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Effect of medications after cardiac surgery on long-term outcomes in patients with cirrhosis

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Abstract

The aim of this study was to evaluate the effect of beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) after cardiac surgery in the liver cirrhosis (LC) patients. We conducted a population-based cohort study using data from the Taiwanese National Health Insurance Research Database (NHIRD) from 2001 to 2013. The outcomes of interest included all-cause mortality, major adverse cardiac and cerebrovascular events (MACCE) and liver and renal outcomes. Among 1470 LC patients, 35.6% (n = 524) received beta-blockers and 33.4% (n = 491) were prescribed ACEIs and/or ARBs after cardiac surgery. The risk of negative liver outcomes was significantly lower in the ARB group compared with the ACEI group (9.6% vs 22.7%, hazard ratio [HR] 0.50, 95% confidence interval [CI] 0.31–0.83). Furthermore, the risk of MACCE (44.2% vs 54.7%, HR 0.79, 95% CI 0.65–0.96), all-cause mortality (35.3% vs 46.4%, HR 0.74, 95% CI 0.60–0.92), composite liver outcomes (9.6% vs 16.5%, HR 0.56, 95% CI 0.38–0.85) and hepatic encephalopathy (2.7% vs 5.7%, HR 0.45, 95% CI 0.21–0.94) were lower in the ARB group than the control group. Our study demonstrated that ARBs provide a greater protective effect than ACEIs in regard to long-term outcomes following cardiac surgery in patients with LC.

Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin receptor blockers, ATC = Anatomical Therapeutic Chemical, CABG = coronary artery bypass graft, CCBs = calcium channel blockers, EV = sophageal varices, HCC = hepatocellular carcinoma, HE = hepatic encephalopathy, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, LC = liver cirrhosis, MACCE = major adverse cardiac and cerebrovascular events, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PPI = proton pump inhibitors, RAS = renin angiotensin system.

Keywords: angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, cardiac surgery, liver cirrhosis

1. Introduction

Long-term adverse cardiovascular events after cardiac surgery are still common and carry great prognostic significance.[1–3] Current medical interventions to prevent these cardiovascular complications include antiplatelet therapy,[4] statins,[5] beta-blockers,[6] angiotensin-converting enzyme inhibitors (ACEIs),[7] and angiotensin receptor blockers (ARBs).[8] Study in the literature reported that the administration of beta-blockers after cardiac surgery was associated with a substantially lower mortality rate during the long-term follow-up period.[9] Furthermore, both experimental studies and clinical trials have shown that ACEIs and ARBs hold promise as cardiovascular protective agents for patients following cardiac surgery.[7–10]

Cirrhosis represents a late stage of progressive hepatic fibrosis, and is characterized by distortion of the hepatic architecture and formation of regenerative nodules.[11] Patients with cirrhosis are susceptible to a variety of complications,[11] many of which are the result of portal hypertension (increased pressure within the portal venous system). This can lead to the formation of venous collaterals (varices) as well as circulatory, vascular, functional and biochemical abnormalities that contribute to the pathogenesis of ascites, esophageal varices, and other complications.[11] The current pharmacological mainstay to reduce portal pressure is beta-blockers, which work by decreasing splanchnic inflow.[12] However, some patients are unable to tolerate beta-blockers, and less than 40% of patients achieve an optimal response.[13] Alternate therapeutic targets, including renin angiotensin system

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(RAS) inhibitors (ACEIs and ARBs), represent potential therapies for the treatment of portal hypertension.[14]

There is a rise in LC patients with cardiac surgery due to improved level of medical care in these patients, including liver transplantation. Despite LC is not included within the most important cardiac surgery scores, such as European system for cardiac operative risk evaluation (EuroSCORE) or Parsonnet score, it is considered at high risk for cardiac surgery.[15,16] Moreover, our previous study clearly demonstrated that, even after successful cardiac surgery, LC patients still have higher rates of liver-related readmission and death due to complications of LC after cardiac surgery.[17] Up-to date, no literatures have investigated the long-term effect of medications in LC patients after cardiac surgery. Because of increasing chance of cardiac surgery in LC patients and improve their long-term outcome after cardiac surgery, urgent need to examine effect of medications after cardiac surgery in these patients. Therefore, the aim of this study was to evaluate the effect of beta-blockers, ACEIs and ARBs on the outcomes of cardiac surgery in LC patients using a nationwide database.

2. Materials and methods

2.1. Data source

This study is based on a longitudinal health insurance database, the National Health Insurance Research Database (NHIRD), provided by the Taiwan National Health Research Institute. Taiwan launched a National Health Insurance (NHI) program on March 1, 1995, and more than 99% of Taiwans population is enrolled. The NHI system offers complete follow-up information on major interventions and medications as well as admission, outpatient clinic and emergency department visit records of the Taiwanese population. Detailed information about the NHI program and claims datasets were described in our previous publication.[17]

After major surgery, patients receive discharge medications and are advised to attend at least 1 follow-up visit at the outpatient clinic to receive their prescriptions within 1 month after discharge, then every 3 months maximum afterwards if they have been diagnosed with a chronic disease and are in a stable condition. Accurate records of health reimbursement ensured by the prescription of medications were followed-up with appropriate examinations and indications. The Bureau of National Health Insurance (BNHI) performs expert reviews on a random sample of every 50 to 100 ambulatory, in-patient and out-patients claims in each hospital and clinic, which is conducted quarterly. False reports of diagnosis and inadequate indication for the prescription of certain medications incur a severe penalty from the BNHI. A large number of studies of medications using the NHIRD have been published.[18,19] Furthermore, patients with advanced disease, such as liver cirrhosis, have unrestricted access to the NHI system regardless of their financial situation. The diagnoses were coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). This study was evaluated and approved by the Ethics Institutional Review Board of Chang Gung Memorial Hospital and the informed consent was waived because this was a retrospective study.

2.2. Study population

This nationwide data-based cohort study was conducted to assess the effect of medications on the long-term outcomes of LC patients after cardiac surgery. The claims data from the NHIRD used in this study include the hospitalization records of all patients admitted to NHI-contracted hospitals for coronary artery bypass graft (CABG) or valve surgeries. CABG was identified according to NHI reimbursement procedure codes 68023, 68024, or 68025, and a valve repair or replacement in any position was identified by procedure codes 68015, 68016, 68017, or 68018. The index date range was defined as patients who first received cardiac surgery between January 1, 2001 and December 31, 2013. To ensure that only first-time isolated cardiac surgical patients were enrolled, we excluded those with repeated admission for cardiac surgery. If patients with missing information (<0.1%), were aged <20 years, received an aortic procedure or died during hospitalization, they were excluded from the study. Patients with follow-up of less than 3 months after the date of discharge from the recorded admission were excluded from long-term medication assessment. After exclusion, we identified 56,346 adult patients who had undergone cardiac surgery for the first time between January 1, 2001 and December 31, 2013. We further identified patients with a diagnosis of cirrhosis (2 consecutive outpatient diagnoses and 1 inpatient diagnosis) according to the ICD-9-CM codes 571.2, 571.5, and 571.6.[20–22] Overall, 1470 cirrhosis patients were eligible for analysis in this study (Fig. 1). Since this was a retrospective database study, no statistical power calculation was conducted prior to the study.

2.3. Covariates

We extracted the baseline characteristics and surgical details of all patients using ICD-9-CM codes and Taiwan NHI procedure codes (billing codes) for prior outpatient visits or hospitalizations. The baseline patient characteristics included age, gender, surgery type, and hospital level. The definition of clinically relevant comorbidities required at least 2 outpatient visits or 1 hospitalization (ICD-9-CM codes are provided in Supplemental Table 1, http://links.lww.com/MD/F234) within 1 year prior to the indexed admission date. Most of these diagnoses were validated in previous NHIRD studies. The patients were categorized according to 3 levels of monthly income: low (NT$ 0–17,880), medium (NT$17,881–22,800), and high (NT$ > 22,800). The urbanization level was categorized as low, medium or high based on population density. Diseases related to cirrhosis included alcoholic cirrhosis, hepatitis B (HBV) or hepatitis C (HCV) infection and hepatocellular carcinoma (HCC) according to diagnosis during prior outpatient visits or hospitalizations. Cirrhosis-related complications included ascites, hepatic encephalopathy (HE), bleeding esophageal varices (EV), coagulopathy, and hypoalbuminemia according to prior hospitalization records. Advanced cirrhosis was defined as any 1 of the above complications.

2.4. Medications

The medications of interest included beta-blockers (selective or non-selective), ACEIs, ARBs, calcium channel blockers (CCBs), alpha-blockers, nitrates, diuretics (including loop diuretics, spironolactone, and thiazide), antidiabetic medications (including oral hypoglycemic agents or insulin), antiplatelet medications, statins, antioxidant medications (such as silymarin), digoxin, and proton pump inhibitors (PPI). To ascertain the long-term use of medications after cardiac surgery, patients were defined as a user of a particular medication if they had filled a

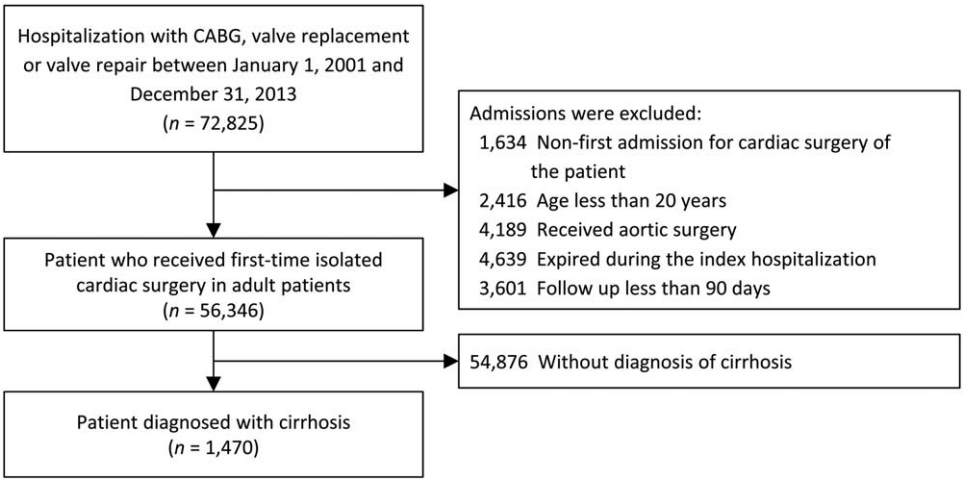

Figure 1. Enrollment of the study patients.

prescription at least twice or refilled a prescription for a chronic illness at least once (usually 2 or 3 months per prescription) within 3 months after discharge according to the indexed admission. The Anatomical Therapeutic Chemical (ATC) codes for the medications assessed in this study are provided in Supplemental Table 2, http://links.lww.com/MD/F235.

2.5. Study outcomes

The outcomes of primary interest for this study were all-cause mortality and major adverse cardiac and cerebrovascular events (MACCE), including any one of all-cause mortality, stroke, myocardial infarction, or heart failure. These diagnoses have been validated in previous NHIRD studies. All-cause mortality was defined by withdrawal from the NHI program.[23] The secondary outcomes included liver outcomes (HE, ascites tapping spontaneous peritonitis, and EV bleeding) and renal outcomes (new-onset chronic kidney disease, new-onset dialysis, and acute kidney injury). All other outcomes were identified according to principal diagnosis at emergency department visit or hospitalization during follow-up. All patients were followed until either December 31, 2013, the date of cardiac event occurrence or the date of death.

2.6. Statistical analysis

Continuous baseline data were expressed as the mean ± standard deviation, and comparisons between the survival and non-survival groups during the overall follow-up period were conducted using independent sample t tests. Categorical baseline data were presented as the frequency and percentage, and groups were compared using a Chi-Squared test. To investigate the potential risk factors for mortality, baseline data (including the variables listed in Tables 1 and 2) were introduced into the multivariable logistic model with a backward elimination selection process. In model 1, ACEIs and ARBs were combined and non-selective and selective beta-blockers were combined in the multivariable model. In model 2, ACEIs, ARBs, non-selective, and selective beta-blockers were considered different covariates and were introduced into the multivariable model. The patients were further separated into ARB users, ACEI users and controls who did not take either medications. We compared the risk of long-term (time to event) outcomes among these 3 groups using the Cox proportional hazard model. A P value $<.05$ was considered to be statistically significant. No adjustment of multiple testing (multiplicity) was made in this study. All statistical analyses were performed using commercial software (SAS 9.4, SAS Institute, Cary, NC)

3. Results

3.1. Study population characteristics

A total of 1470 LC patients who had undergone cardiac surgery from 2001 to 2013 were included in our study. Table 1 lists the general characteristics of the patients. Based on the occurrence of death during the follow-up period (mean 4.3 years, SD 3.2 years), the patients were separated into 2 groups: non-survival (654 cases) and survival (816 cases). The non-survival cohort were older, had a higher prevalence of all comorbidities (except for peripheral arterial disease and atrial fibrillation), higher CCI scores, and were more likely to have undergone CABG or combined CABG and valve surgery. The non-survival cohort had a significantly higher proportion of individuals with a low monthly income ($P = .004$) and low urbanization level ($P = .025$). In relation to complications associated with cirrhosis, the prevalence of HCV infection, HCC, coagulopathy, hypoalbuminemia, and advanced cirrhosis (with any complication) was significantly higher in the non-survival cohort. There were no significant differences in sex distribution or hospital level between the 2 groups (Table 1).

Table 2 lists the discharge medications of LC patients after cardiac surgery. Loop diuretics (51.2%) were the most commonly prescribed post-discharge medicine, following by antiplatelet drugs (45.3%), beta-blockers (35.6%), and ACEIs and/or ARBs (33.4%). Individuals in the survival group were more likely to be prescribed beta-blockers (especially selective beta-blocker), ACEIs/ARBs (especially ARBs), antiplatelet drugs, and statins during follow-up. On the other hand, the non-survival group was more likely to be prescribed alpha-blockers, nitrates, and insulin.

Table 1

Demographic and clinical characteristics of cirrhotic patients by the occurrence of death.

Variable	Total (n = 1470)	Non-survival (n = 654)	Survival (n = 816)	*P* value
Characteristics				
Age, years	62.6 ± 12.3	65.6 ± 11.7	60.2 ± 12.2	<.001
Male gender	1,124 (76.5)	485 (74.2)	639 (78.3)	.062
Comorbidity				
Hypertension	942 (64.1)	444 (67.9)	498 (61.0)	.006
Diabetes mellitus	633 (43.1)	309 (47.2)	324 (39.7)	.004
Hyperlipidemia	405 (27.6)	156 (23.9)	249 (30.5)	.004
Heart failure	564 (38.4)	294 (45.0)	270 (33.1)	<.001
Coronary artery disease	1,017 (69.2)	494 (75.5)	523 (64.1)	<.001
Myocardial infarction	231 (15.7)	117 (17.9)	114 (14.0)	.040
Peripheral arterial disease	80 (5.4)	44 (6.7)	36 (4.4)	.052
Atrial fibrillation	345 (23.5)	152 (23.2)	193 (23.7)	.854
Old stroke	228 (15.5)	119 (18.2)	109 (13.4)	.011
Old gastrointestinal bleeding	561 (38.2)	276 (42.2)	285 (34.9)	.004
Chronic kidney disease	410 (27.9)	232 (35.5)	178 (21.8)	<.001
ESRD (dialysis)	108 (7.3)	68 (10.4)	40 (4.9)	<.001
Malignancy	124 (8.4)	74 (11.3)	50 (6.1)	<.001
CCI score	3.7 ± 2.2	4.2 ± 2.3	3.3 ± 2.0	<.001
Surgical type				
CABG	660 (44.9)	312 (47.7)	348 (42.6)	.017
Valve	673 (45.8)	273 (41.7)	400 (49.0)	
CABG + valve	137 (9.3)	69 (10.6)	68 (8.3)	
Operational hospital level				
Medical center (teaching hospital)	1,073 (73.0)	465 (71.1)	608 (74.5)	.143
Regional / district hospital	397 (27.0)	189 (28.9)	208 (25.5)	
Monthly income, NTD$				
Low (0–17880)	580 (39.5)	279 (42.7)	301 (36.9)	.004
Medium (17881–22800)	515 (35.0)	235 (35.9)	280 (34.3)	
High (> 22800)	375 (25.5)	140 (21.4)	235 (28.8)	
Urbanization level				
Low	668 (45.4)	319 (48.8)	349 (42.8)	.025
Median	469 (31.9)	206 (31.5)	263 (32.2)	
High	333 (22.7)	129 (19.7)	204 (25.0)	
Disease related to cirrhosis				
Alcoholic cirrhosis	249 (16.9)	89 (13.6)	160 (19.6)	.002
Hepatitis B virus infection	275 (18.7)	106 (16.2)	169 (20.7)	.028
Hepatitis C virus infection	268 (18.2)	146 (22.3)	122 (15.0)	<.001
Hepatocellular carcinoma	54 (3.7)	33 (5.0)	21 (2.6)	.012
Complication of cirrhosis				
Hepatic encephalopathy	44 (3.0)	23 (3.5)	21 (2.6)	.292
Ascites (diagnosis or treatment)	196 (13.3)	93 (14.2)	103 (12.6)	.371
Esophageal varices bleeding (diagnosis or treatment)	64 (4.4)	29 (4.4)	35 (4.3)	.892
Admission for FFP (coagulopathy)	291 (19.8)	147 (22.5)	144 (17.6)	.021
Admission for albumin infusion (hypoalbuminemia)	143 (9.7)	86 (13.1)	57 (7.0)	<.001
Severity of cirrhosis				
Early cirrhosis	968 (65.9)	394 (60.2)	574 (70.3)	<.001
Advanced cirrhosis	502 (34.1)	260 (39.8)	242 (29.7)	
Catastrophic illness certificate	32 (2.2)	15 (2.3)	17 (2.1)	.784

ESRD = end-stage renal disease, CCI = Charlson Comorbidity Index, CABG = coronary artery bypass graft, NTD = New Taiwan Dollar, FFP = fresh frozen plasma.

3.2. Analysis of risk factors for mortality

Table 3 presents the results of the analysis of risk factors for mortality. Both multivariable model analyses identified age, comorbidities (including diabetes mellitus, heart failure, coronary artery disease, old stroke, chronic kidney disease, and end stage renal disease with dialysis), HCV infection, HCC, hypoalbuminemia, and advanced cirrhosis as predictors of mortality. In terms of discharge medications, antiplatelet medications were significantly associated with a lower risk of mortality in both models. ACEIs and ARBs were found to be protective against mortality in model 1 (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.65–0.92), and model 2 demonstrated that this protective effect was mainly due to ARBs (OR 0.73, 95% CI 0.60–0.90). In terms of beta-blockers, neither the beta-blocker nor the subtype of beta-blocker were identified as independent predictors of mortality.

3.3. Long-term outcomes of ACEIs, ARBs, and controls

We further evaluated the outcomes in patients who were prescribed ACEIs or ARBs and controls who did not use either of these medications. In this analysis, 27 patients were excluded

Table 2

Discharge medication of cirrhotic patients by the occurrence of death.

Discharge medication	Total (n = 1,470)	Non-survival (n = 654)	Survival (n = 816)	*P* value
β-blocker	524 (35.6)	202 (30.9)	322 (39.5)	.001
Selective β-blocker	219 (14.9)	73 (11.2)	146 (17.9)	<.001
Non-selective β-blocker	323 (22.0)	137 (20.9)	186 (22.8)	.396
ACEIs / ARBs	491 (33.4)	200 (30.6)	291 (35.7)	.040
ACEIs	199 (13.5)	97 (14.8)	102 (12.5)	.194
ARBs	319 (21.7)	116 (17.7)	203 (24.9)	.001
DCCBs	309 (21.0)	152 (23.2)	157 (19.2)	.061
α-blocker	71 (4.8)	42 (6.4)	29 (3.6)	.011
Nitrates	189 (12.9)	103 (15.7)	86 (10.5)	.003
Loop diuretics	752 (51.2)	341 (52.1)	411 (50.4)	.499
Spironolactone (K sparing)	172 (11.7)	74 (11.3)	98 (12.0)	.680
Thiazide	62 (4.2)	28 (4.3)	34 (4.2)	.913
OHA	377 (25.6)	165 (25.2)	212 (26.0)	.743
Insulin	127 (8.6)	67 (10.2)	60 (7.4)	.0499
Anti-platelet	666 (45.3)	271 (41.4)	395 (48.4)	.008
Statin	241 (16.4)	73 (11.2)	168 (20.6)	<.001
Silymarin	99 (6.7)	43 (6.6)	56 (6.9)	.827
Digoxin	329 (22.4)	139 (21.3)	190 (23.3)	.353
PPI	148 (10.1)	73 (11.2)	75 (9.2)	.212

ACEIs = angiotensin-converting-enzyme inhibitor, ARBs = angiotensin receptor blockers, DCCBs = dihydropyridine calcium channel blockers, OHA = oral hypoglycemic agent, PPI = proton pump inhibitor.

because both ACEIs and ARBs were prescribed during follow-up. Adverse liver outcomes were significantly reduced in the ARB group compared with the ACEI group (9.6% vs 22.7%, hazard ratio [HR] 0.50, 95% CI 0.31–0.83). Furthermore, the risk of MACCE (44.2% vs 54.7%, HR 0.79, 95% CI 0.65–0.96), all-cause mortality (35.3% vs 46.4%, HR 0.74, 95% CI 0.60–0.92), liver outcomes (9.6% vs 16.5%, HR 0.56, 95% CI 0.38–0.85) and hepatic encephalopathy (2.7% vs 5.7%, HR 0.45, 95% CI 0.21–0.94) were lower in the ARB group than in controls. In contrast, there were no statistically significant differences in the risk of MACCE, all-cause mortality, liver outcomes, and renal outcomes between the ACEI and control groups (Table 4).

Figure 2 presents the survival curves for all-cause mortality and liver outcomes for the group that used ARBs and the group that did not during the first 3 years of the follow-up period. The risk of all-cause mortality and composite liver outcomes were significantly higher in non-ARB users compared to ARB users ($P < .001$ and $P = .001$, respectively; Fig. 2A and B). As shown in Figure 3, we further compared the risks of all-cause mortality (Fig. 3A) and composite liver outcomes among the ARB, ACEI, and control

Table 3

Risk factor analysis of death.

	Model 1		Model 2	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years	1.03 (1.02, 1.04)	<.001	1.03 (1.02, 1.04)	<.001
Diabetes mellitus	1.26 (1.07, 1.49)	.006	1.27 (1.08, 1.50)	.004
Heart failure	1.45 (1.23, 1.70)	<.001	1.46 (1.24, 1.72)	<.001
Coronary artery disease	1.39 (1.13, 1.72)	.002	1.41 (1.14, 1.74)	.002
Old stroke	1.37 (1.12, 1.68)	.003	1.36 (1.11, 1.66)	.003
Chronic kidney disease	1.49 (1.23, 1.80)	<.001	1.52 (1.26, 1.83)	<.001
ESRD (dialysis)	1.76 (1.32, 2.36)	<.001	1.77 (1.32, 2.36)	<.001
Malignancy	–	–	1.35 (0.97, 1.86)	.072
Operation in medical center	0.85 (0.71, 1.01)	.062	0.86 (0.72, 1.02)	.086
Urbanization level				
Low	Reference	–	Reference	–
Median	0.85 (0.71, 1.01)	.068	0.83 (0.69, 0.99)	.036
High	0.78 (0.63, 0.96)	.017	0.77 (0.62, 0.95)	.014
Hepatitis C virus infection	1.28 (1.06, 1.55)	.012	1.32 (1.09, 1.60)	.005
Hepatocellular carcinoma	2.42 (1.68, 3.49)	<.001	1.91 (1.19, 3.06)	.007
Admission for albumin infusion (hypoalbuminemia)	1.30 (1.00, 1.69)	.053	1.31 (1.01, 1.71)	.045
Advanced cirrhosis	1.30 (1.08, 1.57)	.005	1.29 (1.07, 1.55)	.008
Anti-platelet	0.64 (0.53, 0.76)	<.001	0.64 (0.54, 0.77)	<.001
ACEIs / ARBs	0.78 (0.65, 0.92)	.003	–	–
Selective β-blocker			0.81 (0.63, 1.04)	.093
ARBs			0.73 (0.60, 0.90)	.003

HR = hazard ratio, CI = confidence interval, ESRD = end-stage renal disease, ACEIs = angiotensin-converting-enzyme inhibitors, ARBs = angiotensin receptor blockers.

Table 4

Follow up outcome in patients who received ACEIs, ARBs and controls.

Outcome	Number of event (%)			Hazard ratio and 95% CI					
				ARBs *vs.* ACEI		ARBs *vs.* Control		ACEIs *vs.* Control	
	ACEIs (n = 172)	ARBs (n = 292)	Control (n = 979)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
MACCE*	111 (64.5)	129 (44.2)	536 (54.7)	0.79 (0.61, 1.03)	.078	0.79 (0.65, 0.96)	.020	1.00 (0.81, 1.23)	.992
All-cause mortality	84 (48.8)	103 (35.3)	454 (46.4)	0.90 (0.67, 1.21)	.491	0.74 (0.60, 0.92)	.007	0.82 (0.65, 1.04)	.109
Composite liver outcome	39 (22.7)	28 (9.6)	162 (16.5)	0.50 (0.31, 0.83)	.006	0.56 (0.38, 0.85)	.006	1.12 (0.78, 1.60)	.539
Hepatic encephalopathy	8 (4.7)	8 (2.7)	56 (5.7)	0.77 (0.29, 2.06)	.596	0.45 (0.21, 0.94)	.034	0.58 (0.28, 1.23)	.157
Ascites tapping	27 (15.7)	23 (7.9)	114 (11.6)	0.65 (0.37, 1.14)	.132	0.67 (0.43, 1.06)	.087	1.04 (0.68, 1.59)	.865
Spontaneous peritonitis	7 (4.1)	8 (2.7)	31 (3.2)	0.78 (0.28, 2.19)	.635	0.83 (0.38, 1.83)	.642	1.07 (0.46, 2.46)	.883
Esophageal varices bleeding	8 (4.7)	9 (3.1)	48 (4.9)	0.82 (0.31, 2.16)	.689	0.64 (0.31, 1.31)	.219	0.78 (0.36, 1.66)	.512
Renal outcome									
New onset CKD	52 (30.2)	64 (21.9)	226 (23.1)	0.86 (0.59, 1.25)	.435	1.10 (0.81, 1.50)	.529	0.95 (0.72, 1.26)	.725
New onset dialysis	7 (4.1)	19 (6.5)	52 (5.3)	1.90 (0.79, 4.60)	.152	0.66 (0.30, 1.46)	.305	1.25 (0.74, 2.14)	.406
Acute kidney injury	29 (16.9)	40 (13.7)	141 (14.4)	0.92 (0.57, 1.50)	.747	1.004 (0.67, 1.51)	.985	0.93 (0.65, 1.32)	.676

* Any of all-cause mortality, stroke, myocardial infarction and heart failure; 27 patients were excluded from the analysis because both ACEIs and ARBs were prescribed during the follow up.

ACEIs = angiotensin-converting-enzyme inhibitors, ARBs = angiotensin receptor blockers, HR = hazard ratio, CI = confidence interval, MACCE = major adverse cardiac and cerebrovascular events, CKD = chronic kidney disease.

groups (Fig. 3B). Users of ARBs showed superior survival compared to users of ACEIs ($P = .055$) and controls ($P < .001$). In terms of composite liver outcomes, the risk of ARB users was significantly lower than that of ACEI users ($P = .002$) and controls ($P = .002$). However, there were no significantly differences between the ACEI and control groups ($P = .532$).

4. Discussion

This is the population-based study to evaluate post-discharge medication use in patients with LC after cardiac surgery. In this study, the survival cohort was more likely to be prescribed beta-blockers, ACEIs, ARBs, antiplatelet medications, and statins during follow-up. However, our multivariable model analysis demonstrated that antiplatelet, ACEI and ARB medications were associated with a marked reduction in mortality rate.

Previous studies have reported that beta-blockers, especially non-selective beta-blockers, may be beneficial in the prevention of complications of cirrhosis and portal hypertension, including variceal hemorrhage.[12,24] Patients suffering from cirrhosis with portal hypertension have a hyperdynamic circulation characterized by increased cardiac output and splanchnic blood inflow and reduced peripheral and splanchnic vascular resistance, which is associated with an increased plasma volume.[12] The effect of beta-blockers in preventing variceal bleeding is thought to be mediated by acting on the hyperdynamic state.[12] However, in our study we demonstrated that both subtypes of beta-blockers had no protective effect in patients with LC after cardiac surgery. A recent study suggested that not all cases of LC can be effectively treated with beta-blockers.[25] Beta-blockers have survival benefits only at the stage of cirrhosis when increased portal pressure complicated with esophageal varices and bleeding.[26] Final stage of cirrhosis with refractory ascites, beta-blockers may aggravate hypotension, or azotemia.[25] We suggested that it is necessary to assess the progression of cirrhosis and closely monitor blood pressure and renal function to determine whether to adjust or stop medications while the patient is being treated with beta-blockers.

Recently, alternate therapeutic targets including RAS antagonists (ACEIs and ARBs) have been developed as potential therapies for portal hypertension.[27] These drugs have shown cardioprotective effects and are recommended as first-line therapy to reduce the risk of adverse cardiovascular events.[7,8,10] In a prospective observational cohort study of 4224 patients who underwent CABG surgery, the initiation of ACEI therapy soon after surgery was associated with improved in-hospital outcomes.[28] Furthermore, in a rat model ARBs were found to be superior to ACEIs for improving hepatic fibrosis, which is a pathological feature of cirrhosis.[29] However, no studies have reported the long-term effects of ACEIs and ARBs in patients with LC after cardiac surgery. Also, no comparison of the clinical effects of ACEIs and ARBs has been performed for LC patients. Therefore, in the present study we evaluated and compared the long-term outcomes of ACEIs and ARBs in patients with LC after cardiac surgery. We found that the risk of composite outcomes (MACCE), all-cause mortality, and liver outcomes were lower in the ARB group than in controls. Adverse liver outcomes were significantly reduced in the ARB group compared with the ACEI group. There were no statistically significant differences in MACCE, all-cause mortality, and liver outcomes in the ACEI group compared to controls.

It has been shown that the RAS is frequently activated in patients with LC due to a decrease in effective circulating volume.[30] Following liver cirrhosis, RAS components including ACE and the AT1 receptor, is markedly increased and is localized to areas of hepatic fibrosis.[31] ACEIs inhibit ANG II synthesis by blocking the conversion of angiotensin I (ANG I) to ANG II, whereas ARBs protect ANG II by binding to AT1-R. Thus, ACEIs and ARBs both have antifibrotic effects and reduce portal hypertension. However, ARBs were found to have a more potent effect than ACEIs in our study. There are several possible reasons for the different effects between ACEIs and ARBs. Firstly, although the initial effects of ACEIs can result in transiently decreased levels of circulating ANG II, continuous administration of ACEIs leads to a dose-dependent compensatory rise in levels of circulating active renin and blood ANG I, which is still partially converted to ANG II even during peak inhibition of the angiotensin-converting enzyme (ACE).[29] However, while increasing the dose of ACEIs may result in higher ACE inhibition, it probably does not result in better suppression of the RAS.[32] Secondly, accumulation of bradykinin secondary to inhibition of ACE by ACEIs plays an

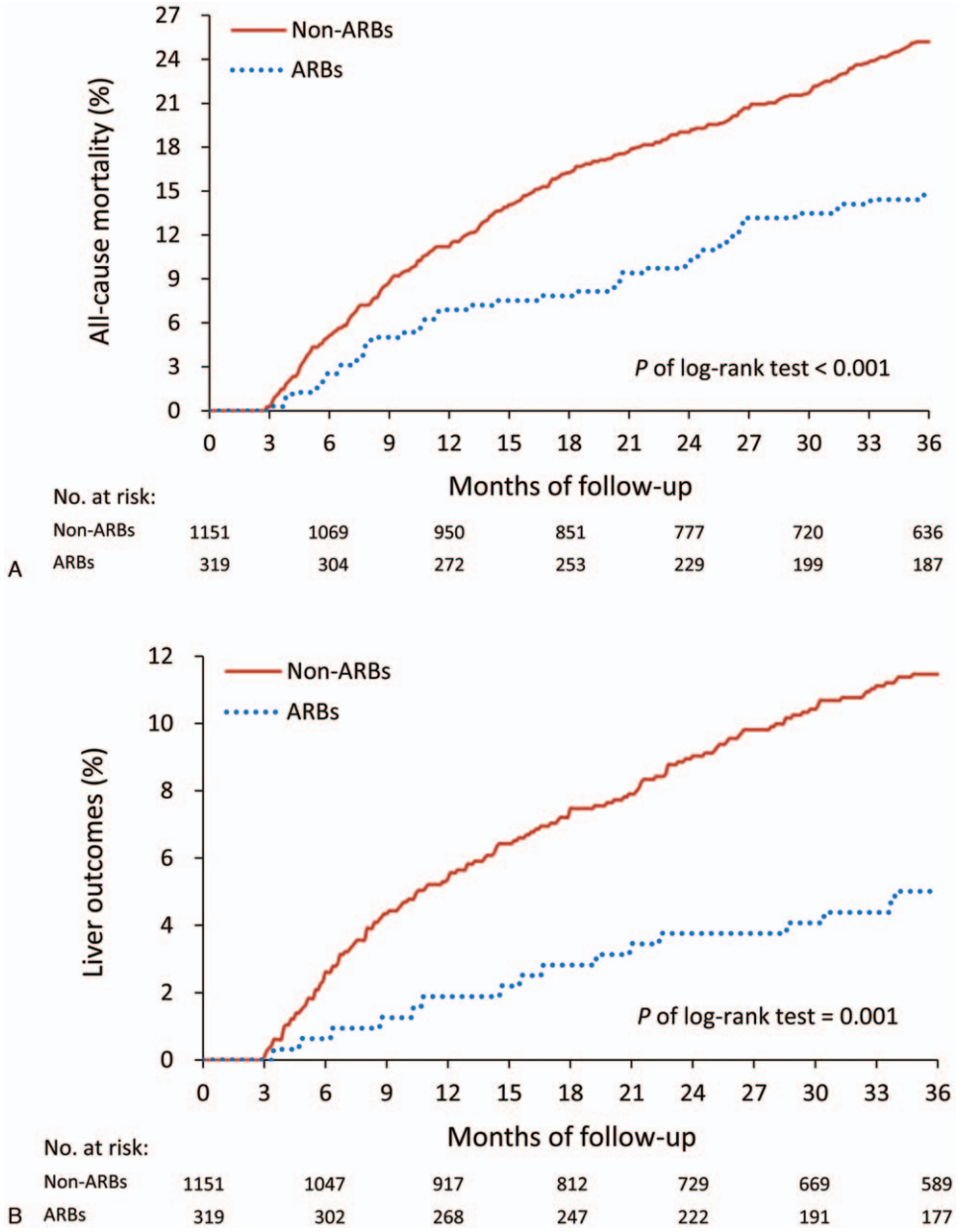

Figure 2. Cumulative event rates of all-cause mortality during the follow up (A) and liver outcome (B) in the ARBs and non-ARBs. ARBs, angiotensin receptor blockers.

important role in the progression of fibrosis.[33] ARBs are AT1-receptor antagonists, and they block the activation of ANG II AT1 receptors. Directly blocking AT1 receptors does not cause the accumulation of renin or bradykinin. These mechanisms may explain why ARBs seem to have more potent effects than ACEIs in LC patients after cardiac surgery. The present study suggested that ARBs are better than ACEIs for long-term treatment of LC patients after cardiac surgery.

Although different clinical trials have shown that ACEIs and ARBs may decrease portal pressure, these 2 types of medication may worsen systemic blood pressure and renal function. In a randomized controlled trial, ARBs did not alter portal pressure, or only caused a moderate decrease, and were associated with adverse effects including arterial hypotension and renal impairment.[34] They suggested that ARBs should not be used in routine clinical practice in patients with LC. Another study suggested that the use of ACEIs and ARBs in LC with ascites may be harmful.[35] In the current study, we evaluated the renal outcomes, including new-onset chronic kidney disease, new-onset dialysis, and acute kidney injury, in patients with LC who used ACEIs or ARBs after cardiac surgery. We found that there were no statistically significant differences in the risk of developing adverse renal outcomes in patients who took ACEIs or ARBs when compared to the control group. Based on the retrospective analysis in our study, further prospective randomized trials are needed to evaluate the renal effect of ACEIs or ARBs in LC patients for cardiac surgery.

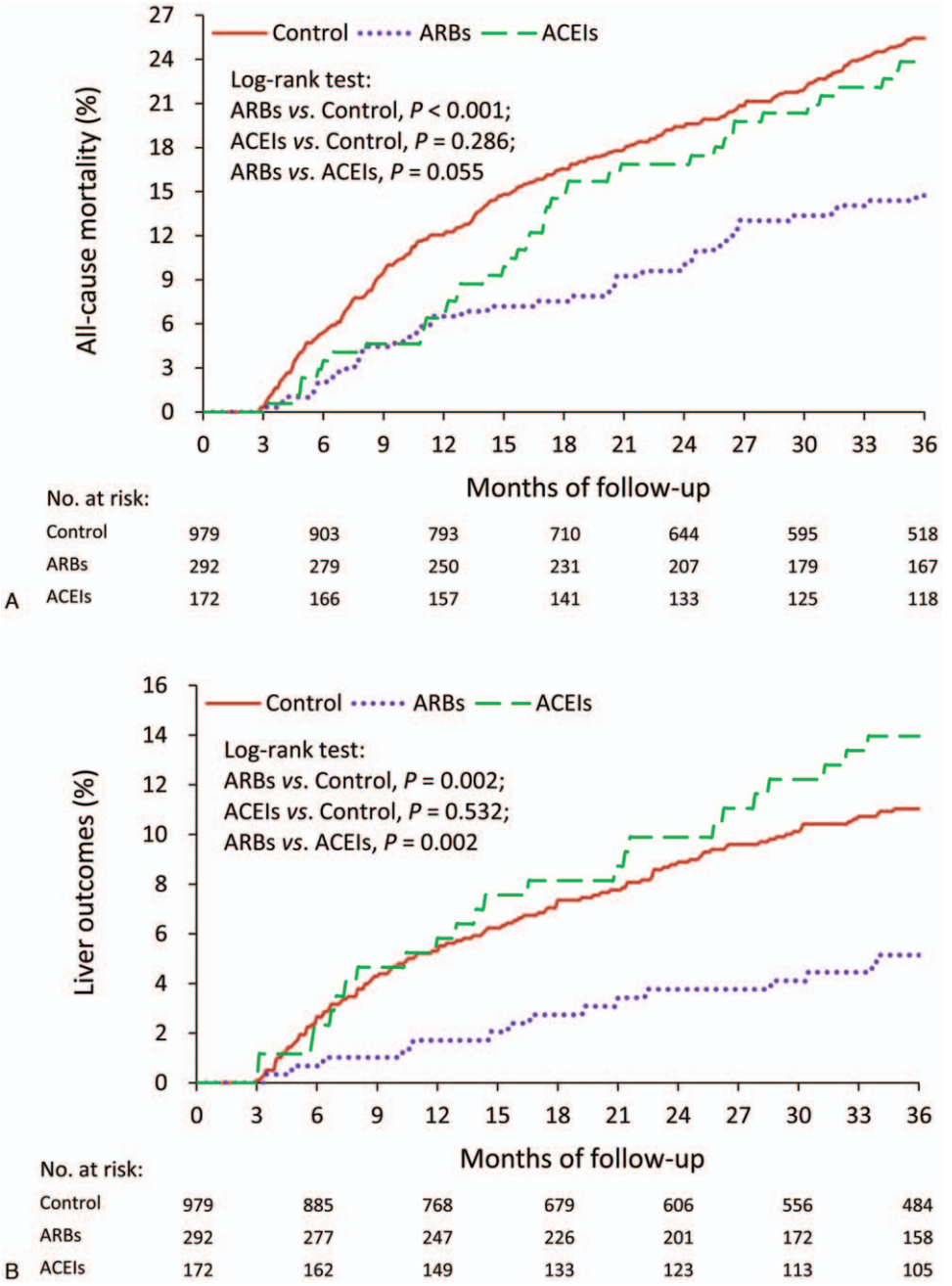

Figure 3. Cumulative event rates of all-cause mortality during the follow up (A) and liver outcome (B) in the ARBs *vs.* control, ACEIs vs control, and ARBs vs ACEIs. ARBs, angiotensin receptor blockers; ACEIs indicate angiotensin-converting enzyme inhibitors.

4.1. Study strengths

This study has several strengths worth mentioning. Firstly, to the best of our knowledge, this is the first population-based study to evaluate post-discharge medication use in patients with LC who had undergone cardiac surgery. Moreover, with total of 1470 LC patients, there was sufficient power to investigate both cardiac and liver outcomes. Furthermore, we used cumulative days with post-discharge medications as the time-dependent covariate to adjust for bias during the course of drug therapy.

4.2. Limitations

There are some limitations of our study. Firstly, we could not identify LC severity by the assigned ICD-9-CM codes. The NHIRD does not record biochemical data, like bilirubin, prothrombin time, or albumin concentration, which are critical for determining the severity of cirrhosis. However, we were able to use proxy variables to evaluate the severity of cirrhosis. According to the natural history and clinical stages of cirrhosis, patients with ascites, EV bleeding and encephalopathy were

defined as having advanced cirrhosis. In addition, hospitalization with infusion of fresh frozen plasma and albumin indicated that patients had coagulopathy and hypoalbuminemia. Secondly, although we used a counting process to calculate drug exposure, the adherence of patients to medical treatment was unknown. Moreover, we could not control for out-of-pocket purchases and adherence to prescribed medication regimens, which could have resulted in misclassification of exposure. However, misclassification is rare because all medications can be reimbursed in NHI programs in Taiwan, and the problem of adherence to medication regimens would have a similar effect across groups. Finally, because our research is based on a homogeneous Asian population, our findings may not be generalizable to other ethnic groups.

5. Conclusions

In conclusion, our study demonstrated that ARBs reduce all-cause mortality, MACCEs and adverse liver outcomes in patients with LC after cardiac surgery, whereas ACEIs appear to have no beneficial effects on these outcomes. We further demonstrated that there were no statistically significant differences in the risk of renal outcomes from ACEIs and ARBs compared to controls. Based on a retrospective analysis in this study, further prospective randomized trials are needed to assess the effects of ACEI or ARB in cardiac surgery in patients with LC. We recommend that ARBs were the preferred drug for long-term treatment of LC patients after cardiac surgery.

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