Medicine®

OBSERVATIONAL STUDY

OPEN

Angiotensin-Converting Enzyme Inhibitors and Active Tuberculosis

A Population-Based Study

Jiunn-Yih Wu, MD, Meng-Tse Gabriel Lee, PhD, Si-Huei Lee, MD, Shih-Hao Lee, MA, Yi-Wen Tsai, MD, Shou-Chien Hsu, MD, Shy-Shin Chang, MD, PhD, and Chien-Chang Lee, MD, ScD

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 were estimated by conditional logistic regression, and adjusted using a TB-specific disease risk score (DRS) with 71 TB-related covariates.

From January, 1997 to December, 2011, a total of 75,536 users of ACEis, and 7720 cases of new active TB were identified. Current use (DRS adjusted RR, 0.87 [95% CI, 0.78–0.97]), but not recent and past use of ACEis, was associated with a decrease in 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 infraction, 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 complication 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 nsurance 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.[3–12] 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.[13–17] Interestingly, use of both ACEis and ARBs also have a pleiotropic effect in lowering the mortality of patients with community-acquired pneumonia (CAP).[10–12,18,19] The lower mortality has been explained by modulation of the patients' inflammatory response.[20,21]

Editor: Steven Callens.
Received: August 18, 2015; revised: March 24, 2016; accepted: April 12, 2016.
From the Department of Emergency Medicine, Chang Gung Memorial Hospital, Keelung; Chang Gung University College of Medicine, Taoyuan (J-YW, S-CH); Department of Emergency Medicine, National Taiwan University Hospital (M-TGL, S-HL, C-CL); Department of Rehabilitation and Physical Medicine, Taipei Veteran General Hospital (S-HL); Department of Medicine, College of Medicine, National Yang Ming University, Taipei (S-HL); Department of Family Medicine, Chang Gung Memorial Hospital; Chang Gung University College of Medicine (Y-WT, S-SC); Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan (S-SC); and Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yun-lin Branch, Douliou (C-CL), Taiwan.
Correspondence: Shy-Shin Chang, Department of Family Medicine, Chang Gung Memorial Hospital, No.5. Fu-Hsing Street, Kuei Shan Hsiang, Taoyuan Hsien, Taiwan (e-mail: sschang0529@gmail.com).
Chien-Chang Lee, Department of Emergency Medicine, National Taiwan University Hospital, Yunlin Branch, No. 579, Yunlin Road, Douliou 640, Taiwan (e-mail: cclee100@gmail.com).
Following guideline: STROBE.
C-CL is guarantor of the paper, and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; J-YW: data collection, data management, statistics, wrote first draft, and reviewed final draft; M-TL data collection, statistics, wrote first draft and reviewed final draft; Si-HL data collection, wrote first draft, and reviewed final draft; Sh-HL data collection, data management, and reviewed final draft; Y-WT data collection and reviewed final draft; S-CH data collection and reviewed final draft; S-SC study design, data collection, data management, statistics, reviewed first draft, reviewed final draft, and research funding; C-CL study design, data collection, data management, statistics, reviewed first draft, reviewed final draft, and research funding.
This study is supported by the Taiwan National Ministry of Science and Technology: NSC101-3114-Y-002-003, MOST 104-2811-B-002-060, and MOST104-2314-B-002-039-MY3; and National Taiwan University Hospital Yunlin Branch Research Grant NTUHYL-102-s008.
No funding bodies had any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.
The authors have no conflicts of interests to disclose.
Supplemental Digital Content is Available for this Article.
Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.
ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003579

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.[22–26] 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).[27] 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.[28–30]

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.[29,31] 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. The

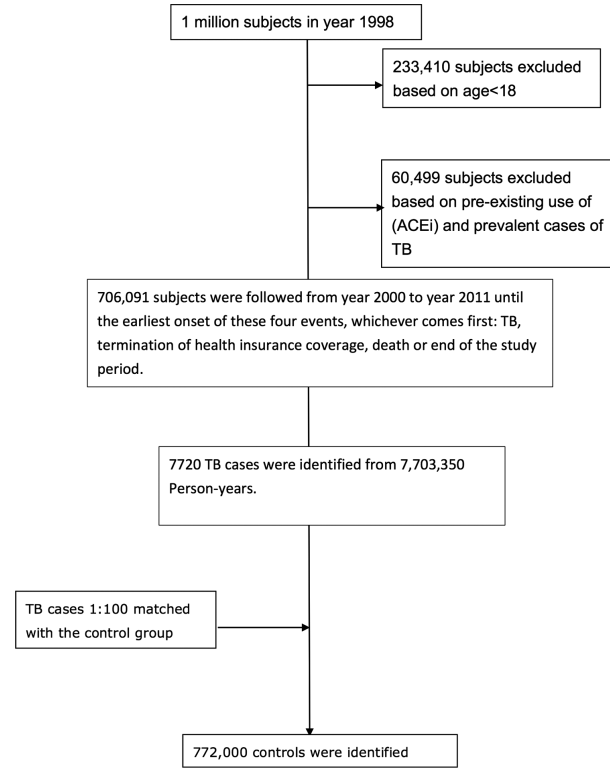

FIGURE 1. Outline of cohort selection.

1-year period preceding index date was used for the assessment of ACEis exposure status.

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, olmesertan medoxomil, ribesartan, 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 ended between 31 and 90 days prior to the index date. Third, past 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.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 1. Characteristics of the Matched Control Sample Stratified by Use of ACEis

	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
	71.85 ± 11.15	58.31 ± 19.46	
Area: urban region	29,423 (39.35)	331,749 (47.58)	<0.0001
Area: metro area	20,404 (27.29)	173,756 (24.92)	
Area: suburban area	18,246 (24.40)	128,521 (18.43)	
Area: countryside area	9090 (12.16)	53,726 (7.71)	
Insurance premiums			
Dependent	9440 (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	8761 (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) 1.81 ± 2.19	0 (0.00) 0.96 ± 1.66	<0.0001
Conditions included in the Charlson index			
Peripheral vascular disease	8690 (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	4466 (5.97)	20,692 (2.97)	<0.0001
Chronic pulmonary disease	37,053 (49.56)	202,611 (29.06)	<0.0001
Rheumatologic disease	2725 (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	4813 (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	8341 (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	2182 (2.92)	13,680 (1.96)	<0.0001
Psychiatric disorder	28,393 (37.97)	162,935 (23.37)	<0.0001
Neurologic disorder	5985 (8.00)	28,450 (4.08)	<0.0001
Obesity	716 (0.96)	4510 (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	5689 (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)	2275 (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	13 (0.00) 18.2 ± 19.8	<0.0001
The number of emergency department visit	0 (0-0) 0.22 ± 0.92	0 (0–0) 0.12 ± 0.65	<0.0001
The number of hospitalization	0 (0–0) 0.41 ± 1.05	0 (0–0) 0.18 ± 0.95	<0.0001

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

	Total Number of Controls = 772,000 Person-years		
	ACEis Users (N = 74,768)	Unexposed (N = 697,232)	*P*-Value
Medication use			
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 and biologics	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

ACEi = 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 nonuser (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

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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.

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% (40503/74768) 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 infraction, 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 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	1.31% (127/9724)	0.96 (0.77–1.21)
61–90 days	0.92% (66/7172)	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.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

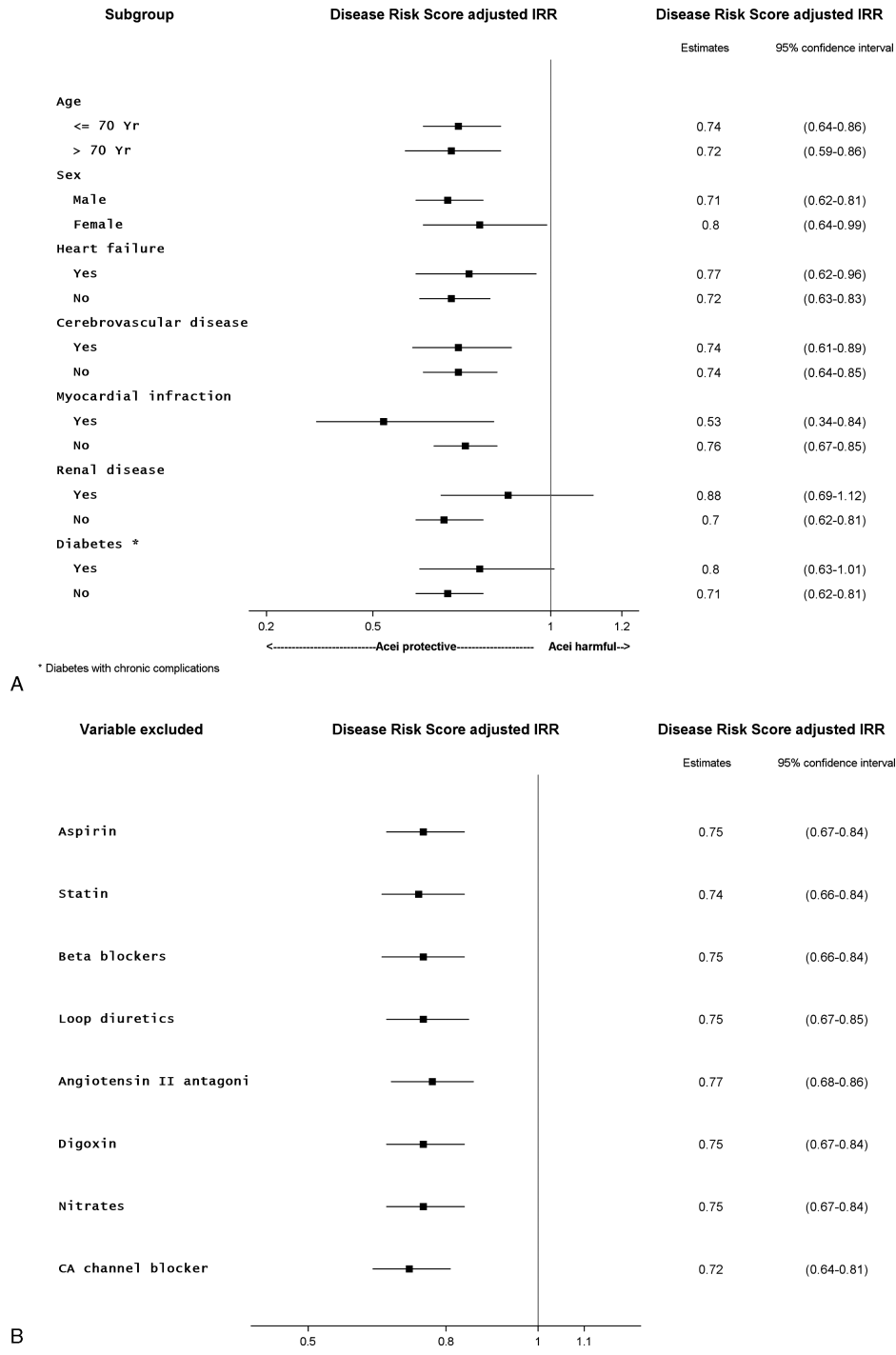

FIGURE 2. Forest plots (A) Subgroup analysis on chronic users of ACEis and risk of TB incident. (B) Effect of different cardiovascular drugs on the effect estimates. IRR refers to incident rate ratio. ACEi = angiotensin converting enzyme inhibitor, IRR = incident rate ratio, TB = tuberculosis.

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

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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.

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 level of cytokines and have up to 10-fold increase in the risk of active TB.[2,20,43–46] 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 cofounding. 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.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

ACKNOWLEDGEMENTS

The authors thank Dr Hsien-Ho Lin (National Taiwan University College of Public Health) and Dr Andrew Malaby (University of Vermont) for reviewing this manuscript, Szu-Ying Lee ((National Taiwan University) for assistance in statistical analysis, the staff of the Core Labs at the Department of Medical Research in National Taiwan University Hospital for technical support, and Medical Wisdom Consulting Group for technical assistance in statistical analysis.

Disclaimer: This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

Ethical approval: This study is approved by institutional review board of National Taiwan University Hospital.

REFERENCES

1. World Health Organization. Global Health Observatory (GHO) Tuberculosis (TB) 2013; http://www.who.int/gho/tb/en/index.html. [Accessed November 27, 2013].
2. Lawn SD, Zumla AI. Tuberculosis. *Lancet.* 2011;378:57–72.
3. van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. *Eur Heart J.* 2012;33:2088–2097.
4. Shearer F, Lang CC, Struthers AD. Renin-angiotensin-aldosterone system inhibitors in heart failure. *Clin Pharmacol Ther.* 2013;94:459–467.
5. Lizakowski S, Tylicki L, Rutkowski B. Direct renin inhibition – a promising strategy for renal protection? *Med Sci Monit.* 2013;19:451.
6. Krum H, Driscoll A. Management of heart failure. *Med J Aust.* 2013;199:334–339.
7. Ong HT, Ong LM, Ho JJ. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in patients at high risk of cardiovascular events: a meta-analysis of 10 randomised placebo-controlled trials. *ISRN Cardiol.* 2013;2013:478597.
8. Hsu TW, Liu JS, Hung SC, et al. Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. *JAMA Intern Med.* 2014;174:347–354.
9. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting–enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med.* 2004;351:1952–1961.
10. Mortensen EM, Nakashima B, Cornell J, et al. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. *Clin Infect Dis.* 2012;55:1466–1473.
11. Mortensen EM, Pugh MJ, Copeland LA, et al. Impact of statins and angiotensin-converting enzyme inhibitors on mortality of subjects hospitalised with pneumonia. *Eur Respir J.* 2008;31:611–617.
12. Wu A, Good C, Downs JR, et al. The association of cardioprotective medications with pneumonia-related outcomes. *PLoS One.* 2014;9:e85797.
13. Okaishi K, Morimoto S, Fukuo K, et al. Reduction of risk of pneumonia associated with use of angiotensin I converting enzyme inhibitors in elderly inpatients. *Am J Hypertens.* 1999;12 (8 Pt 1): 778–783.
14. Newnham DM, Hamilton SJ. Sensitivity of the cough reflex in young and elderly subjects. *Age Ageing.* 1997;26:185–188.
15. Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. *Chest J.* 2003;124:328–336.
16. Arai T, Yasuda Y, Toshima S, et al. ACE inhibitors and pneumonia in elderly people. *Lancet.* 1998;12:1998;352:1937–1938.
17. Arai T, Yasuda Y, Takaya T, et al. ACE inhibitors and reduction of the risk of pneumonia in elderly people. *Am J Hypertens.* 2000;13:1050–1051.
18. Mortensen EM, Restrepo MI, Anzueto A, et al. The impact of prior outpatient ACE inhibitor use on 30-day mortality for patients hospitalized with community-acquired pneumonia. *BMC Pulm Med.* 2005;5:12.
19. Caldeira D, Alarcão J, Vaz-Carneiro A, et al. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ (Clin Res Ed).* 2012;345:e4260.
20. Gullestad L, Aukrust P, Ueland T, et al. Effect of high- versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. *J Am Coll Cardiol.* 1999;34: 2061–2067.
21. Antunes G, Evans SA, Lordan JL, et al. Systemic cytokine levels in community-acquired pneumonia and their association with disease severity. *Eur Respir J.* 2002;20:990–995.
22. Rock RB, Hu S, Gekker G, et al. Mycobacterium tuberculosis-induced cytokine and chemokine expression by human microglia and astrocytes: effects of dexamethasone. *J Infect Dis.* 2005;192: 2054–2058.
23. Vankayalapati R, Wizel B, Weis SE, et al. Serum cytokine concentrations do not parallel Mycobacterium tuberculosis-induced cytokine production in patients with tuberculosis. *Clin Infect Dis.* 2003;36:24–28.
24. Bruunsgaard H, Skinhøj P, Qvist J, et al. Elderly humans show prolonged in vivo inflammatory activity during pneumococcal infections. *J Infect Dis.* 1999;180:551–554.
25. Kragsbjerg P, Holmberg H, Vikerfors T. Dynamics of blood cytokine concentrations in patients with bacteremic infections. *Scand J Infect Dis.* 1996;28:391–398.
26. Puren AJ, Feldman C, Savage N, et al. Patterns of cytokine expression in community-acquired pneumonia. *Chest J.* 1995;107:1342–1349.
27. Centers for Disease Control DoH, ROC (Taiwan). Taiwan Tuberculosis Control Report 2012. *Centers for Disease Control, Department of Health, ROC (Taiwan).* 2012.
28. Lee MS, Lin RY, Chang YT, et al. The risk of developing non-melanoma skin cancer, lymphoma and melanoma in patients with psoriasis in Taiwan: a 10-year, population-based cohort study. *Int J Dermatol.* 2012;51:1454–1460.
29. Baker MA, Lin HH, Chang HY, et al. The risk of tuberculosis disease among persons with diabetes mellitus: a prospective cohort study. *Clin Infect Dis.* 2012;54:818–825.
30. Chen YJ, Wu CY, Shen JL, et al. Association between traditional systemic antipsoriatic drugs and tuberculosis risk in patients with psoriasis with or without psoriatic arthritis: results of a nation-wide cohort study from Taiwan. *J Am Acad Dermatol.* 2013;69:25–33.
31. Lin HH, Ezzati M, Chang HY, et al. Association between tobacco smoking and active tuberculosis in Taiwan: prospective cohort study. *Am J Respir Crit Care Med.* 2009;180:475–480.
32. Gagne JJ, Glynn RJ, Avorn J, et al. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol.* 2011;64:749–759.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

33. Lubin JH, Gail MH. Biased selection of controls for case-control analyses of cohort studies. *Biometrics.* 1984;40:63–75.
34. Glynn RJ, Gagne JJ, Schneeweiss S. Role of disease risk scores in comparative effectiveness research with emerging therapies. *Pharmacoepidemiol Drug Saf.* 2012;21(Suppl 2):138–147.
35. Rafailidis PI, Matthaiou DK, Varbobitis I, et al. Use of ACE inhibitors and risk of community-acquired pneumonia: a review. *Eur J Clin Pharmacol.* 2008;64:565–573.
36. Ohkubo T, Chapman N, Neal B, et al. Effects of an angiotensin-converting enzyme inhibitor-based regimen on pneumonia risk. *Am J Respir Crit Care Med.* 2004;169:1041–1045.
37. Liu C-L, Shau W-Y, Wu C-S, et al. Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and pneumonia risk among stroke patients. *J Hypertens.* 2012;30:2223–2229.
38. Sekizawa K, Matsui T, Nakagawa T, et al. ACE inhibitors and pneumonia. *Lancet.* 1998;352:1069.
39. Platten M, Youssef S, Hur EM, et al. Blocking angiotensin-converting enzyme induces potent regulatory T cells and modulates TH1- and TH17-mediated autoimmunity. *Proc Nat Acad Sci U S A.* 2009;106:14948–14953.
40. Gage JR, Fonarow G, Hamilton M, et al. Beta blocker and angiotensin-converting enzyme inhibitor therapy is associated with decreased Th1/Th2 cytokine ratios and inflammatory cytokine production in patients with chronic heart failure. *Neuroimmunomodulation.* 2003;11:173–180.
41. De Albuquerque DA, Saxena V, Adams DE, et al. An ACE inhibitor reduces Th2 cytokines and TGF-beta1 and TGF-beta2 isoforms in murine lupus nephritis. *Kidney Int.* 2004;65:846–859.
42. Walzl G, Ronacher K, Hanekom W, et al. Immunological biomarkers of tuberculosis. *Nat Rev Immunol.* 2011;11:343–354.
43. Descamps-Latscha B, Chatenoud L. T cells and B cells in chronic renal failure. *Semin Nephrol.* 1996;16:183–191.
44. Nitta K, Akiba T, Kawashima A, et al. Characterization of TH1/TH2 profile in uremic patients. *Nephron.* 2002;91:492–495.
45. Dobler CC, McDonald SP, Marks GB. Risk of tuberculosis in dialysis patients: a nationwide cohort study. *PloS One.* 2011;6:e29563.
46. Hussein MM, Mooij JM, Roujouleh H. Tuberculosis and chronic renal disease. *Semin Dialysis.* 2003;16:38–44.
47. Hsueh P-R, Liu Y-C, So J, et al. Mycobacterium tuberculosis in Taiwan. *J Infect.* 2006;52:77–85.
48. Takahashi T, Morimoto S, Okaishi K, et al. Reduction of pneumonia risk by an angiotensin I-converting enzyme inhibitor in elderly Japanese inpatients according to insertion/deletion polymorphism of the angiotensin I-converting enzyme gene. *Am J Hypertens.* 2005;18:1353–1359.
49. Teramoto S, Yamamoto H, Yamaguchi Y, et al. ACE inhibitors prevent aspiration pneumonia in Asian, but not Caucasian, elderly patients with stroke. *Eur Respir J.* 2007;29:218–219author reply 219–220.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.