Risk of active tuberculosis among COPD patients treated with fixed combinations of long-acting beta2 agonists and inhaled corticosteroids

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Abstract

Objectives: To investigate the incidence of active tuberculosis (TB) among COPD patients using fluticasone/salmeterol or budesonide/formoterol, and to identify any differences between these two groups of patients.

Methods: The study enrolled COPD patients from Taiwan NHIRD who received treatment with fluticasone/salmeterol or budesonide/formoterol for > 90 days between 2004 and 2011. The incidence of active TB was the primary outcome.

Results: Among the intention-to-treat population prior to matching, the incidence rates of active TB were 0.94 and 0.61% in the fluticasone/salmeterol and budesonide/formoterol groups, respectively. After matching, the fluticasone/salmeterol group had significantly higher rates of active TB (adjusted HR, 1.41, 95% CI, 1.17–1.70) compared with the budesonide/formoterol group. The significant difference between these two groups remained after a competing risk analysis (HR, 1.45, 95% CI, 1.21–1.74). Following propensity score matching, the fluticasone/salmeterol group had significantly higher rates of active TB compared with the budesonide/formoterol group (adjusted HR, 1.45, 95% CI, 1.14–1.85). A similar trend was observed after a competing risk analysis (HR, 1.44, 95% CI, 1.19–1.75). A higher risk of active TB was observed in the fluticasone/salmeterol group compared with the budesonide/formoterol group across all subgroups, but some differences did not reach statistical significance.

Conclusion: Fluticasone/salmeterol carried a higher risk of active TB compared with budesonide/formoterol among COPD patients.

Keywords: Fluticasone/salmeterol, Budesonide/formoterol, COPD, Tuberculosis
Introduction
Tuberculosis (TB) is a serious public health problem in many countries, including Taiwan [1–6]. In addition to the use of appropriate anti-TB treatment, early detection in vulnerable populations is an important way of preventing its spread [7]. Many well-known risk factors, including HIV infection, diabetes mellitus, socioeconomic status, alcoholism and immunocompromised condition have been reported as being significantly associated with TB [8–10]. In addition to these risk factors, many studies have shown that the use of corticosteroids, in both systemic and inhaled forms, can also increase a patient’s risk of TB [11–15]. Regarding the association between inhaled corticosteroid (ICS) and TB, one meta-analysis of 25 trials by Dong et al. showed ICS treatment was associated with a significantly higher risk of TB (Peto OR, 2.29; 95% CI, 1.04–5.03, 14) and another meta-analysis of nine non-randomized studies by Castellana et al. showed that any ICS use was associated with an increased risk of TB versus no ICS use (OR ≥ 1.46; 95% CI 1.06 to 2.01), and a similar trend was also found for current ICS use versus prior/no ICS use, as well as for high, moderate and low ICS dose versus no ICS [15].

However, ICS are a major treatment component for patients with chronic obstructive pulmonary disease (COPD), and the combination of inhaled long-acting β2-agonists (LABAs) and ICSs has been shown to be effective for the reduction of COPD exacerbations [16–18]. Although many LABA/ICS combinations have been developed, clinical experience using budesonide/formoterol and fluticasone/salmeterol, as well as associated studies, are most plentiful because these two combinations were developed earliest. Recently, several studies have revealed safety differences between fluticasone/salmeterol and budesonide/formoterol [19–21]. These studies found that fluticasone/salmeterol users have a higher risk of pneumonia, sepsis, and death compared with budesonide/formoterol users [19–21]. However, no study has previously compared the risk of TB between fluticasone/salmeterol and budesonide/formoterol. Therefore, the current study investigated the incidence of active TB among COPD patients using fluticasone/salmeterol and budesonide/formoterol, and to see if there were any differences between these two groups.

Methods
Data source
The current study used a subset of the Taiwan National Health Insurance Research Database (NHIRD), which contained information on 2,200,000 individuals with heart or lung disease. Because the records of patients have been anonymized and de-identified, no informed consent was required. Ethical approval was obtained from the Institutional Review Board of Cardinal Tien hospital (No. CTH 108–3-5-013).

Patients selection
COPD patients aged 40 to 100 years were identified using International Classification of Disease, Ninth Revision (ICD-9)-CM codes 491, 492 and 496 according to previous study [20]. The present study consisted of COPD patients who received treatment with fluticasone/salmeterol or budesonide/formoterol for > 90 days between 2004 and 2011. Patients with a reported history of AIDS were excluded (n = 5). Patients were followed until 31 December 2011, the end of the fixed combination treatment, emigration or death, whichever came first.

Figure 1 describes the study population selection process.

Measurement of outcome
The case of active TB cases was defined using the ICD-9 codes (010–018, including all subcategories) and based on the use of at least 28 days anti-TB drug as previous studies [12, 22].

Definition of exposure and confounding factor
We defined fixed LABA/ICS combinations using Anatomical Therapeutic Chemical (ATC) codes R03AK06 or R03AK07, according to previously reported [20]. We only calculated the event of COPD exacerbation during the usage of same fixed LABA/ICS combination period. In contrast, once the patient changed to the other fixed combination, the case was censored. We also collected the data regarding the use of ICSs (ATC code R03BA), LABAs (ATC codes R03AC12 and R03AC13), short-acting β2-agonists (ATC code R03AC) and other related drugs.

Statistical analysis
To reduce potential confounding caused by unbalanced covariates, we used the pairwise 1:1 propensity score matching and logistic regression to construct two comparable groups. We start the process with the smallest group (the budesonide/formoterol group 7436 patients) and matches them 1:1 to the larger treatment population (the fluticasone/salmeterol group). After the matching process, the two groups were no differences in the underlie characteristics including: age, sex, year of index date, monthly income, hospital level, COPD medications, comorbidities and the episodes of previous severe COPD exacerbations (emergency department visits or COPD-related hospitalizations).

We conduct both Intention-to-treat (ITT) and as-treated (AT) analyses to see the effects. ITT analyses ignore noncompliance, drug switching, subsequent withdrawal or deviation after their original treatment.
allocation. In AT analyses, the patients were censored on the day of medication switching, add-on or discontinuation.

The crude and adjusted hazard ratios (HRs) of active TB between the two study groups were calculated by Cox regression models with adjustment for age, gender and propensity scores. A P value of < 0.05 indicated statistical significance in all analyses. The analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).
Results

Patient characteristics
Initially, 18,951 patients received a fixed LABA/ICS combination (11,515 received fluticasone/salmeterol and 7436 received budesonide/formoterol). Before propensity score matching, the fluticasone/salmeterol group were older, more likely to be male, had higher Charlson scores and more comorbidities (including myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, diabetes, and malignancy) than the budesonide/formoterol group (Table 1). In addition, the fluticasone/salmeterol group had a lower income, more episodes of COPD exacerbations and less use of COPD inhaled and oral drugs (except LAMA), than the budesonide/formoterol group. Further pairwise matching (1:1) of fluticasone/salmeterol and budesonide/formoterol group identified two similar subgroups each comprising 7284 cases (Table 1).

Risk of incidental active TB
Among the intention-to-treat population prior to matching, the incidence rates of active TB were 0.94 and 0.61% in the fluticasone/salmeterol and budesonide/formoterol groups, respectively. The fluticasone/salmeterol group had significantly higher rates of active TB (adjusted HR, 1.41, 95% CI, 1.17–1.70) than the budesonide/formoterol group (Table 2). The significant difference between these two groups remained after competing risk analysis (HR, 1.45, 95% CI, 1.21–1.74). Even following propensity score matching, the fluticasone/salmeterol group had a significantly higher rate of active TB compared with the budesonide/formoterol group (adjusted HR, 1.45, 95% CI, 1.14–1.85), and this was maintained after competing risk analysis (HR, 1.44, 95% CI, 1.19–1.75). Furthermore, the higher risk of active TB among the fluticasone/salmeterol group compared with the budesonide/formoterol group remained in the as-treated population analysis (Table 2) but the difference was not significant.

Subgroup analysis
A subgroup analysis was performed using an intention-to-treat analysis. A higher incidence of active TB was observed in the fluticasone/salmeterol group compared with the budesonide/formoterol group across all subgroups (male patients, 1.06% vs 0.70%; patients without diabetes mellitus, 0.91% vs 0.62%; patients without cancer, 0.91% vs 0.63%; and patients without autoimmune disease, 0.89% vs 0.62%; all p < 0.05), but some differences did not reach statistical significance (female patients, 0.48% vs 0.42%; patients with diabetes mellitus, 0.78% vs 0.59%; patients with cancer, 0.52% vs 0.33%; and patients with autoimmune disease, 1.18% vs 0.62%) (Fig. 2).

Discussion
The present national population-based study demonstrated that COPD patients receiving fluticasone/salmeterol had a higher risk of active TB compared with those receiving budesonide/formoterol. In contrast to previous meta-analyses [14, 15] showed that ICS increased the risk of tuberculosis, this study is the first one to point out patients using fluticasone/salmeterol are at higher risk of tuberculosis than patients using budesonide/formoterol. This significant difference between budesonide/formoterol and fluticasone/salmeterol was confirmed in various populations, including intention-to-treat and after propensity score matching methods and competing risk analysis. This trend was also observed in the as-treated population with nearly the same proportion using different methods. However, the non-significant difference could be due to the low case number in as treated analysis. Even in the subgroup analysis, the fluticasone/salmeterol group remained associated with a higher risk of active TB compared with the budesonide/formoterol group. This intra-class difference has been shown in a previous study [21], and there may be different risks for other infectious diseases between budesonide/formoterol and fluticasone/salmeterol. In the PATHOS study, the rate of pneumonia and the pneumonia event rate per 100 patients were higher in fluticasone/salmeterol compared with budesonide/formoterol [19]. Another study showed that fluticasone/salmeterol carried a higher risk of sepsis (aHR, 1.15; 95%CI, 1.07–1.24) and septic shock (aHR, 1.14; 95%CI, 1.11–1.29) compared with budesonide/formoterol [21]. However, the present study is the first to confirm an intra-class difference for the risk of active TB between fluticasone/salmeterol and budesonide/formoterol. Therefore, these findings confirmed the significant differences between budesonide/formoterol and fluticasone/salmeterol in terms of the risk of infectious diseases, including TB, in patients with COPD.

As this study was an observational cohort study, it was not possible to investigate the possible mechanisms that caused the differences between fluticasone and budesonide. However, several different pharmacologic characteristics between these two agents may give some explanations. First, the uptake and elimination rates are slower for fluticasone than budesonide, as reported in a previous pharmacokinetic study [23]. The mean residence time of budesonide was shorter than fluticasone, and the amount of expectorated fluticasone was significantly higher compared with budesonide [24]. Second, fluticasone and budesonide also differ in the immune response that they influence. In vitro studies have shown that fluticasone is about 10 times more potent than budesonide in inhibiting the release of IL-6, IL-8, and TNF-α production [25]. Third, budesonide is less...
Table 1 Baseline characteristics of Fluticasone/salmeterol and budesonide/formoterol cohort before and after matching

| Variables                        | Before PS matching | After PS matching |
|----------------------------------|--------------------|-------------------|
|                                  | Fluticasone/salmeterol cohort (n = 11,515) | Budesonide/formoterol cohort (n = 7436) | p value |
|                                  | n (%)              | n (%)             | Fluticasone/salmeterol cohort (n = 7284) | Budesonide/formoterol cohort (n = 7284) | p value |
| Index year                       |                    |                   |                                     |                                      |        |
| 2004                             | 1963 (17.04)       | 1430 (19.23)      | <.0001                              | 1434 (19.69)                         | 1407 (19.32) | 0.7872 |
| 2005                             | 1261 (10.95)       | 1230 (16.54)      |                                      | 1118 (15.35)                         | 1138 (15.62) |        |
| 2006                             | 1326 (11.51)       | 990 (13.31)       |                                      | 976 (13.4)                           | 970 (13.32)  |        |
| 2007                             | 1485 (12.89)       | 973 (13.08)       |                                      | 1002 (13.76)                         | 967 (13.28)  |        |
| 2008                             | 1375 (11.94)       | 843 (11.34)       |                                      | 835 (11.46)                           | 833 (11.44)  |        |
| 2009                             | 1542 (13.39)       | 762 (10.25)       |                                      | 749 (10.28)                           | 761 (10.45)  |        |
| 2010                             | 1570 (13.63)       | 815 (10.96)       |                                      | 822 (11.29)                           | 815 (11.19)  |        |
| 2011                             | 993 (8.62)         | 393 (5.28)        |                                      | 348 (4.78)                            | 393 (5.40)   |        |
| Age (year)                       | 65.95 ± 10.26      | 63.29 ± 10.40     | <.0001                              | 63.77 ± 10.35                         | 63.53 ± 10.31 | 0.1535 |
| Male Gender                      | 8798 (76.38)       | 5433 (73.05)      | <.0001                              | 5403 (74.18)                          | 5348 (73.42) | 0.3001 |
| Monthly income                   |                    |                   |                                     |                                      | 0.0007 | 0.9766 |
| < 19,100                         | 4037 (35.05)       | 2481 (33.36)      |                                      | 2443 (33.54)                          | 2451 (33.65) |        |
| 19,100-41,999                    | 6011 (52.19)       | 3874 (52.09)      |                                      | 3812 (52.33)                          | 3799 (52.16) |        |
| $\geq$42,000                    | 1467 (12.74)       | 1081 (14.54)      |                                      | 1029 (14.13)                          | 1034 (14.20) |        |
| Hospital level                   |                    |                   | <.0001                              |                                      | 0.9562 |        |
| Level 1                          | 4649 (40.36)       | 3076 (41.36)      |                                      | 2970 (40.77)                          | 3001 (41.20) |        |
| Level 2                          | 4886 (42.42)       | 2907 (39.09)      |                                      | 2893 (39.72)                          | 2877 (39.50) |        |
| Level 3                          | 1476 (12.81)       | 1016 (13.66)      |                                      | 997 (13.69)                           | 991 (13.61)  |        |
| Level 4 (rural area)             | 504 (4.38)         | 437 (5.88)        |                                      | 424 (5.82)                            | 415 (5.70)   |        |
| COPD medications                 |                    |                   |                                     |                                      |        |        |
| Oral steroids                    | 4544 (39.45)       | 2691 (36.18)      | <.0001                              | 2683 (36.83)                          | 2660 (36.52) | 0.6925 |
| Antibiotics                      | 8142 (70.69)       | 5344 (71.86)      | 0.0855                              | 5202 (71.42)                          | 5227 (71.76) | 0.6460 |
| LABA                             | 412 (3.58)         | 366 (4.92)        | <.0001                              | 336 (4.61)                            | 347 (4.76)   | 0.6664 |
| SABA                             | 3400 (29.52)       | 2514 (33.80)      | <.0001                              | 2419 (33.21)                          | 2434 (33.42) | 0.7920 |
| LAMA                             | 1488 (12.92)       | 711 (9.56)        | <.0001                              | 701 (9.62)                            | 711 (9.76)   | 0.7794 |
| Theophylline                     | 8144 (70.71)       | 5378 (72.31)      | 0.0175                              | 5248 (72.05)                          | 5257 (72.17) | 0.8679 |
| Aminophylline                    | 4884 (42.40)       | 3211 (43.18)      | 0.2969                              | 3145 (43.18)                          | 3142 (43.14) | 0.9600 |
| ICS                              | 3155 (27.39)       | 2591 (34.84)      | <.0001                              | 2465 (33.84)                          | 2478 (34.02) | 0.8200 |
| Severe AE                        | 6339 (55.04)       | 4579 (61.57)      | <.0001                              | 4459 (61.22)                          | 4451 (61.11) | 0.9873 |
| 1                                | 1914 (16.62)       | 1102 (14.82)      |                                      | 1090 (14.96)                          | 1090 (14.96) |        |
| 2+                               | 3262 (28.32)       | 1755 (23.60)      |                                      | 1735 (23.82)                          | 1743 (23.93) |        |
| Charlson Score                   | 1.64 ± 1.00        | 1.55 ± 0.90       | <.0001                              | 1.55 ± 0.91                           | 1.55 ± 0.90  | 0.7699 |
| Myocardial infarction            | 190 (1.65)         | 95 (1.28)         | 0.0397                              | 97 (1.33)                             | 95 (1.30)    | 0.8845 |
| Congestive heart failure         | 1030 (8.94)        | 584 (7.85)        | 0.0086                              | 566 (7.77)                            | 579 (7.95)   | 0.6890 |
| Peripheral vascular disease      | 92 (0.80)          | 52 (0.70)         | 0.4405                              | 52 (0.71)                             | 51 (0.70)    | 0.9212 |
| Cerebrovascular disease          | 578 (5.02)         | 279 (3.75)        | <.0001                              | 277 (3.80)                            | 277 (3.80)   | 1.0000 |
| Dementia                         | 193 (1.68)         | 67 (0.90)         | <.0001                              | 66 (0.91)                             | 67 (0.92)    | 0.9306 |
| Rheumatologic disease            | 114 (0.99)         | 74 (1.00)         | 0.9722                              | 67 (0.92)                             | 71 (0.97)    | 0.7323 |
lipophilic than fluticasone. In summary, all of these factors suggest that fluticasone can reside in humans for longer and could cause a more potent immunosuppressive effect than budesonide, thereby facilitating TB infection.

The present study had two major strengths. First, it was conducted using data from the NHIRD database, which includes nearly all patients in Taiwan. Using this database, it is possible to enroll a large population and obtain long-term follow-up data for the included subjects. Therefore, the findings can be considered representative and truly reflective of the real-world. Second, TB remains prevalent in Taiwan, and the incidence of TB in Taiwan is much higher than in Western countries. Therefore, the cohort contained a large number of TB cases, which can help increase the statistical power of the analysis for subgroup and confounding factor adjustment. Nevertheless, the current study had several limitations. First, although many variables were collected to minimize the confounding effect, the effect of some potential confounder, such as BMI, pulmonary function, the status of smoking and history of latent TB, data for which was not available in the NHIRD database. However, the status of smoking and latent TB could have significant impact on the development of active TB. Further study is warranted to assess their effect on the risk of TB. Second, microbiological data is lacking in the NHIRD database, however, this data is the key diagnostic criteria for active TB. To overcome potential misclassification of TB in the claims database, cases of

**Table 1** Baseline characteristics of Fluticasone/salmeterol and budesonide/formoterol cohort before and after matching (Continued)

| Variables                      | Fluticasone/salmeterol cohort (n = 11,515) | Budesonide/formoterol cohort (n = 7436) | p value | Fluticasone/salmeterol cohort (n = 7284) | Budesonide/formoterol cohort (n = 7284) | p value |
|-------------------------------|------------------------------------------|----------------------------------------|---------|----------------------------------------|----------------------------------------|---------|
|                               | n (%)                                    | n (%)                                  |         | n (%)                                   | n (%)                                  |         |
| Peptic ulcer disease          | 1702 (14.78)                             | 1052 (14.15)                           | 0.2271  | 1032 (14.17)                            | 1030 (14.14)                           | 0.9621  |
| Hemiplegia or paraplegia      | 7 (0.06)                                 | 2 (0.03)                               | 0.2957  | 3 (0.04)                                | 2 (0.03)                               | 0.6547  |
| Renal disease                 | 270 (2.34)                               | 153 (2.06)                             | 0.1913  | 149 (2.05)                              | 146 (2.00)                             | 0.8599  |
| Diabetes                      | 1253 (10.88)                             | 706 (9.49)                             | 0.0022  | 690 (9.47)                              | 703 (9.65)                             | 0.7142  |
| Moderate or severe liver      | 374 (3.25)                               | 239 (3.21)                             | 0.8977  | 229 (3.14)                              | 235 (3.23)                             | 0.7771  |
| Tumor                         | 372 (3.23)                               | 202 (2.72)                             | 0.0438  | 201 (2.76)                              | 199 (2.73)                             | 0.9192  |
| Autoimmune                    | 660 (5.73)                               | 442 (5.94)                             | 0.5418  | 445 (6.11)                              | 428 (5.88)                             | 0.5529  |

**Table 2** Incidence rates, hazard ratios and competing risk of active TB associated with Fluticasone/salmeterol relative to Budesonide/formoterol in patients with COPD in intent-to-treat and as treated analysis

| Fluticasone/salmeterol cohort event | PERSON-YEAR | IR* | Budesonide/formoterol cohort event | PERSON-YEAR | IR* | Crude HR (95%CI) | Adjustedd HR (95%CI) | Competing risk subHR (95%CI) |
|------------------------------------|-------------|-----|-----------------------------------|-------------|-----|------------------|----------------------|---------------------------|
| ITT analysis                       |             |     |                                   |             |     |                  |                      |                           |
| Before propensity score matching   | TB          | 358 | 38,123.37 | 0.94% | 175 | 28,559.41 | 0.61% | 1.50 (1.26–1.80) | 1.41 (1.17–1.70) | 1.45 (1.21–1.74) |
| After propensity score matching    | TB          | 247 | 27,392.73 | 0.90% | 172 | 27,689.85 | 0.62% | 1.34 (1.07–1.69) | 1.45 (1.14–1.85) | 1.44 (1.19–1.75) |
| As treated analysis                |             |     |                                   |             |     |                  |                      |                           |
| Before propensity score matching   | TB          | 126 | 14,256.75 | 0.88% | 66  | 10,120.93 | 0.65% | 1.32 (0.98–1.78) | 1.28 (0.94–1.73) | 1.27 (0.94–1.71) |
| After propensity score matching    | TB          | 85  | 9512.25  | 0.89% | 66  | 9872.11  | 0.67% | 1.23 (0.73–2.07) | 1.38 (0.79–2.42) | 1.31 (0.95–1.81) |

*IR Incidence rate
Adjusted for age, gender, propensity score
active TB were only identified when they had concurrent ICD-9 codes for TB and a history of anti-TB medication. Third, the effect of dose and duration of LABA/ICS was not assessed in this study.

Conclusions
Fluticasone/salmeterol carried a higher risk of active TB than budesonide/formoterol among COPD patients.

Abbreviations
COPD: Chronic obstructive pulmonary disease; TB: Tuberculosis; NHIRD: National Health Insurance Research Database; ICS: Inhaled corticosteroid; LABA: Long-acting β2-agonists; ATC: Anatomical Therapeutic Chemical

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Authors’ contributions
TMH, KCK, YHW, CYW, CCL, HCW, LC, and CJY designed the research. HCW, LC, and CJY collected the data and established the database. All statistical analyses were performed by YHW. CCL and CYW wrote the first draft of the manuscript. All authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the manuscript, ensuring that questions related to the accuracy or integrity of any part of the manuscript were appropriately investigated and resolved.

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Availability of data and materials
The original databases used and/or analyzed during the current study, which were released and permitted by the National Health Research Institutes, are closed for releasing now. The working datasets for statistical analysis in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Because the records of patients have been anonymized and de-identified, no informed consent was required. Ethical approval was obtained from the Institutional Review Board of Cardinal Tien hospital (No. CTH 108–3–5-013).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.
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