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 patients with 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] 0.49, 95% confidence interval [CI] 0.31–0.90). 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 = esophageal varices, 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 antplatelet 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
(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 Taiwan’s 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
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.[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.
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.
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 composite 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 groups (Table 4).

### 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    |
| Nitrate              | 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 inhibitors, ARBs = angiotensin receptor blockers, DCCBs = dihydropyridine calcium channel blockers, OHA = oral hypoglycemic agent, PPI = proton pump inhibitor.

### Table 3
Risk factor analysis of death.

| Variable                                | Model 1 |                | Model 2 |                |
|-----------------------------------------|---------|----------------|---------|----------------|
|                                        | 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 (diagnosis)                        | 1.76 (1.32, 2.36) | <.001    | 1.77 (1.32, 2.36) | <.001 |
| Malignancy                              | –       | –             | –       | –             |
| Operation in medical center             | 0.85 (0.71, 1.01) | <.062    | 0.86 (0.72, 1.02) | .086 |
| Urbanization level                      | Reference | –            | Reference | –             |
| Low                                     | 0.85 (0.71, 1.01) | <.068    | 0.83 (0.69, 0.99) | .036 |
| Median                                  | 0.78 (0.63, 0.96) | <.017    | 0.77 (0.62, 0.95) | .014 |
| High                                    | 1.28 (1.06, 1.55) | <.012    | 1.32 (1.09, 1.60) | .005 |
| Hepatitis C virus infection             | 2.42 (1.68, 3.40) | <.001    | 1.91 (1.13, 3.06) | .007 |
| Hepatocellular carcinoma                | 1.30 (1.00, 1.69) | .053     | 1.31 (1.01, 1.71) | .045 |
| Admission for albumin infusion (thrombocytopenia) | 1.30 (1.08, 1.57) | <.005    | 1.29 (1.07, 1.55) | .008 |
| Advanced cirrhosis                      | 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.
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 = .332).

### 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. 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. The effect of beta-blockers in preventing variceal bleeding is thought to be mediated by acting on the hyperdynamic state. 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. Beta-blockers have survival benefits only at the stage of cirrhosis when increased portal pressure complicated with esophageal varices and bleeding. Final stage of cirrhosis with refractory ascites, beta-blockers may aggravate hypotension, or azotemia. 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. These drugs have shown cardioprotective effects and are recommended as first-line therapy to reduce the risk of adverse cardiovascular events.

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. Furthermore, in a rat model ARBs were found to be superior to ACEIs for improving hepatic fibrosis, which is a pathological feature of cirrhosis.

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. Following liver cirrhosis, RAS components including ACE and the AT1 receptor, is markedly increased and is localized to areas of hepatic fibrosis. 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 a significant fall in blood pressure, their effect is usually not sustained. Second, ACEIs have significant first-pass metabolism, its effect is usually not sustained. Finally, the ACEI group had a significantly lower incidence of adverse liver outcomes than the ARB group. Adverse liver outcomes were significantly reduced in the ARB group compared with the ACEI group. Therefore, in the present study we evaluated and compared the long-term outcomes of ACEIs and ARBs in patients with LC after cardiac surgery.
important role in the progression of fibrosis. 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. 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. 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.
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 a 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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References
[1] Brown PP, Kugelmas AD, Cohen DJ, et al. The frequency and cost of complications associated with coronary artery bypass grafting surgery: results from the United States Medicare program. Ann Thorac Surg 2008;85:1980–6.
[2] Vaughan-Sarrazin MS, Hannan EL, Gormley CJ, et al. Mortality in Medicare beneficiaries following coronary artery bypass graft surgery in states with and without certificate of need regulation. JAMA 2002;288:1859–66.
[3] Alexander KP, Anstrom KJ, Mulhbaier LH, et al. Outcomes of cardiac surgery in patients = 80 years: results from the National Cardiovascular Network. J Am Coll Cardiol 2000;35:731–8.
[4] Mangano DT. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002;347:1309–17.
[5] Liakopoulos OJ, Choi YH, Haldenwang PL, et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30000 patients. Eur Heart J 2008;29:1548–59.
[6] Ferguson TBjr, Coombs LP, Peterson ED. Preoperative beta-blocker use and mortality and morbidity following CABG surgery in North America. JAMA 2002;287:2221–7.
[7] Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000;355:1575–81.
[8] Akazawa H, Yabumoto C, Yano M, et al. ARB and cardioprotection. Cardiovasc Drugs Ther 2013;27:155–60.
[9] Chan AY, McAinter FA, Norris CM, et al. Effect of beta-blocker use on outcomes after discharge in patients who underwent cardiac surgery. J Thorac Cardiovasc Surg 2010;140:182–7.
[10] Lazar HL. Role of angiotensin-converting enzyme inhibitors in the coronary artery bypass patient. Ann Thorac Surg 2005;79:1081–9.
[11] Schuppan D, AfdhalNH. Liver cirrhosis. Lancet 2002;359:1385–8.
[12] Giannelli V, Lattanzi B, Thalheimer U, et al. Beta-blockers in liver cirrhosis. Ann Gastroenterol 2014;27:20–6.
[13] Feu F, Garcia-Pagan JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995;346:1046–9.
[14] Grace JA, Herath CB, Mak KY, et al. Update on new aspects of the renin-angiotensin system in liver disease: clinical implications and new therapeutic options. Clin Sci 2012;123:225–39.
[15] Nashed SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.
[16] Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. Ann Thorac Surg 2000;69:823–8.
[17] Chou AH, Chen TH, Chen CY, et al. Long-term outcome of cardiac surgery in 1,040 liver cirrhosis patient- nationwide population-based cohort study. Circ J 2017;81:476–84.
[18] Huang YW, Lee CL, Yang SS, et al. Statins reduce the risk of cirrhosis and its decompensation in chronic hepatitis b patients: a nationwide cohort study. Am J Gastroenterol 2016;111:976–85.
[19] Lee CG, Lee MT, Chen YS, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. JAMA Intern Med 2015;175:1859–47.
[20] Gopaladass RR, Chu D, Cornell LD, et al. Cirrhosis as a moderator of outcomes in coronary artery bypass grafting and off-pump coronary artery bypass operations: a 12-year population-based study. Ann Thorac Surg 2013;96:1310–5.
[21] Shaheen AA, Kaplan GG, Hubbard JD, et al. Morbidity and mortality following coronary artery bypass graft surgery in patients with cirrhosis: a population-based study. Liver Int 2009;29:1141–51.
[22] Gokces F, Wong FK, et al. Nationwide volume and mortality after elective surgery in cirrhotic patients. J Am Coll Surg 2009;208:96–103.
[23] Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. JAMA 2012;308:1906–13.
[24] Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med 2010;362:823–32.
[25] Ge PS, Runyon BA. The changing role of beta-blocker therapy in patients with cirrhosis. J Hepatol 2010;53:643–53.
[26] Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005;353:2254–61.
[27] Tandon P, Abrales JD, Bergizotti A, et al. Renin-angiotensin-aldosterone inhibitors in the reduction of portal pressure: a systematic review and meta-analysis. J Hepatol 2010;53:273–82.
[28] Drenger B, Fontes ML, Miao Y, et al. Patterns of use of perioperative angiotensin-converting enzyme inhibitors in coronary artery bypass graft surgery with cardiopulmonary bypass: effects on in-hospital morbidity and mortality. Circulation 2012;126:261–8.
[29] Kim MY, Baik SK, Park DH, et al. Angiotensin receptor blockers are superior to angiotensin-converting enzyme inhibitors in the suppression of hepatic fibrosis in a bile duct-ligated rat model. J Gastroenterol 2008;43:889–96.
[30] Wilkinson SP, Williams R. Renin-angiotensin-aldosterone system in cirrhosis. Gut 1980;21:545–54.
[31] Bedossa P, Houglum K, Trautwein C, et al. Stimulation of collagen alpha 1(I) gene expression is associated with lipid peroxidation in hepatocellular injury: a link to tissue fibrosis? Hepatology 1994;19: 1262–71.
[32] Mooser V, Nussberger J, Juillerat L, et al. Reactive hyperreninemia is a major determinant of plasma angiotensin II during ACE inhibition. J Cardiovasc Pharmacol 1990;15:276–82.
[33] el-Dahr SS, Dipp S, Yosipiv IV, et al. Bradykinin stimulates c-fos expression, AP-1-DNA binding activity and proliferation of rat glomerular mesangial cells. Kidney Int 1996;50:1850–5.
[34] Gonzalez-Abraldes J, Albillos A, Banares R, et al. Randomized comparison of long-term losartan versus propranolol in lowering portal pressure in cirrhosis. Gastroenterology 2001;121:382–8.
[35] Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis. Hepatology 2013;57:1651–3.