Angiotensin-Converting Enzyme Inhibitors and Active Tuberculosis

A Population-Based Study

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Abstract: Numerous epidemiological data suggest that the use of angiotensin-converting enzyme inhibitors (ACEis) can improve the clinical outcomes of pneumonia. Tuberculosis (TB) is an airborne bacteria like pneumonia, and we aimed to find out whether the use of ACEis can decrease the risk of active TB.

We conducted a nested case–control analysis by using a 1 million longitudinally followed cohort, from Taiwan national health insurance research database. The rate ratios (RRs) for TB of ACEis can decrease the risk of active TB. The rate ratios for TB of ACEis can decrease the risk of active TB. Interestingly, it was found that chronic use (>90 days) of ACEis was associated with a further decrease in the risk of TB (aRR, 0.74, [95% CI, 0.66–0.83]). There was also a duration response effect, correlating decrease in TB risk with longer duration of ACEis use. The decrease in TB risk was also consistent across all patient subgroups (age, sex, heart failure, cerebrovascular diseases, myocardial infarction, renal diseases, and diabetes) and patients receiving other cardiovascular medicine.

In this large population-based study, we found that subjects with recent and chronic use of ACEis were associated with decrease in TB risk.

(Medicine 95(19):e3579)

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor, DRS = disease risk score, TB = Tuberculosis.

INTRODUCTION

Tuberculosis (TB) is one of the most important global health issues. According to the World Health Organization (WHO), there are approximately 9 million cases of new active TB, and 1.5 million people died from the associated complications in 2013.1,2 The WHO plans to eradicate TB by the year of 2050, but it will be difficult to achieve that goal without improving the downward trends in active infection rate. Our goal is to evaluate whether the use of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) can be associated with a decrease risk of active TB, by carrying out a pharmacoepidemiology analysis using a nationwide health insurance database registry.

ACEis and ARBs are established first-line drugs for a number of cardiovascular and renal diseases. They have been used interchangeably to treat patients with hypertension, heart failure, albuminuria, or nephropathy and even as an effective prevention therapy for patients with high risk of vascular/renal disease.3–5 However, the use of ACEis has a much more pronounced coughing effect than ARBs. The cough associated with ACEis is found to lower the risk of pneumonia in elderly patients, who had age-related impairments in the cough reflex and the swallowing function.6–7 Interestingly, use of both ACEis and ARBs also have a pleiotropic effect in lowering the mortality of patients with community-acquired pneumonia (CAP).8–12,18,19 The lower morality has been explained by modulation of the patients’ inflammatory response.20,21
TB is an airborne bacterial infection like *Streptococcus pneumoniae* and can infect humans by adhering to components in the respiratory epithelium. After infection, the causative bacteria in both *S. pneumoniae* and TB can trigger changes in hosts’ immune response. Thus, we hypothesize that use of ACEIs can reduce the risk of active TB through either the induced coughing effect or the modulation of the immune system. As far as we were aware of, there is no research examining this proposition. We set out to test our hypothesis in a high TB burden country like Taiwan. According to Taiwan Centers for Disease Control, in 2011 there were 12,634 new TB cases (55 cases per 100,000 population). We conducted a population-based study, nested in a national representative cohort, to assess whether use of ACEIs can modulate the risk of active TB.

### METHODS

#### Study Population

Under the approval of institutional review board of National Taiwan University Hospital, we conducted a population-based nested case–control analysis using the National Health Insurance Research Database (NHIRD) of Taiwan. The database contains deidentified secondary data, and met the requirements of the “Personal Information Protection Act” in Taiwan. Thus, the data were analyzed anonymously and the need for informed consent was waived. NHIRD records the complete claim history of 1 million randomly selected participants enrolled in Taiwan National Health Insurance (NHI), which is a single compulsory national health insurance. These 1 million participants are believed to be representative of the entire Taiwanese population. The claim history includes outpatient and inpatient electronic claim records, individual diagnoses, operations, and medications prescribed. Detailed information is also available for the name of the prescribed drugs, route of administration, quantity, and number of days of supply. Several studies have already shown that this database is appropriate for the use in pharmacoepidemiologic research.

#### Study Cohort

Data are available from January, 1998 to December, 2011, and the study cohort is selected according to the outline on Figure 1. First, we excluded any existing users of ACEIs and any prevalent cases of TB in year 1998 and 1999. Hence, cohort members were followed from January 1st, 2000 until the earliest onset of these 4 events, whichever comes first: TB, termination of health insurance coverage, death, or end of the study period. We found that there was less than 1% missing data in every calendar year.

#### Selection of Cases and Controls

We identified new active TB disease using the following criteria: at least 1 outpatient visit or 1 hospital admission with ICD-9-CM codes of TB (010-018, including all subcategories), plus the prescription of more than 2 anti-TB medications for more than 28 days. Patients with a subsequent diagnosis of non-TB mycobacterial infection or lung cancer were excluded. This TB case definition had been used in previous studies and validated in a linked survey database. Index date referred to the 1st date of TB diagnosis. For each case, 100 controls were randomly selected using the incidence density sampling method and were matched by index date, 5-year age group, and sex.

#### Medication Exposure

A user with exposure to medication of interest was defined by having a drug prescription record ≥ 7 days. ACEIs were defined as drugs with any of the following compounds: benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, and ramipril. ARBs were defined as drugs that contain the following compounds: candesartan, eprosartan, losartan, olmesartan medoxomil, telmisartan, and valsartan. Exposure was defined using 4 different time frames. First, current use referred to prescriptions that had ended within 30 days of the index date. Second, recent use referred to prescriptions that had ended between 31 and 90 days prior to the index date. Third, use was defined as a prescription ending between 91 days and 1 year prior to the index date. Fourth, chronic use was defined as total drug prescription ≥ 90 days, in the whole 1 year prior to the index date.

#### Covariates

To be as comprehensive as possible in adjusting for factors that might affect outcome, we identified 62 covariates (Table 1). A combined weighted comorbidity index was used to quantify each individual’s burden of comorbidity. The combined weighted comorbidity index developed by Gagne et al 32 is a summary score that combines the Charlson Index with the Elixhauser system, and was found to have better mortality predictability than either the Charlson or the Elixhauser system.
TABLE 1. Characteristics of the Matched Control Sample Stratified by Use of ACEis

| Characteristic                                                                 | Total Number of Controls = 772,000 Person-years |
|-------------------------------------------------------------------------------|-----------------------------------------------|
|                                                                               | ACEIs Users (N = 74,768)                      | Unexposed (N = 697,232) | P-Value |
| Demographics                                                                  |                                              |                           |         |
| Male sex, %                                                                    | 56,397 (75.43)                               | 472,003 (67.70)          | <0.0001 |
| Age mean, year                                                                 | 74 (0.10)                                    | 61 (0.01)                | <0.0001 |
| Area: urban region                                                             | 71.85 ± 11.15                                | 58.31 ± 19.46            |         |
| Area: metro area                                                               | 29,423 (39.35)                               | 331,749 (47.58)          | <0.0001 |
| Area: suburban area                                                            | 20,404 (27.29)                               | 173,756 (24.92)          |         |
| Area: countryside area                                                         | 18,246 (24.40)                               | 128,521 (18.43)          |         |
| Area: countryside area                                                         | 9,090 (12.16)                                | 53,726 (7.71)            |         |
| Insurance premiums                                                             |                                              |                           |         |
| Dependent                                                                     | 9,440 (12.63)                                | 60,880 (8.73)            | <0.0001 |
| <666 USD                                                                      | 31,155 (41.67)                               | 191,765 (27.50)          |         |
| 666–1331 USD                                                                  | 27,807 (37.19)                               | 287,870 (41.29)          |         |
| >1331 USD                                                                     | 8,761 (11.72)                                | 147,237 (21.12)          |         |
| Baseline cardiovascular comorbidities                                         |                                              |                           |         |
| Stroke or transient ischemic attack                                           | 11,214 (15.00)                               | 37,506 (5.38)            | <0.0001 |
| Angina                                                                         | 14,037 (18.77)                               | 48,200 (6.91)            | <0.0001 |
| Other ischemic heart disease                                                  | 34,969 (46.77)                               | 116,101 (16.65)          | <0.0001 |
| Percutaneous coronary/coronary artery bypass graft intervention               | 847 (1.13)                                   | 1255 (0.18)              | <0.0001 |
| Comorbidity score                                                             |                                              |                           |         |
| Baseline combined comorbidity score                                           | 1 (0.00)                                     | 0 (0.00)                  |         |
| Conditions included in the Charlson index                                     |                                              |                           |         |
| Peripheral vascular disease                                                   | 8,690 (11.62)                                | 32,677 (4.69)            | <0.0001 |
| Congestive heart failure                                                       | 17,973 (24.04)                               | 46,072 (6.61)            | <0.0001 |
| Myocardial infarction/acute coronary syndromes                                | 5212 (6.97)                                  | 12,206 (1.75)            | <0.0001 |
| Cerebrovascular disease                                                       | 25,581 (34.21)                               | 94,028 (13.49)           | <0.0001 |
| Dementia                                                                       | 4,466 (5.97)                                 | 20,692 (2.97)            | <0.0001 |
| Chronic pulmonary disease                                                     | 37,053 (50.56)                               | 202,611 (29.06)          | <0.0001 |
| Rheumatologic disease                                                         | 2,725 (3.64)                                 | 15,575 (2.23)            | <0.0001 |
| Peptic ulcer disease                                                          | 34,223 (45.77)                               | 199,123 (28.56)          | <0.0001 |
| Mild liver disease                                                            | 25,377 (33.94)                               | 157,620 (22.61)          | <0.0001 |
| Diabetes without chronic complications                                         | 29,012 (38.80)                               | 100,223 (14.37)          | <0.0001 |
| Diabetes with chronic complications                                           | 11,542 (15.44)                               | 28,557 (4.10)            | <0.0001 |
| Hemiplegia or paraplegia                                                      | 4,813 (6.44)                                 | 20,202 (2.90)            | <0.0001 |
| Renal disease                                                                 | 11,060 (14.79)                               | 39,427 (5.65)            | <0.0001 |
| Any malignancy, including leukemia and lymphoma                               | 8,341 (11.16)                                | 47,701 (6.84)            | <0.0001 |
| Moderate or severe liver disease                                              | 440 (0.59)                                   | 3026 (0.43)              | <0.0001 |
| Metastatic solid tumor                                                        | 737 (0.99)                                   | 5329 (0.76)              | <0.0001 |
| AIDS/HIV                                                                      | 22 (0.03)                                    | 318 (0.05)               | 0.03    |
| Additional comorbidities                                                       |                                              |                           |         |
| Alcohol/drug use                                                               | 2,182 (2.92)                                 | 13,680 (1.96)            | <0.0001 |
| Psychiatric disorder                                                          | 28,393 (37.97)                               | 162,935 (23.37)          | <0.0001 |
| Neurologic disorder                                                           | 5,985 (8.00)                                 | 28,450 (4.08)            | <0.0001 |
| Obesity                                                                       | 716 (0.96)                                   | 4,510 (0.65)             | <0.0001 |
| Other Cancer except Metastatic solid tumor                                     | 21,814 (29.18)                               | 158,484 (22.73)          | <0.0001 |
| COPD                                                                          | 28,749 (38.45)                               | 141,768 (20.33)          | <0.0001 |
| Silicosis                                                                      | 124 (0.17)                                   | 664 (0.10)               | <0.0001 |
| Gastrointestinal or esophageal hemorrhage                                     | 5,689 (7.61)                                 | 28,235 (4.05)            | <0.0001 |
| Risk factors                                                                   |                                              |                           |         |
| Solid organ transplantation such as renal or heart transplantation             | 35 (0.05)                                    | 111 (0.02)               | <0.0001 |
| Malnutrition                                                                   | 504 (0.67)                                   | 2,275 (0.33)             | <0.0001 |
| Postgastric surgery                                                           | 23 (0.03)                                    | 109 (0.02)               | 0.005   |
| OPD and hospitalization (within 1 year before the index date)                 |                                              |                           |         |
| The number of OPD visit                                                       | 29 (0.04)                                    | 35.05 ± 24.9             |         |
| The number of emergency department visit                                      | 0 (0–0)                                      | 0.22 ± 0.92              | <0.0001 |
| The number of hospitalization                                                 | 0 (0–0)                                      | 0.41 ± 1.05              | <0.0001 |

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Medication use

| Medication                        | ACEis Users (N = 74,768) | Unexposed (N = 697,232) | P-Value |
|----------------------------------|--------------------------|-------------------------|---------|
| NSAID                            | 36,386 (48.67)           | 198,502 (28.47)         | <0.0001 |
| Aspirin                          | 29,887 (39.97)           | 75,528 (10.83)          | <0.0001 |
| Systemic immunosuppressive agents| 192 (0.26)               | 1214 (0.17)             | <0.0001 |
| Systemic corticosteroids         | 14,349 (19.19)           | 72,973 (10.47)          | <0.0001 |
| DMARDs                           | 801 (1.08)               | 6595 (0.95)             | 0.03    |
| Statin                           | 10,546 (14.10)           | 31,195 (4.47)           | <0.0001 |
| Beta blockers                    | 22,474 (30.06)           | 64,728 (9.28)           | <0.0001 |
| Loop diuretics                   | 9946 (13.30)             | 22,307 (3.20)           | <0.0001 |
| Angiotensin II antagonists        | 11,175 (14.95)           | 47,637 (6.83)           | <0.0001 |
| Digoxin                          | 4822 (6.45)              | 8182 (1.17)             | <0.0001 |
| Nitrates                         | 12,669 (16.94)           | 25,282 (3.63)           | <0.0001 |
| Antipsychotics                   | 374 (0.50)               | 2482 (0.36)             | <0.0001 |
| PPI                              | 3852 (5.15)              | 20,196 (2.90)           | <0.0001 |
| CA channel blocker               | 44,931 (60.09)           | 113,403 (16.26)         | <0.0001 |

ACEis = angiotensin converting enzyme inhibitor, COPD = chronic obstructive pulmonary disease, DMARD = disease modifying antirheumatic drug, NSAID = nonsteroidal anti-inflammatory drugs, OPD = outpatient department, PPI = proton-pump inhibitors.

Data Analysis

Baseline subject characteristics were described and compared between ACE inhibitor user and nonuser. The continuous variables were presented in 2 ways: median and 25% to 75% percentile, and mean ± standard deviation. Categorical variables were presented with frequency and percentage. Comparison of characteristics was assessed with Kruskal–Wallis tests for continuous variables, and Pearson Chi-square tests for categorical variables.

The rate ratio was estimated by a time matched case–control-sampling scheme and conditional logistic regression analysis adjusted for all covariates.33 To balance disease risks between different drug exposure groups, we constructed a study-specific disease risk score (DRS). The DRS was defined as the probability for developing active TB among the participants unexposed to ACEis based on individual’s baseline covariates. To estimate DRS, we carried out multivariate logistic regression analysis, where active TB was treated as the dependent variable, and all empirical clinical predictors were treated as independent variables. Hence, our DRS can adjust for confounders, and be used to compare different exposures in a case–control study design.34 On supplemental appendix 1, http://links.lww.com/MD/A957, we reported the c-statistic (0.81) of the DRS model, component variables, and the respective weights of the component variables. To avoid potential unrealistic linear assumption of continuous variables in the regression model, such as age, comorbidity score, and DRS, we entered these variables into the model with a main term plus a quadratic term to allow a nonlinear association between these variables and active TB. Considering the possibility of latent period between new TB infections, we set 3 additional risk windows (6, 12, and 36 months before index dates) for sensitivity analysis. A duration response analyses and subgroup analyses in high-risk patients was also carried out to further assess the robustness of our results. All analyses were carried out with SAS 9.3 for Windows (SAS Institute Inc, Cary, NC) and the data are reported in accordance with STROBE guidelines.

RESULTS

Participant Enrollment and Baseline Characteristics

Cases and controls are selected using the outline on Figure 1. We found 7720 cases of active TB, 772,000 non-TB controls, 75,536 new ACEis users, and 704, 220 non-ACEis users. Table 1 compares the baseline demographics for ACEis users and non-ACEis users without active TB. ACEis users are defined as having a drug prescription record ≥ 7 days. The ACEis users were found to be older than nonusers (71.85 ± 11.15 vs 58.31 ± 19.46 years old). In addition, the ACEis users have a higher combined comorbidity score than nonusers (1.81 ± 2.19 vs 0.96 ± 1.66). This is probably a reflection that ACEis users are associated with more cardiovascular/renal diseases than nonusers. ACEis users also receive more cardiovascular/renal medications than nonusers.

Use of ACEis/ARBs and Risk of New Active TB Onset

Table 2 compares the effects of ACEis and ARBs on the risk of new active TB onset. Three different approaches were used to calculate the effect estimate. The 1st method, which is matching on age group, gender, and year, is the unadjusted estimate; while individual confounder and DRS-adjusted effect estimate can be considered more accurate as it includes more covariates. DRS-adjusted effect estimate is believed to be the most suitable adjustment method in this study, as most patients taking ACEis are already predisposed to heart disease. In most instances, all 3 types of users (current, recent, and past) of ACEis/ARBs are not associated with significant decrease in the risk of active TB onset. The only exception is in the current use of ACEis, in which, there is a significant decrease in the risk of active TB upon the 2 different types of adjustments.

Since the use of ACEis/ARBs often requires long-term usage, we also looked at chronic usage (>90 days). Strikingly, both the unadjusted and adjusted analysis showed that chronic
use of ACEis/ARBs was associated with a substantial decrease in the risk of active TB. The effect estimates associated with chronic use of ACEis were slightly lower than the effect estimates associated with chronic use of ARBs; however, there was no significant difference upon head to head comparison.

Duration-Response Analysis

The results in Table 2 suggest that different duration of ACEis usage might change the effect estimate on active TB incidence. Thus, we stratified ACEis users into different use durations and carried out a more rigorous examination (Table 3). We found that both the crude incidence rate and the DRS adjusted effect estimate decrease upon longer duration of ACEis usage. In addition, we found that our chronic user definition (>90 days) represents about 54% (40,503/74,768) of the ACEis exposed cohort.

Effects of Chronic ACEis Participant Subgroups on Risk of New TB Incident

To find out if chronic ACEis users with different conditions have different risk of TB onset, we conducted a series of stratified analyses (Figure 2A). The TB protective effects of ACEis are consistent across all patient subgroups (age, sex, heart failure, cerebrovascular diseases, myocardial infarction, renal diseases, and diabetes). The risk decrease of TB in chronic ACEIs users (compared to nonusers) was most substantial in patients with myocardial infarction (0.53, 95% CI 0.34–0.84) and least substantial in patients with renal diseases (0.88, 95% CI 0.69–1.12).

Sensitivity Analysis

Chronic users of ACEis might be exposed to other cardiovascular drugs. Our main model has looked at the exposure of 8 different cardiovascular drugs (aspirin, statin, beta blockers, loop diuretics, ARBs, digoxin, nitrates, and calcium channel blockers) 1 year prior to the TB index year, and corrects for their effects via DRS. To find out the individual effects of different cardiovascular drugs, we removed the correction for each individual cardiovascular drug and looked at the changes in the effect estimates (Figure 2B). There is little difference in effect estimates, when correction for each drug is removed.

Latent Period Analysis

The latent period between new TB infection and the active onset of TB can range from months to years (Table 4). To gain insight into whether ACEis protect users’ from active infection or latent reactivation, we performed a sensitivity analysis by setting latent period of 6, 12, and 24 months. We found that all the latent periods increase the effect estimates and diminished the protective effect of active TB onset.

| TABLE 2. Comparing Effect of ACEis and ARBs on Risk of TB Incident |
|---------------------------------------------------------------|
| **Effect Estimate Matched on Age Group, Gender, and Year**    |
| (RR, 95% CI) | **Confounder Adjusted Effect Estimate** (RR, 95% CI) | **Disease Risk Score Adjusted (RR, 95% CI)** |
|---------------------------------|
| **ACEis** | | |
| Current use | 0.94 (0.85–1.05) | 0.89 (0.80–1.00)* | 0.87 (0.78–0.97)* |
| Recent use | 1.10 (0.93–1.31) | 0.99 (0.83–1.18) | 0.97 (0.82–1.16) |
| Past use | 1.22 (1.09–1.37) | 1.02 (0.91–1.15) | 1.02 (0.91–1.15) |
| Chronic use (>90 days) | 0.81 (0.73–0.91)*** | 0.75 (0.67–0.85)*** | 0.74 (0.66–0.83)*** |
| **ARBs** | | |
| Current use | 0.93 (0.84–1.04) | 0.92 (0.82–1.03) | 0.93 (0.83–1.04) |
| Recent use | 1.15 (0.97–1.37) | 1.18 (0.99–1.41) | 1.18 (0.99–1.41) |
| Past use | 1.24 (1.06–1.45)** | 1.06 (0.90–1.24) | 1.13 (0.96–1.32) |
| Chronic user (>90 days) | 0.82 (0.74–0.91)*** | 0.79 (0.69–0.87)*** | 0.82 (0.74–0.92)*** |
| **ACEi vs ARBs** | | |
| Chronic user (>90 days) | 1.04 (0.89–1.22) | 1.02 (0.87–1.21) | 0.99 (0.84–1.17) |

*Refers to P < 0.05. **Refers to P < 0.01. ***Refers to P < 0.001. ARB = angiotensin II antagonist, ACEi = angiotensin-converting enzyme inhibitor, CI = confidence interval, RR = rate ratio, TB = tuberculosis.

| TABLE 3. Relationship Between Number of Days That Participants Are Prescribed With ACEis and Risk of TB Incident |
|---------------------------------------------------------------|
| Use of ACEis | Incidence Rate % (Case/Person-years) | Disease Risk Score Adjusted RR (95% CI) |
|---------------------------------|
| 7–30 days (reference) | 1.40% (244/17,369) | Reference |
| 31–60 days | 1.11% (127/9,724) | 0.96 (0.77–1.21) |
| 61–90 days | 0.92% (66/7,172) | 0.70 (0.53–0.93)* |
| >90 days | 0.82% (331/40,503) | 0.63 (0.53–0.75)** |

*Refers to P < 0.05. **Refers to P < 0.01. ACEi = angiotensin-converting enzyme inhibitor, CI = confidence interval, RR = rate ratio, TB = tuberculosis.
DISCUSSION

A case–control study, nested in a national representative cohort of Taiwan’s NHIRD was conducted. Our data showed that chronic and current use of ACEis, but not recent and past use of ACEis can significantly decrease the risk of active TB after adjusting for potential confounders. Consistently, higher cumulative days of ACEis usage is associated with further decrease in the risk of active TB. It was found that the protective effect of ACEis is consistent across all patient subgroups (age, sex, heart failure, cerebrovascular diseases, myocardial infarction, renal diseases, and diabetes) and patients receiving other cardiovascular medicine. Latent period analysis found that the

FIGURE 2. Forest plots (A) Subgroup analysis on chronic users of ACEis and risk of TB incident. (B) Effect of different cardiovascular drugs on the effect estimates. IRR refers to incident rate ratio. ACEi = angiotensin converting enzyme inhibitor, IRR = incident rate ratio, TB = tuberculosis.
TABLE 4. Latent Period Analysis for Chronic Use of ACEis

| Effect Estimate Matched on Age Group, Gender, and Year (RR, 95% CI) | Confounder Adjusted Effect Estimate (RR, 95% CI) | Disease Risk Score Adjusted (RR, 95% CI) |
|---------------------------------------------------------------|------------------------------------------------|---------------------------------|
| **Chronic ACEis user**                                        |                                                |                                 |
| No latent period                                              | 0.94 (0.85–1.05)                               | 0.89 (0.80–1.00)                | 0.87 (0.78–0.97)                |
| Latent period 180 days                                        | 1.00 (0.80–1.26)                               | 0.87 (0.69–1.10)                | 0.84 (0.67–1.06)                |
| Latent period 365 days                                        | 1.07 (0.84–1.36)                               | 0.91 (0.71–1.17)                | 0.90 (0.70–1.15)                |
| Latent period 730 days                                        | 1.05 (0.86–1.27)                               | 0.94 (0.77–1.14)                | 0.92 (0.76–1.12)                |

*Refers to P < 0.05. ACEi = angiotensin-converting enzyme inhibitor, CI = confidence interval, RR = rate ratio.

The protective effect of ACEis was diminished in the presence of latent periods between infection and onset. In addition, chronic use of ARB has an attenuated TB protective effect as compared to chronic use of ACEis.

To the best of our knowledge, there is no direct information on how ACEis can prevent the active onset of TB. However, our results on the protective effects of ACEis on active TB onset agree with reports that ACEis can improve the clinical outcome of pneumonia.13,16,19,35–38 In addition, our duration response results also agree with report that long-term usage of ACEis is more beneficial than short-term usage in pneumonia prevention.13

Our study design does not permit direct mechanistic insights into the how ACEis exerted its TB protective effect. However, our latent period analysis suggests that the ACEis induced cough cannot explain the decrease in risk of active TB. This is because mechanical coughing is expected to remove the *Mycobacterium* directly and should not be influenced by the different latent periods.

In addition, our results can be explained by the hypothesis that the use of ACEis can modulate the hosts’ inflammatory response and result in less latent TB reactivation. The use of ACEis have been found to modulate levels of both T-cells (TH1 and TH2) and cytokines (IL-6, IL-10, TNF-alpha, and interferon-gamma).20,39–41 During latent TB, the bacteria are contained inside granulomas, surrounded by T helper (TH) cell and B cells.42 It is unclear what is the optimal level of immune cells to prevent activation of latent TB. However, there is good evidence showing that renal failure patients have unbalanced levels of cytokines and have up to 10-fold increase in the risk of active TB.43–46 Thus, we felt that it is reasonable to hypothesize that the ACEis associated decrease in risk of TB is due to changes in patients’ immune function.

A strength of this study is that Taiwan’s NHIRD contains a large homogenous TB population and a complete claim records of all individual patients. As far as we are aware of, there is no other country with an electronic claims record of so many TB patients. We identified 7720 cases of new TB cases, which is large enough to carry out subgroup analyses and comprehensively adjusting for multiple confounders. The incidence of TB in this sample is 0.059% (59.4 cases per 100,000 person-years), which agrees with the Taiwan TB control report released by the government, but is much larger than the approximately 0.00005% (2.5–5 cases per 100,000 person-year) rate in most western developed countries.2,27 The lack of nationwide TB surveillance system and the inadequate current TB control infrastructure are some reasons for the high TB incidence in Taiwan.47

Despite the strengths of this study, our study has some inherent limitations. Active TB disease was defined on the basis of ICD-9 codes with compatible anti-TB prescription history. Although microbiological data are lacking, past linked survey data suggest that our definition is highly accurate.29,31 If there is indeed outcome misclassification, nondifferential outcome misclassification is likely. This is because the use of ACEis and ARBs do not appear to be a clear clinical indication for the treatment of early symptoms of active TB.

Another limitation is that we cannot exclude the possibility of residual confounding. Like all claims databases, there is no data on lifestyle factors, such as alcohol and tobacco usage. However, we tried our best to adjust for these missing confounding factors by using alcohol- or smoking-related diseases (Table 1).

In addition, to overcome the problem of indication bias, we constructed a disease-specific DRS with high predictability to balance disease risk among users and nonusers of ACEis. A DRS can be used for balancing disease risks among multiple drug exposure groups independent of the changing indications for ACEis. DRS can also adjust for several rare covariates in the source cohort and can avoid the over-fitting problem by adjusting individual covariates in the case–control sample. Furthermore, we used ARBs as a control for ACEis. Except for the coughing side effects, ARBs have nearly identical function as ACEis. Hence, patients under the prescription of ARBs and ACEis should have similar confounders, characteristics, and risk factors. Our research design thus makes us believe that the role of ACEis in reducing active TB onset is not due to confounding factors associated with coughing.

Asian ethnicity is another factor in influencing whether ACEis can decrease the risk of pneumonia. Several case reports and a randomized controlled trials have reported that risk of pneumonia is attenuated in Asian but not in Caucasian prescribed with ACEis.19,36,48,49 However, there is still no definitive genetic evidence to explain this phenomenon. Current research on ACE polymorphisms and risk of pneumonia is still debatable.19 Nevertheless, there is good evidence to suggest that Asians and Caucasian might have different risks of bacterial infection when prescribed with ACEis.19,36,48,49 Since we used Taiwan NHIRD database for our experiments, 98% of the Taiwanese population are Chinese. Care should be taken when reproducing our result in other ethnicities.

In conclusion, we found that the chronic use of ACEis was associated with approximately 26% decrease in risk of active TB. The associations that we have found may be causal, but they are also consistent with the possibility that there is residual confounding and healthy user bias in the Taiwanese data. Given the observational nature of this study, we welcomed more follow-up research, especially randomized trial to confirm our data.
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