial infarction. Although the usage of antiplatelet therapy may increase the risk of major bleeding in patients with IE, there was no statistical significance. In addition, the risk of myocardial infarction was contingent on heart failure.

About 25% of patients have embolic complications at the time of diagnosis with IE.⁵ Embolism often occurs in major arterial beds including the brain, coronary arteries, lungs, spleen, bowel, and extremities. Despite the advance in medicine in recent decades, infective endocarditis complicated with thromboembolic events remains life-threatening.^{1-3,9,10} The greatest risk of embolic complications appears to occur with vegetations >10 mm on the anterior mitral leaflet.^{19,23} Antiplatelet agents are widely used to interfere with the platelet aggregations in patients with myocardial infarction and cerebral infarction.¹² In addition, these drugs have also been demonstrated to reduce the vegetation weight and bacterial density in infected vegetation.²⁴

How to reduce the embolic complications is an important issue for physicians. Antiplatelet therapy, a commonly used

preventive strategy in other thromboembolic diseases, had been applied in the management of infective endocarditis.^{11,12} There are many studies conducted to evaluate the efficacy of antiplatelet therapy in infective endocarditis.²⁵ However, to the best of our knowledge, only one large prospective, randomized, double-blinded controlled trial reported until today. This trial, reported by Chan *et al.*, enrolled total 115 IE patients. There were neither no benefit nor no significant trend to increase in total bleeding events of the treated group.¹⁶ Conversely, others studies, including a small prospective, randomized study, reported that prior antiplatelet therapy exhibited benefit on further embolic events in IE patients.^{26,27}

The routine use of antiplatelet therapy for those IE patients remains controversial. In our study, we found that routine antiplatelet therapy has no preventive effect on the following embolic complications (only focus on cerebral infarction and myocardial infarction in this study) for IE patients. The adjusted odd ratios for the risk of subsequent cerebral infarction and myocardial infarction during hospitalization for IE patients treated with antiplatelet agents were 1.29 and 1.18, respectively. Moreover, there was also no significant difference on the major bleeding risks between antiplatelet user and nonuser.

In subgroup analysis, prior antiplatelet therapy in IE patients without heart failure increased the risk of myocardial infarction than those without prior antiplatelet therapy with borderline statistical significance (HR: 4.575, *P* = 0.053). There was no similar finding in those with heart failure. This looks like a paradoxical finding. It is reasonable that those with heart failure may have received several medications, such as lipid-lowering agents, anti-arrhythmic agents, and antihypertensive agents. All these medications may subsequently protect them from myocardial infarction.^{28,29} While antiplatelet agents have also been widely used in noncardiac diseases, such as ischemic stroke and peripheral artery diseases. These noncardiac diseases themselves are also risk factors for myocardial infarctions. In these patients, they received only antiplatelet agents but not medications for heart failure. The difference in the medications used for heart failure may contribute to this conflicting finding. Due to this retrospective study had inherent limitations, we could not elucidate the exact mechanism of this phenomenon. Further

Table 3: Subgroup analysis for the risk of ischemic stroke from infective endocarditis with oral antiplatelet drug use

Characteristic	OR (95% CI)*	<i>P</i>	Interaction (<i>P</i>)
Sex			
Male	1.150 (0.701-1.887)	0.579	0.461
Female	1.557 (0.824-2.939)	0.172	
Age (years)			
20-65	1.612 (0.950-2.738)	0.077	0.214
>65	0.979 (0.546-1.755)	0.943	
Hypertension			
Yes	1.144 (0.719-1.820)	0.571	0.350
No	1.723 (0.830-3.575)	0.144	
Heart failure			
Yes	1.276 (0.688-2.368)	0.439	0.962
No	1.301 (0.787-2.152)	0.305	
Dyslipidemia			
Yes	0.890 (0.450-1.762)	0.738	0.193
No	1.548 (0.959-2.498)	0.074	
Hemodialysis			
Yes	0.611 (0.193-1.940)	0.404	0.170
No	1.428 (0.940-2.169)	0.095	
Using statin			
Yes	0.639 (0.136-3.003)	0.570	0.355
No	1.353 (0.904-2.027)	0.142	

**P* < 0.05. OR=Odds ratio; CI=Confidence interval

studies are needed to confirm this finding and delineate its underlying mechanism.

The new oral anticoagulants (NOACs), which have been thought to have less bleeding complications and equal or even more effective than traditional antiplatelet agents for preventing thromboembolic events in high-risk groups, have been widely used in recent years.³⁰ They have also been considered as options for preventive therapy in those IE patients.³¹ However, during the time in this study, NOACs have not been introduced into Taiwan. Therefore, the role of NOACs has not been discussed in this study.

There are several limitations to our study. First, patients received even one dosage of antiplatelet agent within 90 days were enrolled in this study. Although the exact effect of such a low-dose antiplatelet agent on the ischemic stroke and myocardial infarction is doubtful, the risk of major bleeding is higher in antiplatelet user than the nonuser. However, the risk of major bleeding between the two groups is of no significant difference. Second, we only evaluated the risk of cerebral embolism and myocardial infarction but not embolism of other organs. The results may not be interpreted as other embolic events, such as spleen, kidney, lung, and skin emboli. A large

Table 4: Subgroup analysis for the risk of myocardial infarction from infective endocarditis with oral antiplatelet drug use

Characteristic	OR (95% CI)*	<i>P</i>	Interaction (<i>P</i>)
Sex			
Male	1.580 (0.514-4.860)	0.425	0.462
Female	0.856 (0.259-2.833)	0.799	
Age (years)			
20-65	1.016 (0.253-4.086)	0.982	0.801
>65	1.266 (0.467-3.434)	0.643	
Hypertension			
Yes	0.833 (0.343-2.024)	0.687	-
No	-		
Heart failure			
Yes	0.438 (0.134-1.433)	0.172	0.010*
No	4.575 (0.983-21.283)	0.053	
Dyslipidemia			
Yes	0.756 (0.201-2.843)	0.679	0.401
No	1.549 (0.548-4.380)	0.409	
Hemodialysis			
Yes	1.011 (0.139-7.322)	0.992	0.863
No	1.224 (0.504-2.969)	0.655	
Using statin			
Yes	1.782 (0.157-20.262)	0.641	0.715
No	1.111 (0.469-2.629)	0.811	

**P* < 0.05. OR=Odds ratio; CI=Confidence interval

number of patients with IE using antiplatelet agents was a major strength of this study. Besides, we used the propensity score-matched analysis to reduce the confounding factors.

CONCLUSIONS

The prior antiplatelet therapy would increase the risk of subsequent major bleeding in IE patients, though no significant statistical difference. Besides, the risks of myocardial infarction and cerebral infarction could not be avoided with the usage of antiplatelet agents before the onset of IE. Thus, clinicians should not preclude the possibility myocardial infarction and cerebral infarction in patients with IE even though those had already received antiplatelet therapy.

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- The study was exempt from full review by the Institutional Review Board of Taipei City Hospital

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Conflicts of interest

There are no conflicts of interest.

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