Long-Term Clinical Outcome of Major Adverse Cardiac Events in Survivors of Infective Endocarditis

A Nationwide Population-Based Study

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Background—Substantial infective endocarditis (IE)–related morbidity and mortality may occur even after successful treatment. However, no previous study has explored long-term hard end points (ie, stroke, myocardial infarction, heart failure, cardiovascular death) in addition to all-cause mortality in IE survivors.

Methods and Results—A nationwide population-based cohort study was conducted among IE survivors identified with the use of the Taiwan National Health Insurance Research Database during 2000 to 2009. IE survivors were defined as those who survived after discharge from first hospitalization with a diagnosis of IE. A total of 10 116 IE survivors were identified. IE survivors were matched to control subjects without IE at a 1:1 ratio through the use of propensity scores. The primary outcomes were stroke, myocardial infarction, readmission for heart failure, and sudden cardiac death or ventricular arrhythmia. The secondary outcomes were repeat IE and all-cause mortality. Compared with the matched cohort, IE survivors had higher risks of ischemic stroke (adjusted hazard ratio [aHR], 1.59; 95% confidence interval [CI], 1.40–1.80), hemorrhagic stroke (aHR, 2.37; 95% CI, 1.90–2.96), myocardial infarction (aHR, 1.44; 95% CI, 1.17–1.79), readmission for heart failure (aHR, 2.24; 95% CI, 2.05–2.43), sudden death or ventricular arrhythmia (aHR, 1.69; 95% CI, 1.44–1.98), and all-cause death (aHR, 2.27; 95% CI, 2.14–2.40). Risk factors for repeat IE were older age, male sex, drug abuse, and valvular replacement after an initial episode of IE.

Conclusion—Despite treatment, the risk of long-term major adverse cardiac events was substantially increased in IE survivors. **(*Circulation*. 2014;130:1684-1691.)**

Key Words: endocarditis ■ epidemiology ■ heart failure ■ mortality ■ myocardial infarction ■ stroke

Infective endocarditis (IE) is an uncommon, but not rare, disease with an estimated incidence of 30 to 100 cases per 1 million patient-years.[1–4] Despite marked improvements in antibiotic therapy and surgical techniques, more than one third of affected patients die within the first year after hospitalization for IE.[1,5,6] IE is characterized by an intense inflammatory response that causes valvular endothelial damage after repeated insults by circulating bacteria.[7] Predisposing conditions may increase the rate of embolic events, which are associated with poor subsequent prognosis.[5,8]

Clinical Perspective on p 1691

European guidelines recommend the active surveillance of signs and symptoms of recurrent IE for 12 months after treatment completion.[9] Short- and long-term mortality risks in IE survivors remain controversial. Some studies have found that mortality is highest in the first year and decreases thereafter (although remaining higher than in the general population) in IE survivors.[10,11] The direct consequence of IE and underlying conditions may explain this increased short-term mortality. In

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Received June 17, 2014; accepted September 4, 2014

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.114.012717/-/DC1.

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addition, a recent nationwide population-based study of patients with IE in Sweden found that the increased risk of long-term mortality persists for up to 5 years.[12] Although the long-term mortality of patients with IE has been studied previously, hard end points other than mortality have not been considered by exploring the risk of major adverse cardiac events (MACEs), including stroke, myocardial infarction, heart failure, cardiovascular death, and all-cause death, in these patients.

To reduce the effects of potential confounders stemming from inadequate control for comorbidities and underpowered sample sizes, we used Taiwan's National Health Insurance (NHI) Research Database (NHIRD) to conduct a propensity score–matching study. Our goal was to evaluate long-term adverse cardiac outcomes and mortality in a large, representative group of patients with IE compared with a matched cohort using this nationwide database.

Methods

Data Source

Data were extracted from the NHIRD, which contains anonymized secondary data released for research purposes. Taiwan's NHI program, launched in 1995, currently covers 99% of the population of 23 million people.[13] The database comprises all registry and claims data from the NHI system, ranging from demographic data to detailed orders for ambulatory and inpatient care. Taiwan's NHI Bureau is responsible for auditing medical payments by comprehensive review of medical records, examination reports, and results of imaging studies. If physicians fail to meet the standards for clinical practice, Taiwan's NHI reserves the right to reject payment and can impose huge financial penalties. Disease diagnoses are coded according to the *International Classification of Disease, Ninth Revision, Clinical Modification* (*ICD-9-CM*). 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, observational, retrospective cohort study was conducted to determine the association between IE and subsequent MACEs. Two cohorts were enrolled in the study: the IE cohort and a matched cohort without IE. The IE cohort, extracted from the entire original NHIRD, consisted of patients with a first-time discharge diagnosis of IE (*ICD-9-CM* code 421.0, 421.1, and 421.9) between January 2000 and December 2009 who received antibiotic treatment during hospitalization. These codes may be a reliable substitute for chart-based IE diagnosis on the basis of the revised Duke criteria.[14,15] The result of validation analysis of coded IE diagnosis in Taiwan's NHIRD also had good agreement with that of clinical definite or possible IE in a tertiary center in Taiwan.[16] Patients with the following characteristics were excluded: age <20 years, history of IE, and mortality during hospitalization for IE. The index date was defined as the first day of discharge from IE. The control cohort was extracted from the Longitudinal Health Insurance Database, a subset of the original NHIRD, which contains data from a random sample of 1 million NHI beneficiaries. The exclusion criteria for the IE cohort were also applied to the control cohort. Index dates for subjects in the control cohort were randomly assigned and corresponded to those of patients in the IE cohort.

We used 1:1 propensity score matching and calculated propensity scores for the likelihood of hospitalization for IE using baseline covariates and multivariate logistic regression analysis (Table I in the online-only Data Supplement). We matched 1 control patient with each patient in the IE cohort with a similar propensity score based on nearest-neighbor matching without replacement using calipers of a width equal to 0.1 SD of the logit of the propensity score.

Outcomes

The following outcomes were of primary interest: hospitalization and principal diagnosis of ischemic stroke (*ICD-9-CM* code 433.x, 434.x, or 436) and hemorrhagic stroke (*ICD-9-CM* code 431 or 432), hospitalization and principal diagnosis of myocardial infarction (*ICD-9-CM* code 410.x), readmission with a principal diagnosis of heart failure (*ICD-9-CM* code 428.x), and hospitalization or emergency department visit with the principal diagnosis of sudden cardiac death (*ICD-9-CM* code 427.5, 798.1, or 798.2) and ventricular arrhythmia (including ventricular tachycardia [*ICD-9-CM* code 427.1] and ventricular fibrillation and flutter [*ICD-9-CM* code 427.4, 427.41, or 427.42]). The secondary outcomes were repeat IE and all-cause death. Repeat IE is defined as any repeat episode of readmission for IE after >1 day after discharge from initial IE episode.[17] Admissions for patients readmitted <1 day after discharge in the same or different hospitals were regarded as the same episode admission. All subjects were followed up until death, loss to follow-up, or December 31, 2010.

Baseline Characteristics

Baseline demographic characteristics examined were age, sex, monthly income (NT$ [New Taiwan dollar] <19 100, NT$19 100–$41 999, and ≥NT$42 000), urbanization, and Charlson Comorbidity Index score. Urbanization levels in Taiwan are divided into 4 strata according to the Taiwan National Health Research Institute. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas. The Charlson Comorbidity Index score is used to determine overall systemic health. Each increase in score indicates a stepwise increase in cumulative mortality.[18] Other systemic diseases and risk factors for cardiovascular disease not included in the Charlson Comorbidity Index were also examined; these included coronary artery disease, dyslipidemia, end-stage renal disease, atrial fibrillation, preexisting valvular heart disease, and drug abuse (database codes in Table II in the online-only Data Supplement). Data on concomitant use of medications at discharge after IE associated with cardiovascular events, including aspirin, clopidogrel, ticlopidine, statin, and warfarin, were also extracted.

Statistical Analysis

Descriptive statistics were used to characterize the baseline characteristics of the study cohorts. Baseline characteristics of the 2 groups were compared by use of the Pearson χ^2 test for categorical variables and the independent *t* test for parametric continuous variables. Propensity scores of the likelihood of IE were determined by multivariate logistic regression analysis, conditional on baseline covariates (Table I in the online-only Data Supplement). The incidence rates of MACEs in the 2 groups were calculated from Poisson distribution. The cumulative incidence or risk of serious cardiovascular events was estimated by use of the Kaplan-Meier method, and differences between cohorts were evaluated with the log-rank test. Cox regression models with a conditional approach using stratification were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of MACEs in each group.[19] We used a bootstrap approach with the inclusion of different criteria for sensitivity analysis to validate the findings of Cox regression models. Correspondence among bootstrap HRs was tested in 1000 replications. The likelihood ratio test was used to examine the interaction between the occurrence of serious cardiovascular events subsequent to IE and the following variables: age, sex, Charlson Comorbidity Index score, hypertension, cerebrovascular disease, myocardial infarction, diabetes mellitus, coronary artery disease, end-stage renal disease, valvular heart disease, valvular replacement, shock, and year of index date. Subgroup analyses were also performed accordingly. Finally, univariate and multivariate Cox regression models using backward elimination were used to identify predictors of MACEs and repeat IE among IE survivors. Risk factors with a value of $P<0.1$ were entered into the multivariate analysis.

The SQL Server 2012 (Microsoft Corp, Redmond, WA) was used for data linkage, processing, and sampling. Propensity scores were calculated with SAS version 9.3 (SAS Institute, Cary, NC). All other statistical analyses were conducted with STATA statistical software (version 12.0; StataCorp, College Station, TX). Statistical significance was defined as $P<0.05$.

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	All Patients With IE	Propensity Score–Matched		
		Patients With IE	Matched Control	*P* Value
Patients, n	10 116	8494	8494	
Mean age (SD), y	54.7 (18.2)	56.2 (19.2)	56.2 (19.2)	0.906
Male, n (%)	6653 (65.7)	5466 (64.3)	5463 (64.3)	0.962
Monthly income, n (%)				1.000
Dependent	2494 (24.6)	2190 (25.7)	2192 (25.8)	
NT$0–$19 100	3275 (32.3)	2685 (31.6)	2680 (31.5)	
NT$19 100–$42 000	3975 (39.2)	3314 (39)	3316 (39)	
>NT$42 000	372 (3.6)	305 (3.5)	306 (3.6)	
Urbanization level, n (%)				1.000
1	5106 (50.4)	4289 (50.4)	4291 (50.5)	
2	3972 (39.2)	3319 (39)	3317 (39)	
3	863 (8.5)	736 (8.6)	737 (8.6)	
4 (Rural)	175 (1.7)	150 (1.7)	149 (1.7)	
Charlson Comorbidity Index score, n (%)				0.998
0	1379 (13.6)	1227 (14.4)	1225 (14.4)	
1	1647 (16.2)	1370 (16.1)	1363 (16)	
2	1452 (14.3)	1190 (14)	1184 (13.9)	
≥3	5638 (55.7)	4707 (55.4)	47 520 (559.4)	
Concomitant medications, n (%)				
Aspirin	1545 (15.2)	1356 (15.9)	1362 (16)	0.900
Clopidogrel	267 (2.6)	227 (2.6)	225 (2.6)	0.924
Ticlopidine	103 (1)	94 (1.1)	95 (1.1)	0.942
Statin	346 (3.4)	317 (3.7)	321 (3.7)	0.872
Warfarin	2072 (20.4)	880 (10.3)	875 (10.3)	0.900
Cardiovascular risk factors and history, n (%)				
Diabetes mellitus	3173 (31.3)	2742 (32.2)	2742 (32.2)	1.000
Hypertension	5183 (51.2)	4441 (52.2)	4443 (52.3)	0.975
History of, n (%)				
Cerebrovascular disease	3102 (30.6)	2614 (30.7)	2622 (30.8)	0.894
Coronary artery disease	3726 (36.8)	3182 (37.4)	3189 (37.5)	0.912
Myocardial infarction	627 (6.1)	535 (6.2)	536 (6.3)	0.975
Heart failure	3468 (34.2)	2568 (30.2)	2567 (30.2)	0.987
Dyslipidemia	2581 (25.5)	2205 (25.9)	2212 (26)	0.903
End-stage renal disease	735 (7.2)	565 (6.6)	560 (6.5)	0.877
Chronic kidney disease	2343 (23.1)	1936 (22.7)	1942 (22.8)	0.913
Atrial fibrillation	1150 (11.3)	878 (10.3)	879 (10.3)	0.980
Cancer	1428 (14.1)	1247 (14.6)	1253 (14.7)	0.897
AIDS	122 (1.2)	73 (0.8)	74 (0.8)	0.934
Drug abuse	1083 (10.7)	788 (9.2)	789 (9.2)	0.979
Preexisting valvular heart disease	4773 (47.1)	3233 (38)	3229 (38)	0.950
Valve replacement with mechanical valve	917 (9)	344 (4)		
Valve replacement with bioprosthetic valve	545 (5.3)	405 (4.7)		
Repeat infective endocarditis				
During entire follow-up period, n (%)	1180 (11.7)	1020 (12.0)		
Duration, d	250 (81–797)	234 (79–724)		
Within first year, n (%)	677 (6.7)	599 (7.1)		
Duration, d	95 (54–181)	93 (55–174)		

NT$ indicates New Taiwan dollars.

Results

Characteristics of the Study Population

Between January 2000 and December 2009, a total of 14 792 episodes of hospitalization for IE were identified. The annual detailed descriptive data are shown in Table III and Figure I in the online-only Data Supplement. Among those, 10 116 patients hospitalized for a first episode of IE between January 2000 and December 2009 who met the inclusion criteria were identified with a mean follow-up period of 4.1 years (SD, 3.1 years). After propensity score matching, we enrolled 8494 patients with IE and 8494 matched cohort in the study. The mean age of the IE cohort was 54.7 years (SD, 18.2 years). The majority of these patients were male (65.7%) and had Charlson Comorbidity Index scores ≥3 (55.7%). Detailed characteristics of both cohorts are provided in Table 1.

Long-Term Risk of MACEs

During the follow-up period, the adjusted HRs for the risk of subsequent MACEs after discharge from hospitalization for IE were 1.59 (95% CI, 1.40–1.80) for ischemic stroke, 2.37 (95% CI, 1.90–2.96) for hemorrhagic stroke, 1.44 (95% CI, 1.17–1.79) for myocardial infarction, 2.24 (95% CI, 2.05–2.43) for readmission for heart failure, 1.69 (95% CI, 1.44–1.98) for sudden cardiac death or ventricular arrhythmia, and 2.27 (95% CI, 2.14–2.40) for all-cause death (Table 2). The cumulative incidence of MACEs in patients with IE and the matched cohort is illustrated in the Figure. In the subgroup analyses shown in Tables IV through VI in the online-only Data Supplement, the results are almost consistent with respect to the higher risk of MACEs in the IE cohort compared with the matched cohort.

Risk Factors for MACEs and Repeat IE Among IE Survivors

Among a total of 10 116 IE survivors, repeat IE was observed in 1180 patients (11.7%); 56.5% of those (n=667) occurred within first year after an initial episode of IE. The median interval between the initial and repeat episodes of IE was 250 days (quartile 1–3, 81–797 days). In multivariate analysis, male sex (HR, 1.30; 95% CI, 1.14–1.48), drug abuse (HR, 1.50; 95% CI, 1.26–1.79), mechanical valve (HR, 2.11; 95% CI, 1.70–2.62), and bioprosthetic valve replacement (HR, 2.60; 95% CI, 2.16–3.13) were found to be significant risk factors for repeat IE. Repeat IE itself also increased the subsequent risk of hemorrhagic stroke and myocardial infarction but not of ischemic stroke. Other risk factors for MACEs and repeat IE are listed in Table 3 and in Tables VII through X in the online-only Data Supplement.

Sensitivity Analysis for Risk of Serious Cardiovascular Events After IE

As shown in Table 4, we performed bootstrap sensitivity analyses excluding patients who were followed up for <1 and 2 years after discharge from hospitalization for IE. The associations between IE and stroke, heart failure, and all-cause death remained consistent. Of note, however, the risk of myocardial infarction was not significantly increased in patients with follow-up period of >1 year. The risk of sudden death or ventricular arrhythmia was not increased at >2 years.

Discussion

To the best of our knowledge, this propensity score–matched, nationwide, population-based study is the first to demonstrate that IE survivors had higher rates of MACEs. In addition, we also found that IE survivors had a substantially increased risk of all-cause mortality.

Previous population-based studies have found that most deaths resulting from IE occurred within 1 year after hospital discharge.[12,20,21] Despite advances in medical and surgical techniques, the treatment of IE remains challenging, with a 5-year mortality rate of ≈40%.[21] One potential explanation was that over their lifetimes IE survivors still carried a risk of 6.3% to 15.6% for a repeat episode in other studies[22–24] and a similar risk of 11.7% in the present study. In contrast, a retrospective Dutch study[25] showed that the 10-year survival rate of patients who had received surgical treatment for IE was comparable to that of the general population. However, these results may have been affected by the small sample (n=138) and exclusion of subjects deemed unsuitable for the protocol.[26] To resolve this important issue, a large unselected IE cohort was examined in the present study, with propensity score–matched analysis conducted to reduce selection bias. We found that long-term mortality remained greater in

Table 2. Associations Between IE and Risks of MACEs

	IE Cohort			Control Cohort			Propensity Score–Matched Crude	
	Events, n	Person-y	Incidence Rate, %*	Events, n	Person-y	Incidence Rate, %*	HR (95% CI)	*P* Value
Ischemic stroke	576	33 106	17.40	435	40 942	10.62	1.59 (1.40–1.80)	<0.001
Hemorrhagic stroke	235	34 035	6.90	118	41 818	2.82	2.37 (1.90–2.96)	<0.001
Myocardial infarction	187	34 160	5.47	156	41 709	3.74	1.44(1.17–1.79)	0.001
Heart failure	1523	30 936	49.23	834	40 288	20.70	2.24 (2.05–2.43)	<0.001
Sudden death/ventricular arrhythmia	378	34 269	11.03	267	41 811	6.39	1.69 (1.44–1.98)	<0.001
All-cause death	3400	34 452	98.69	1,770	42 012	42.13	2.27 (2.14–2.40)	<0.001

CI indicates confidence interval; HR, hazard ratio; IE, infective endocarditis; and MACE, major adverse cardiac event.
*Per 10^3 person-years.

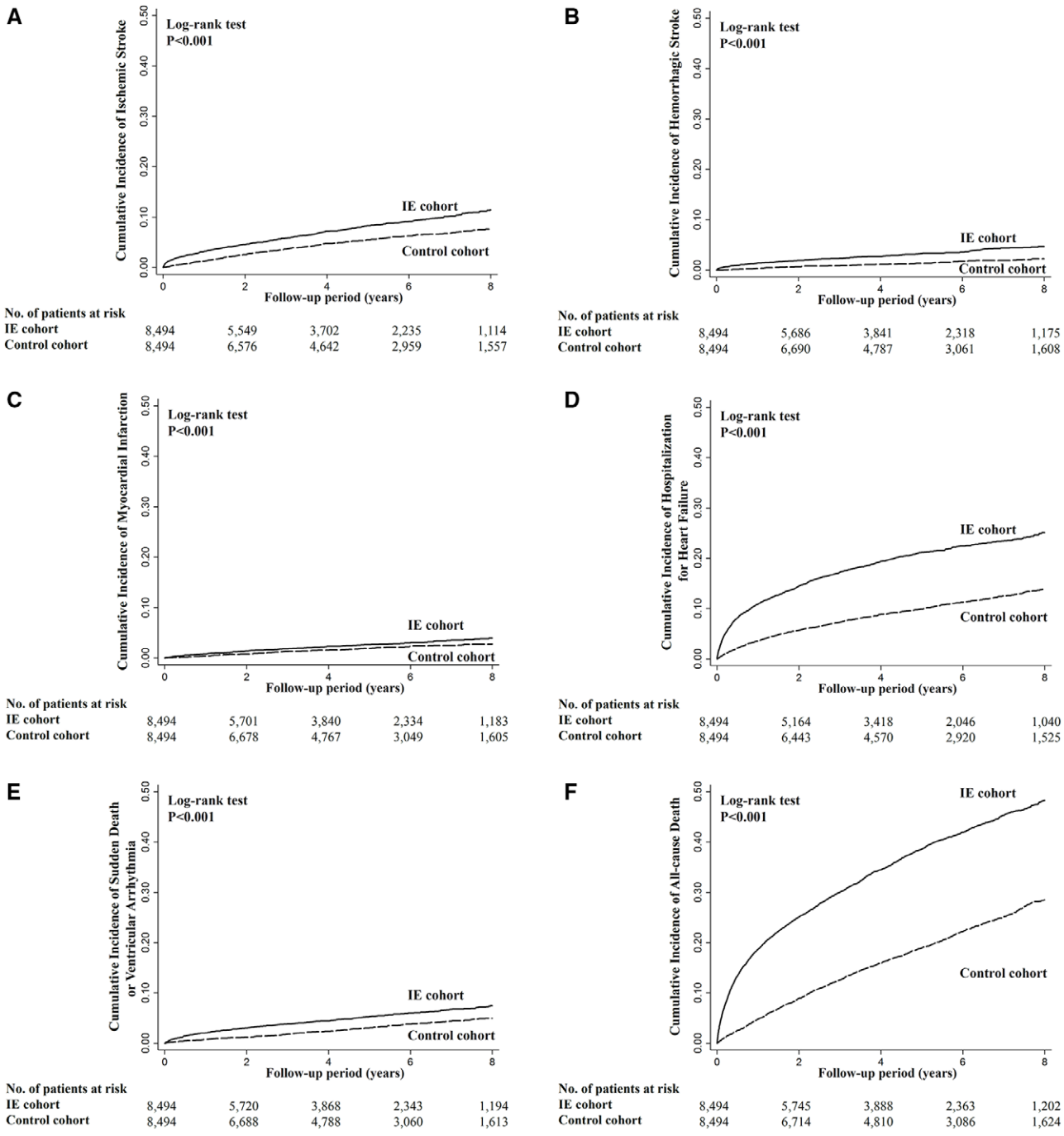

Figure. Cumulative incidence of ischemic stroke (**A**), hemorrhagic stroke (**B**), myocardial infarction (**C**), readmission for heart failure (**D**), sudden death or ventricular arrhythmia (**E**), and all-cause death (**F**) in patients with infective endocarditis (IE) and matched control subjects.

patients with IE (even those who underwent valve replacement) than in the matched cohort. A previous study found that IE-related complication such as heart failure was a significant predictor of long-term cardiac mortality in IE survivors.[15] Our study also supported that the risks of heart failure, sudden cardiac death/ventricular arrhythmia, and mortality in IE survivors were 2.2, 1.7, and 2.3 times higher, respectively, than in the matched cohort. The risk of MACEs was consistently elevated in subgroup analyses regardless of age, sex, baseline comorbidities, heart valve replacement surgery performed before IE or to treat IE, shock events during hospitalization for IE, and different time cohorts (2000–2006 and 2007–2010).

The most frequent and severe complications occurring during the course of IE are neurological.[7] Approximately 40% to 50% of IE-related embolic events affect the central nervous system.[27,28] Moderate to severe stroke has been independently associated with a worse prognosis in patients with IE.[8] Although adequate antibiotic treatment significantly reduces the occurrence of IE-related embolic events,[29] the

Table 3. Risk Factors for MACEs and Repeat IE Among Patients With IE

	Adjusted* HR (95% CI)	*P* Value
Ischemic stroke		
Age, per year	1.02 (1.01–1.02)	<0.001
Hypertension	1.34 (1.10–1.65)	0.005
Cerebrovascular disease	2.29 (1.93–2.72)	<0.001
Heart failure	1.26 (1.06–1.50)	0.010
Atrial fibrillation	1.29 (1.06–1.57)	0.013
Repeat IE†	1.31 (0.98–1.75)	0.066
Hemorrhagic stroke		
Male	1.45 (1.12–1.87)	0.004
Warfarin	1.76 (1.28–2.43)	0.001
Cerebrovascular disease	1.66 (1.28–2.15)	<0.001
Repeat IE†	1.55 (1.06–2.27)	0.025
Myocardial infarction		
Age, per year	1.03 (1.02–1.04)	<0.001
Diabetes mellitus	1.54 (1.11–2.12)	0.009
Coronary artery disease	1.53 (1.10–2.12)	0.011
Myocardial infarction	1.51 (1.01–2.26)	0.047
Heart failure	1.39 (1.03–1.88)	0.029
End-stage renal disease	1.85 (1.21–2.83)	0.005
Chronic kidney disease	1.56 (1.06–2.28)	0.022
Repeat IE†	1.81 (1.18–2.79)	0.007
Repeat IE		
Age, per year	0.99 (0.99–1.00)	0.002
Male	1.30 (1.14–1.48)	<0.001
Drug abuse	1.50 (1.26–1.79)	<0.001
Mechanical valve	2.11 (1.70–2.62)	<0.001
Bioprosthetic valve	2.60 (2.16–3.13)	<0.001

CI indicates confidence interval; HR, hazard ratio; IE, infective endocarditis; and MACE, major adverse cardiac event.

*Only significant factors and repeat IE are shown in this table. The detailed Cox models are shown in Tables VI through IX in the online-only Data Supplement..

†Calculated as a time-varying covariate in the Cox model.

Table 4. Bootstrap Sensitivity Analysis of the Cox Regression Model for Cardiovascular Events in Patients With IE

	Adjusted HR* (95% CI)	*P* Value
Primary analysis		
Ischemic stroke	1.54 (1.36–1.75)	<0.001
Hemorrhagic stroke	2.33 (1.88–2.89)	<0.001
Myocardial infarction	1.40 (1.12–1.74)	0.003
Heart failure	2.16 (1.99–2.35)	<0.001
Sudden death or ventricular arrhythmia	1.63 (1.40–1.91)	<0.001
All-cause death	2.23 (2.11–2.36)	<0.001
Excluding patients with <1-y follow up†		
Ischemic stroke	1.21 (1.04–1.40)	0.013
Hemorrhagic stroke	1.75 (1.32–2.31)	<0.001
Myocardial infarction	1.23 (0.94–1.60)	0.128
Heart failure	1.57 (1.39–1.77)	<0.001
Sudden death or ventricular arrhythmia	1.30 (1.07–1.58)	0.009
All-cause death	1.61 (1.50–1.73)	<0.001
Excluding patients with <2-y follow up‡		
Ischemic stroke	1.25 (1.04–1.50)	0.020
Hemorrhagic stroke	1.75 (1.26–2.42)	0.001
Myocardial infarction	1.18 (0.87–1.58)	0.283
Heart failure	1.48 (1.28–1.71)	<0.001
Sudden death or ventricular arrhythmia	1.09 (0.87–1.37)	0.440
All-cause death	1.53 (1.41–1.66)	<0.001

CI indicates confidence interval; HR, hazard ratio; and IE, infective endocarditis.

*Adjusted for propensity score.

†Index date was defined as the date of 1 year after enrollment to avoid immortal time bias.

‡Index date was defined as the date of 2 years after enrollment to avoid immortal time bias.

rate of ischemic stroke remains 12.9% to 14% after successful treatment.[8,27] Most such events occur within the first week, and the rate decreases thereafter. However, the long-term risk of new ischemic stroke events in IE survivors had not been explored before the present study. We found that this risk was 1.6 times higher in IE survivors than in the matched cohort. This result may be explained by the difficulty of completely eradicating microvegetation or a subsequent thrombogenic tendency induced by endocardial damage in IE survivors undergoing prolonged treatment. Although hemorrhagic stroke may occur in only 4% to 7% of patients with IE during the acute stage,[8,30] many previous studies found that asymptomatic cerebral microbleeds occurred frequently in patients with IE and probably were associated with future events of hemorrhagic stroke.[31–34] This finding was also confirmed in the present study, which showed that patients with IE had a 2.37-times higher risk of developing long-term hemorrhagic stroke than the matched cohort. Thus, long-term surveillance for neurological complications in IE survivors is essential.

At autopsy, emboli have been found in the epicardial branches of coronary arteries in most patients with IE.[35] However, clinically recognized myocardial infarction is uncommon in patients with IE, and most were reported in case reports or series.[36–38] The event rate of myocardial infarction in a small-scale study of 481 patients with IE in Spain[39] was similar to that obtained in our study (2.9% versus 2.2%). That study found that most episodes of myocardial infarction (12 of 14 cases) occurred during the first 2 weeks after IE diagnosis. Our findings also support the notion that myocardial infarction is an early complication of IE, probably attributable to direct compression of the coronary arteries by periannular abscess or pseudoaneurysm and coronary embolism.[39] After 1 year of follow-up, no significantly increased risk of myocardial infarction in IE survivors was noted in our study.

This study has several strengths. First, it involved an unselected nationwide population with the most extensive sample of patients with IE available, minimizing the possibility of referral bias. Second, the IE cohort comprised 8494 patients during the 10-year study period, providing adequate statistical power for the analysis of uncommon IE-related

long-term MACE outcomes, including stroke, myocardial infarction, heart failure, and sudden death or ventricular arrhythmia. Additionally, we compared study subjects with propensity score–matched control subjects, instead of conducting age- and sex-adjusted analyses in comparison with a general population.

Some limitations of our study should be noted. First, the misclassification of IE is possible, but potential misclassification likely occurred at the same rate in patients with IE and the matched cohort, so this bias likely did not affect the results of the present study. Nevertheless, to overcome the inherent limitations of observational studies based on administrative claims databases, we conducted a propensity score–matched analysis, allowing us to reduce the effects of confounding when using observational data.[40] Second, claims data did not include individual factors such as history of smoking or alcohol use and body mass index. However, both IE and comparator cohorts were so large that the uncollected variables were very likely to have been distributed in a nondifferential pattern, as were the measured variables with approximate propensity to IE. Additionally, data on the type of organisms in patients with IE were not completely recorded in Taiwan's NHIRD because *ICD-9-CM* codes can be difficult to translate into a microbiological classification. However, our study found that the risk for long-term MACEs did not differ significantly between IE patients with and without diagnosis codes of organism type (data shown in Table XI in the online-only Data Supplement).

European guidelines recommend the careful monitoring of patients with IE for 1 year after discharge because of the high risk of IE recurrence.[9] The results of the present study highlight the substantially increased risk of MACEs in IE survivors. Thus, long-term (>1 year) surveillance of MACEs should also be considered, beyond the period of the greatest risk of IE recurrence.

Acknowledgments

This study was based in part on data from the NHIRD provided by the Bureau of National Health Insurance of the Department of Health and managed by the National Health Research Institute. The conclusions presented in this study are those of the authors and do not necessarily reflect the views of the Bureau of National Health Insurance, the Department of Health, or the National Health Research Institute. Drs Y.-T. Chen and S.-M. Ou had full access to all the data used in the study and take responsibility for the integrity of the data and accuracy of analysis.

Disclosures

None.

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CLINICAL PERSPECTIVE

Previous epidemiological studies have found that infective endocarditis (IE) is associated with an increased morbidity and mortality after successful treatments. However, existing studies lack assessment of other major adverse cardiac events in addition to mortality. This nationwide, population-based, propensity score–matched study investigated long-term risk of major adverse cardiac events in 8494 IE survivors during the 10-year study period. We found that IE survivors (even those who underwent valve replacement) were at greater risks of stroke, myocardial infarction, heart failure, ventricular arrhythmia, sudden death, and all-cause mortality. After 1 year of follow up, however, there was no significant difference in the risk of myocardial infarction among IE survivors. In addition, risk factors for repeat IE (defined as any repeat episode of readmission for IE after initial discharge) included older age, male sex, drug abuse, and valvular replacement. IE survivors who had repeat IE were associated with increased risk of hemorrhagic stroke and myocardial infarction instead of ischemic stroke. Therefore, long-term surveillance of IE survivors for >1 year should be recommended for early identification and treatment of complications of major adverse cardiac events, even beyond the period of the greater risk of IE recurrence.

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Long-Term Clinical Outcome of Major Adverse Cardiac Events in Survivors of Infective Endocarditis: A Nationwide Population-Based Study

Chia-Jen Shih, Hsi Chu, Pei-Wen Chao, Yi-Jung Lee, Shu-Chen Kuo, Szu-Yuan Li, Der-Cherng Tarng, Chih-Yu Yang, Wu-Chang Yang, Shuo-Ming Ou and Yung-Tai Chen

Circulation. 2014;130:1684-1691; originally published online September 15, 2014;
doi: 10.1161/CIRCULATIONAHA.114.012717
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

Figure legend

Supplementary Table 1. Propensity Score Model Results of Probability of Diagnosis of Infective Endocarditis

			95% CI		
Parameter	**Estimate**	**Odds Ratios**	**Lower**	**Upper**	**P value**
Age, per year	-0.00330	0.997	0.995	0.998	0.0002
Year of Index Date					
2000		1			
2001	-0.1468	0.863	0.769	0.969	0.0126
2002	-0.2444	0.783	0.700	0.876	<.0001
2003	-0.3578	0.699	0.624	0.783	<.0001
2004	-0.4222	0.656	0.588	0.731	<.0001
2005	-0.5208	0.594	0.532	0.663	<.0001
2006	-0.6492	0.522	0.467	0.584	<.0001
2007	-0.8040	0.448	0.399	0.501	<.0001
2008	-0.8960	0.408	0.364	0.457	<.0001
2009	-0.9472	0.388	0.346	0.435	<.0001
Month of Index Date					
January		1			
February	0.0147	1.015	0.898	1.147	0.8140
March	-0.0244	0.976	0.867	1.099	0.6872
April	0.0415	1.042	0.925	1.175	0.4959
May	-0.0374	0.963	0.857	1.083	0.5296
June	-0.0111	0.989	0.880	1.111	0.8513
July	0.00167	1.002	0.892	1.124	0.9773
August	-0.0399	0.961	0.857	1.078	0.4964
September	0.0110	1.011	0.900	1.136	0.8536
October	0.0165	1.017	0.906	1.141	0.7794
November	-0.0682	0.934	0.830	1.050	0.2550
December	-0.0690	0.933	0.831	1.049	0.2456
Male	0.7662	2.151	2.045	2.263	<.0001
Monthly income					
Dependent		1			
NT 0–19,100	0.1306	1.139	1.067	1.217	0.0001
NT 19,100–42,000	-0.1657	0.847	0.796	0.901	<.0001
>NT 42,000	-0.7325	0.481	0.425	0.543	<.0001
Urbanization level[a]					
1		1			
2	0.1651	1.179	1.122	1.240	<.0001

3	0.1176	1.125	1.029	1.229	0.0096
4	0.2561	1.292	1.074	1.554	0.0066
Charlson comorbidity index score	0.1632	1.177	1.157	1.197	<.0001
Concomitant medications					
Aspirin	-0.6242	0.536	0.485	0.592	<.0001
Clopidogrel	-0.3121	0.732	0.560	0.956	0.0222
Ticlopidine	-0.6147	0.541	0.376	0.778	0.0009
Warfarin	-0.3937	0.675	0.565	0.805	<.0001
Statin	-0.7894	0.454	0.383	0.538	<.0001
Coexisting conditions					
Cerebrovascular disease	0.5126	1.670	1.557	1.790	<.0001
Hypertension	0.2641	1.302	1.219	1.391	<.0001
Myocardial infarction	0.1431	1.154	1.015	1.311	0.0281
Coronary artery disease	-0.3703	0.691	0.645	0.739	<.0001
Heart failure	0.9716	2.642	2.457	2.842	<.0001
Valvular heart disease	4.1303	62.198	58.607	66.008	<.0001
Atrial fibrillation	0.2756	1.317	1.182	1.468	<.0001
Diabetes mellitus	0.2116	1.236	1.154	1.323	<.0001
Cancer	0.0896	1.094	0.994	1.203	0.0658
AIDS	1.8676	6.473	4.935	8.490	<.0001
Chronic kidney disease	0.3235	1.382	1.275	1.498	<.0001
End-stage renal disease	1.6766	5.347	3.842	7.442	<.0001
Drug abuse	2.3326	10.304	9.474	11.208	<.0001

Abbreviations: NT$, new Taiwan dollars; AIDS, acquired immunodeficiency syndrome.

[a]Urbanization 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.

[b]Charlson Comorbidity Index (CCI) score is used to determine overall systemic health. With each increased level of CCI score, there are stepwise increases in the cumulative mortality.

Supplementary Table 2. Characteristics and Database Codes

Characteristics	Database ICD-9 code
Infective endocarditis	421.0, 421.1, 421.9
Ischemic stroke	433.x, 434.x, 436
Hemorrhagic stroke	431, 432
Myocardial infarction/ History of myocardial infarction	410.x /412.x
Ventricular tachycardia/ Ventricular fibrillation /Sudden death	427.1 / 427.4, 427.41, 427.42 / 427.5, 798.1, 798.2
Heart failure	428.x
Diabetes mellitus	250.x
Hypertension	401.x – 405.x
Cerebrovascular disease	430.x – 438.x
Coronary artery disease	411.x, 413.x, 414.x
Dyslipidemia	272.0, 272.1, 272.2, 272.4
Chronic kidney disease	580.x – 587.x
Atrial fibrillation	427.31
Cancer	140.x – 208.x
Acquired immunodeficiency syndrome.	042, 0.43, 044
Drug abuse	304.x – 305.x
Valvular heart disease	394.x, 395.x, 396.x, 424.x, 746.x

Supplementary Table 3. Hospitalizations and Outcomes of Infective Endocarditis in Taiwan, 2000 to 2009

	2000-2009	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Denominator, person-years	167,700,568	15,698,216	15,975,337	16,240,758	16,476,882	16,709,375	16,921,080	17,122,228	17,307,389	17,525,876	17,723,427
Number of IE hospitalization	14,792	1,053	1,210	1,381	1,456	1,687	1,773	1,589	1,553	1,574	1,516
IE hospitalization rate per 100,000 person-years	8.80	6.71	7.57	8.50	8.84	10.10	10.48	9.28	8.97	8.98	8.55
Outcome											
Length of stay, days	30.2 (29.6-30.8)	28.6 (26.6-30.7)	28.0 (26.5-29.5)	28.5 (26.5-30.5)	30.6 (28.5-32.8)	30.6 (29.0-32.2)	28.4 (27.1-29.6)	31.8 (29.2-34.3)	30.8 (29.4-32.2)	32.7 (30.2-35.2)	30.8 (29.3-32.2)
Using mechanical valve, %	8.9	10.8	10.0	9.6	8.8	8.7	8.0	7.9	9.1	8.4	7.7
Using bioprosthetic valve, %	5.4	3.5	3.6	4.3	5.2	6.0	4.8	5.6	7.6	8.0	5.0
In-hospital mortality,%	15.6	15.1	16.2	13.3	15.9	15.0	15.5	15.9	16.4	16.8	15.6
30-day mortality, %	18.9	19.4	19.9	16.3	19.6	17.7	18.7	19.0	19.8	20.4	18.6
Repeat IE, %	13.9	16.5	15.7	15.4	17.6	15.3	14.2	12.0	11.1	11.6	11.2

Abbreviations: IE, infective endocarditis

Supplementary Table 4. Subgroup analysis of Risk of Ischemic Stroke among Patients with Infective Endocarditis and Matched Cohort

Characteristic	Case	Control	Adjusted[a]		Interaction p Value
	No. of Event/ No. of Patients	No. of Event/ No. of Patients	Hazard Ratio (95% CI)	p Value	
Gender					
Male	367/5,466	291/5,463	1.440 (1.234-1.680)	<0.001	0.118
Female	209/3,028	144/3,031	1.753 (1.417-2.168)	<0.001	
Age					
20-39	44/2,091	13/2,074	3.429 (1.845-6.372)	<0.001	0.012
40-59	141/2,411	86/2,415	1.901 (1.452-2.487)	<0.001	
≧60	391/3,992	336/4,005	1.530 (1.321-1.770)	<0.001	
Charlson Comorbidity Index score					
Score 0	23/1,227	13/1,225	1.834 (0.923-3.645)	<0.001	0.600
Score 1	72/1,370	42/1,365	1.858 (1.264-2.730)	0.002	
Score 2	77/1,190	43/1,184	2.005 (1.376-2.920)	<0.001	
Score ≧3	404/4,707	337/4,720	1.564 (1.353-1.808)	<0.001	
Hypertension					
Yes	416/4,441	362/4,443	1.508 (1.310-1.737)	<0.001	0.003
No	160/4,053	73/4,051	2.244 (1.697-2.966)	<0.001	
Cerebrovascular disease					
Yes	324/2,614	263/2,622	1.644 (1.396-1.935)	<0.001	0.954
No	252/5,880	172/5,872	1.637 (1.347-1.989)	<0.001	
Myocardial infarction					
Yes	49/535	48/536	1.445 (0.970-2.154)	0.070	0.600
No	527/7,959	387/7,958	1.568 (1.375-1.788)	<0.001	
Diabetes mellitus					
Yes	248/2,742	225/2,742	1.467 (1.224-1.758)	<0.001	0.137
No	328/5,752	210/5,752	1.716 (1.442-2.041)	<0.001	
Dyslipidemia					
Yes	210/2,205	139/2,212	1.923 (1.552-2.383)	<0.001	0.022
No	366/6,289	296/6,282	1.395 (1.196-1.627)	<0.001	
Coronary artery disease					
Yes	324/3,182	262/3,189	1.582 (1.344-1.862)	<0.001	0.703
No	252/5,312	173/5,305	1.624 (1.337-1.974)	<0.001	
Atrial fibrillation					
Yes	108/878	94/879	1.429 (1.084-1.884)	0.011	0.390
No	468/7,616	341/7,615	1.588 (1.381-1.827)	<0.001	

ESRD					
Yes	36/565	40/560	1.374 (0.873-2.163)	0.1691	0.472
No	540/7,929	395/7,934	1.570 (1.379-1.788)	<0.001	
Pre-existing valvular heart disease					
Yes	252/3,233	172/3,229	1.506 (1.240-1.828)	0.024	0.649
No	324/5,261	263/5,265	1.597 (1.355-1.881)	<0.001	
Valvular replacement before IE					
Yes	76/1,012	54/1,012	1.496 (1.054-2.124)	0.024	0.782
No	500/7,482	381/7,482	1.552 (1.358-1.773)	<0.001	
Valvular replacement after IE [b]					
Yes	60/742	42/742	1.401 (0.950-2.064)	0.089	0.425
No	516/7,752	390/7,752	1.570 (1.376-1.791)	<0.001	
Year of index date					
2000-2006	116/2,640	63/2,804	2.216 (1.630-3.011)	<0.001	0.010
2007-2009	460/5,854	372/5,690	1.421 (1.239-1.630)	<0.001	

[a] Adjusted for propensity score.

[b] Compared with matched control subjects.

Abbreviations: ESRD, end-stage renal disease; IE, infective endocarditis; CI, confidence interval.

Supplementary Table 5. Subgroup analysis of Risk of Hemorrhagic Stroke among Patients with Infective Endocarditis and Matched Cohort

Characteristic	Case	Control	Adjusted[a]		
	No. of Event/ No. of Patients	No. of Event/ No. of Patients	Hazard Ratio (95% CI)	p Value	Interaction p Value
Gender					
Male	165/5,466	79/5,463	2.388 (1.825-3.125)	<0.001	0.679
Female	70/3,028	39/3,031	2.161 (1.460-3.199)	<0.001	
Age					
20-39	48/2,091	11/2,074	4.355 (2.260-8.393)	<0.001	<0.001
40-59	84/2,411	24/2,415	4.038 (2.563-6.363)	<0.001	
≧60	103/3,992	83/4,005	1.623 (1.214-2.169)	0.001	
Charlson Comorbidity Index score					
Score 0	22/1,227	10/1,225	2.162 (1.018-4.590)	0.045	0.159
Score 1	47/1,370	11/1,365	4.509 (2.328-8.735)	<0.001	
Score 2	36/1,190	18/1,184	2.032 (1.147-3.599)	0.015	
Score ≧3	130/4,707	79/4,720	2.129 (1.609-2.818)	<0.001	
Hypertension					
Yes	129/4,441	98/4,443	1.716 (1.319-2.233)	<0.001	<0.001
No	106/4,053	20/4,051	5.539 (3.427-8.953)	<0.001	
Cerebrovascular disease					
Yes	92/2,614	55/2,622	2.173 (1.554-3.037)	<0.001	0.512
No	143/5,880	63/5,872	2.532 (1.881-3.409)	<0.001	
Myocardial infarction					
Yes	4/535	8/536	0.734 (0.219-2.453)	0.615	0.031
No	231/7,959	110/7,958	2.425 (1.932-3.044)	<0.001	
Diabetes mellitus					
Yes	71/2,742	56/2,742	1.659 (1.168-2.356)	0.005	0.011
No	164/5,752	62/5,752	2.954 (2.203-3.960)	<0.001	
Dyslipidemia					
Yes	66/2,205	34/2,212	2.383 (1.575-3.605)	<0.001	0.879
No	169/6,289	84/6,282	2.313 (1.779-3.007)	<0.001	
Coronary artery disease					
Yes	85/3,182	58/3,189	1.836 (1.314-2.564)	<0.001	0.056
No	150/5,312	60/5,305	2.746 (2.033-3.710)	<0.001	
Atrial fibrillation					
Yes	26/878	18/879	1.703 (0.933-3.110)	0.011	0.275
No	209/7,616	100/7,615	2.423 (1.908-3.077)	<0.001	

ESRD					
Yes	16/565	19/560	1.341 (0.687-2.618)	0.389	0.043
No	219/7,929	99/7,934	2.551 (2.011-3.236)	<0.001	
Pre-existing valvular heart disease					
Yes	97/3,233	50/3,229	2.036 (1.446-2.866)	<0.001	0.249
No	138/5,261	68/5,265	2.710 (2.021-3.633)	<0.001	
Valvular replacement before IE					
Yes	38/1,012	17/1,012	2.338 (1.317-4.151)	0.004	0.917
No	197/7,482	101/7,482	2.317 (1.822-2.946)	<0.001	
Valvular replacement after IE [b]					
Yes	34/742	13/742	2.757 (1.453-5.231)	0.002	0.648
No	201/7,752	105/7,752	2.279 (1.799-2.887)	<0.001	
Year of index date					
2000-2006	61/2,640	21/2,804	3.414 (2.079-5.607)	<0.001	0.072
2007-2009	174/5,854	97/5,690	2.102 (1.639-2.696)	<0.001	

[a] Adjusted for propensity score.

[b] Compared with matched control subjects.

Abbreviations: ESRD, end-stage renal disease; IE, infective endocarditis; CI, confidence interval.

Supplementary Table 6. Subgroup analysis of Risk of Myocardial Infarction among Patients with Infective Endocarditis and Matched Cohort

Characteristic	Case	Control	Adjusted[a]		Interaction p Value
	No. of Event/ No. of Patients	No. of Event/ No. of Patients	Hazard Ratio (95% CI)	p Value	
Gender					
Male	110/5,466	109/5,463	1.152 (0.883-1.502)	0.297	0.014
Female	77/3,028	47/3,031	1.985(1.380-2.854)	<0.001	
Age					
20-39	9/2,091	5/2,074	1.804 (0.603-5.396)	0.291	0.785
40-59	36/2,411	31/2,415	1.317(0.813-2.132)	0.264	
≧60	142/3,992	120/4,005	1.566(1.227-1.998)	<0.001	
Charlson Comorbidity Index score					
Score 0	3/1,227	6/1,225	0.595(0.148-2.396)	0.465	0.397
Score 1	15/1,370	14/1,365	1.318(0.630-2.758)	0.463	
Score 2	27/1,190	18/1,184	1.560(0.853-2.853)	0.149	
Score ≧3	142/4,707	118/4,720	1.580(1.237-2.018)	<0.001	
Hypertension					
Yes	143/4,441	131/4,443	1.439(1.134-1.824)	0.003	0.308
No	44/4,053	25/4,051	1.806(1.100-2.967)	0.020	
Cerebrovascular disease					
Yes	72/2,614	79/2,622	1.226(0.891-1.688)	0.211	0.139
No	115/5,880	77/5,872	1.650(1.235-2.205)	0.001	
Myocardial infarction					
Yes	28/535	30/536	1.287(0.768-2.158)	0.338	0.654
No	159/7,959	126/7,958	1.453(1.150-1.837)	0.002	
Diabetes mellitus					
Yes	89/2,742	90/2,742	1.313(0.979-1.761)	0.069	0.272
No	98/5,752	66/5,752	1.631(1.192-2.231)	0.002	
Dyslipidemia					
Yes	73/2,205	52/2,212	1.790(1.253-2.557)	0.001	0.127
No	114/6,289	104/6,282	1.235(0.946-1.612)	0.121	
Coronary artery disease					
Yes	126/3,182	107/3,189	1.480(1.143-1.918)	0.003	0.980
No	63/5,312	49/5,305	1.458(1.156-1.839)	0.001	
Atrial fibrillation					
Yes	25/878	27/879	1.114 (0.646-1.920)	0.698	0.354
No	162/7,616	129/7,615	1.588 (1.381-1.827)	<0.001	

ESRD					
Yes	26/565	19/560	2.056(1.133-3.732)	0.018	0.166
No	161/7,929	137/7,934	1.351(1.075-1.698)	0.010	
Pre-existing valvular heart disease					
Yes	83/3,233	61/3,229	1.375(0.987-1.915)	0.060	0.772
No	104/5,261	95/5,265	1.443(1.090-1.910)	0.010	
Valvular replacement before IE					
Yes	19/1,012	24/1,012	0.814(0.445-1.489)	0.504	0.059
No	168/7,482	132/7,482	1.510(1.202-1.897)	<0.001	
Valvular replacement after IE [b]					
Yes	16/742	20/742	0.799(0.413-1.546)	0.506	0.068
No	171/7,752	136/7,752	1.497(1.194-1.876)	<0.001	
Year of index date					
2000-2006	40/2,640	35/2,804	1.358(0.862-2.138)	0.186	0.882
2007-2009	147/5,854	121/5,690	1.414(1.111-1.800)	0.005	

[a] Adjusted for propensity score.

[b] Compared with matched control subjects.

Abbreviations: ESRD, end-stage renal disease; IE, infective endocarditis; CI, confidence interval.

Supplementary Table 7. Risk factors of Ischemic Stroke among Patients with Infective Endocarditis

	Univariate		Multivariate[†]	
Variables	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**
Age, per year	1.04 (1.03-1.04)	<0.001	1.02 (1.01-1.02)	<0.001
Male	0.94 (0.80-1.10)	0.418		
Monthly income				
Dependent	1			
NT$0–19,100	0.63 (0.51-0.79)	<0.001		
NT$19,100–42,000	0.92 (0.76-1.11)	0.392		
>NT$42,000	0.29 (0.15-0.55)	<0.001		
Urbanization level				
1	1			
2	0.93 (0.79-1.10)	0.404		
3	1.18 (0.90-1.54)	0.223		
4 (rural)	0.56 (0.25-1.25)	0.155		
Charlson Comorbidity Index score, per score	1.16 (1.13-1.18)	<0.001		
Concomitant medications				
Aspirin	1.99 (1.60-2.48)	<0.001		
Clopidogrel	2.48 (1.43-4.30)	0.001		
Ticlopidine	1.30 (0.49-3.47)	0.603		
Statin	2.41 (1.67-3.48)	<0.001		
Warfarin	1.40 (0.94-2.05)	0.090		
CV risk factors and history				
Diabetes	2.15 (1.83-2.53)	<0.001	1.36 (1.12-1.65)	0.002
Hypertension	3.25 (2.73-3.88)	<0.001	1.31 (1.05-1.64)	0.015
History of				
Cerebrovascular disease	3.91 (3.34-4.59)	<0.001	2.55 (2.12-3.06)	<0.001
Coronary artery disease	2.58 (2.20-3.02)	<0.001		
Myocardial infarction	2.00 (1.51-2.64)	<0.001		
Heart failure	2.02 (1.72-2.37)	<0.001	1.22 (1.01-1.47)	0.040
Dyslipidemia	2.09 (1.77-2.46)	<0.001		
End-stage renal disease	1.85 (0.96-3.57)	0.068		
Chronic renal disease	1.60 (1.34-1.92)	<0.001		
Atrial fibrillation	2.40 (1.96-2.93)	<0.001	1.42 (1.14-1.76)	0.002
Valvular heart disease	1.28 (1.09-1.49)	0.002		
Cancer	1.15 (0.91-1.46)	0.239		

AIDS	*			
Drug abuse	0.27 (0.17-0.42)	<0.001		
Mechanical valve	1.63 (0.23-11.61)	0.624		
Bioprosthetic valve	2.06 (0.51-8.24)	0.309		
Repeat IE‡	1.47 (1.10-1.98)	0.009	1.48 (1.10-1.98)	0.009

* Can not calculate.

† All factors with a P < .1 on univariate analyses were included in the multivariate analysis.

‡ Calculated as a time-varying covariate.

Abbreviations: HR = hazard ratio; CI = confidence interval; NT$, new Taiwan dollars; AIDS, acquired immunodeficiency syndrome; IE, infective endocarditis.

Supplementary Table 8. Risk factors of Hemorrhagic Stroke among Patients with Infective Endocarditis

	Univariate		Multivariate[†]	
Variables	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**
Age, per year	1.01 (1.00-1.02)	0.002		
Male	1.28 (0.98-1.66)	0.066	1.39 (1.07-1.81)	0.015
Monthly income				
Dependent	1			
NT$0–19,100	0.89 (0.63-1.26)	0.522		
NT$19,100–42,000	1.17 (0.86-1.59)	0.316		
>NT$42,000	0.79 (0.39-1.58)	0.499		
Urbanization level				
1	1			
2	0.83 (0.63-1.08)	0.167		
3	1.70 (1.19-2.42)	0.003		
4 (rural)	0.21 (0.03-1.53)	0.125		
Charlson Comorbidity Index score, per score	1.08 (1.04-1.12)	<0.001		
Concomitant medications				
Aspirin	0.52 (0.29-0.93)	0.027		
Clopidogrel	1.71 (0.64-4.59)	0.287		
Ticlopidine	2.99 (1.11-8.03)	0.030		
Statin	0.17 (0.02-1.25)	0.082		
Warfarin	1.81 (1.08-3.05)	0.026	1.71 (1.01-2.92)	0.046
CV risk factors and history				
Diabetes	1.24 (0.95-1.61)	0.111		
Hypertension	1.56 (1.22-1.99)	<0.001		
History of				
Cerebrovascular disease	1.78 (1.38-2.28)	<0.001	1.55 (1.17-2.07)	0.003
Coronary artery disease	1.13 (0.88-1.46)	0.332		
Myocardial infarction	0.47 (0.21-1.05)	0.065		
Heart failure	1.30 (1.01-1.68)	0.046		
Dyslipidemia	1.31 (1.00-1.72)	0.048		
End-stage renal disease	1.89 (0.70-5.07)	0.209		
Chronic renal disease	1.24 (0.93-1.66)	0.146		
Atrial fibrillation	1.26 (0.86-1.85)	0.230		
Valvular heart disease	1.21 (0.95-1.53)	0.128		
Cancer	1.14 (0.79-1.63)	0.485		

AIDS	1.43 (0.46-4.49)	0.532		
Drug abuse	0.41 (0.23-0.74)	0.003		
Mechanical valve	4.13 (0.58-29.45)	0.157		
Bioprosthetic valve	2.49 (0.35-17.71)	0.364		
Repeat IE[‡]	1.77 (1.20-2.61)	0.004	1.84 (1.24-2.72)	0.002

[†] All factors with a P < .1 on univariate analyses were included in the multivariate analysis.

[‡] Calculated as a time-varying covariate.

Abbreviations: HR = hazard ratio; CI = confidence interval; NT$, new Taiwan dollars; AIDS, acquired immunodeficiency syndrome; IE, infective endocarditis.

Supplementary Table 9. Risk factors of Myocardial Infarction among Patients with Infective Endocarditis

	Univariate		Multivariate[†]	
Variables	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**
Age, per year	1.05 (1.04-1.06)	<0.001	1.03 (1.02-1.04)	<0.001
Male	0.76 (0.57-1.00)	0.046		
Monthly income				
Dependent	1			
NT$0–19,100	0.46 (0.32-0.67)	<0.001		
NT$19,100–42,000	0.66 (0.48-0.90)	0.009		
>NT$42,000	0.35 (0.14-0.87)	0.023		
Urbanization level				
1	1			
2	0.91 (0.68-1.23)	0.546		
3	1.29 (0.82-2.03)	0.265		
4 (rural)	0.84 (0.27-2.65)	0.768		
Charlson Comorbidity Index score, per score	1.22 (1.18-1.27)	<0.001		
Concomitant medications				
Aspirin	2.45 (1.71-3.49)	<0.001		
Clopidogrel	5.07 (2.50-10.31)	<0.001		
Ticlopidine	2.06 (0.51-8.31)	0.308		
Statin	3.83 (2.27-6.49)	<0.001		
Warfarin	1.52 (0.81-2.87)	0.195		
CV risk factors and history				
Diabetes	2.80 (2.13-3.69)	<0.001	1.42 (1.01-1.98)	0.042
Hypertension	4.05 (2.94-5.57)	<0.001		
History of				
Cerebrovascular disease	1.87 (1.41-2.48)	<0.001		
Coronary artery disease	4.24 (3.18-5.66)	<0.001	1.65 (1.16-2.33)	0.005
Myocardial infarction	3.89 (2.65-5.71)	<0.001	1.70 (1.12-2.58)	0.012
Heart failure	2.83 (2.15-3.72)	<0.001		
Dyslipidemia	2.23 (1.68-2.96)	<0.001		
End-stage renal disease	5.55 (2.73-11.28)	<0.001		
Chronic renal disease	3.62 (2.74-4.77)	<0.001	1.84 (1.27-2.66)	0.001
Atrial fibrillation	1.89 (1.30-2.76)	0.001		
Valvular heart disease	1.29 (0.98-1.69)	0.067		
Cancer	1.73 (1.20-2.58)	0.003		
AIDS	*			
Drug abuse	0.26 (0.12-0.59)	0.001		

Mechanical valve	*			
Bioprosthetic valve	*			
Repeat IE[‡]	1.60 (1.00-2.55)	0.050	1.55 (0.97-2.48)	0.067

* Can not calculate.

[†] All factors with a P < .1 on univariate analyses were included in the multivariate analysis.

[‡] Calculated as a time-varying covariate.

Abbreviations: HR = hazard ratio; CI = confidence interval; NT$, new Taiwan dollars; AIDS, acquired immunodeficiency syndrome; IE, infective endocarditis.

Supplementary Table 10. Risk factors of Repeat Infective Endocarditis among Patients with Infective Endocarditis

	Univariate		Multivariate*	
Variables	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**
Age, per year	0.99 (0.99-0.99)	<0.001	0.99 (0.99-1.00)	0.002
Male	1.42 (1.25-1.61)	<0.001	1.30 (1.14-1.48)	<0.001
Monthly income				
Dependent	1			
NT$0–19,100	1.34 (1.15-1.57)	<0.001		
NT$19,100–42,000	1.06 (0.90-1.24)	0.483		
>NT$42,000	1.310 (0.98-1.76)	0.070		
Urbanization level				
1	1			
2	0.87 (0.77-0.98)	0.023		
3	0.97 (0.79-1.20)	0.791		
4 (rural)	1.34 (0.91-1.97)	0.135		
Charlson Comorbidity Index score, per score	0.99 (0.98-1.02)	0.633		
Concomitant medications				
Aspirin	0.94 (0.80-1.11)	0.498		
Clopidogrel	1.08 (0.74-1.57)	0.690		
Ticlopidine	0.93 (0.50-1.73)	0.405		
Statin	0.98 (0.71-1.36)	0.924		
Warfarin	1.62 (1.43-1.84)	<0.001		
CV risk factors and history				
Diabetes	0.87 (0.77-1.00)	0.047		
Hypertension	0.85 (0.76-0.96)	0.009		
History of				
Cerebrovascular disease	0.98 (0.86-1.11)	0.743		
Coronary artery disease	0.87 (0.76-0.98)	0.024		
Myocardial infarction	0.86 (0.65-1.14)	0.294		
Heart failure	1.14 (1.01-1.28)	0.039		
Dyslipidemia	0.96 (0.84-1.10)	0.579		
End-stage renal disease	1.16 (0.91-1.47)	0.225		
Chronic renal disease	1.02 (0.88-1.18)	0.806		
Atrial fibrillation	0.90 (0.74-1.09)	0.289		
Valvular heart disease	1.36 (1.21-1.52)	<0.001		
Cancer	1.01 (0.84-1.203)	0.940		
AIDS	1.10 (0.66-1.84)	0.702		
Drug abuse	1.55 (1.32-1.81)	<0.001	1.50 (1.26-1.79)	<0.001

Mechanical valve	2.18 (1.88-2.52)	<0.001	2.11 (1.70-2.62)	<0.001
Bioprosthetic valve	2.51 (2.10-2.99)	<0.001	2.60 (2.16-3.13)	<0.001

[*] All factors with a P < .1 on univariate analyses were included in the multivariate analysis.

Abbreviations: HR = hazard ratio; CI = confidence interval; NT$, new Taiwan dollars; AIDS, acquired immunodeficiency syndrome.

Supplementary Table 11. Association between Microorganism and Major Cardiovascular Events and Repeat Infective Endocarditis among Patients with Infective Endocarditis (N=2,885)

	Adjusted*	
	Hazard Ratio (95% CI)	***p* Value**
Ischemic stroke		
Without codes of microorganism	1	
With codes of microorganism	0.97 (0.82-1.15)	0.743
Staphylococci (n=1,379, 47.8%)	0.94 (0.42-2.12)	0.889
Streptococcus (n=1,106, 38.3%)	0.67 (0.30-1.51)	0.338
Gram-negative bacteria (*n*=296, 10.3%)	0.98 (0.46-2.11)	0.958
Others (n=104, 3.6%)	0.72 (0.31-1.69)	0.450
Hemorrhagic stroke		
Without codes of microorganism	1	
With codes of microorganism	0.90 (0.70-1.17)	0.441
Staphylococci (n=1,379, 47.8%)	0.79 (0.24-2.57)	0.697
Streptococcus (n=1,106, 38.3%)	1.47 (0.46-4.68)	0.519
Gram-negative bacteria (n=296, 10.3%)	1.28 (0.42-3.85)	0.661
Others (n=104, 3.6%)	0.83 (0.20-3.37)	0.793
Myocardial infarction		
Without codes of microorganism	1	
With codes of microorganism	0.99 (0.73-1.35)	0.962
Staphylococci (n=1,379, 47.8%)	1.58 (0.43-5.84)	0.493
Streptococcus (n=1,106, 38.3%)	1.24 (0.34-4.59)	0.746
Gram-negative bacteria (n=296, 10.3%)	1.01 (0.28-3.68)	0.989
Others (n=104, 3.6%)	0.76 (0.15-3.83)	0.739
Repeat infective endocarditis		
Without codes of microorganism	1	
With codes of microorganism	1.33 (1.20-1.46)	<0.001
Staphylococci (n=1,379, 47.8%)	0.99 (0.60-1.65)	0.980
Streptococcus (n=1,106, 38.3%)	0.83 (0.50-1.38)	0.471
Gram-negative bacteria (n=296, 10.3%)	0.79 (0.48-1.30)	0.355
Others (n=104, 3.6%)	0.84 (0.48-1.47)	0.547

* Adjusted all covariate listed in Table 1. Abbreviations: CI, confidence interval
List of ICD-9-CM codes adopted: *Staphylococci*: 038.1x, 041.1x; *Streptococcus*: 038.0x, 038.2x, 041.0x, 041.2x; Gram-negative bacteria: 003.1x, 038.4x, 041.3x, 041.4x, 041.5x, 041.6x, 041.7x; others: 038.3x, 041.3x, 041.8x, 098.84x, 112.81x

Supplementary Figure 1. Hospitalization Rates for Infective Endocarditis in Taiwan, 2000 to 2009