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# BMJ Open Evidence of potential bias in a comparison of $\beta$ blockers and calcium channel blockers in patients with chronic obstructive pulmonary disease and acute coronary syndrome: results of a multinational study

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## ABSTRACT

**Objectives:** A number of observational studies have reported that, in patients with chronic obstructive pulmonary disease (COPD),  $\beta$  blockers (BBs) decrease risk of mortality and COPD exacerbations. To address important methodological concerns of these studies, we compared the effectiveness and safety of cardioselective BBs versus non-dihydropyridine calcium channel blockers (non-DHP CCBs) in patients with COPD and acute coronary syndromes (ACS) using a propensity score (PS)-matched, active comparator, new user design. We also assessed for potential unmeasured confounding by examining a short-term COPD hospitalisation outcome.

**Setting and participants:** We identified 22 985 patients with COPD and ACS starting cardioselective BBs or non-DHP CCBs across 5 claims databases from the USA, Italy and Taiwan.

**Primary and secondary outcome measures:** Stratified Cox regression models were used to estimate HRs for mortality, cardiovascular (CV) hospitalisations and COPD hospitalisations in each database after variable-ratio PS matching. Results were combined with random-effects meta-analyses.

**Results:** Cardioselective BBs were not associated with reduced risk of mortality (HR, 0.90; 95% CI 0.78 to 1.02) or CV hospitalisations (HR, 1.06; 95% CI 0.91 to 1.23), although statistical heterogeneity was observed across databases. In contrast, a consistent, inverse association for COPD hospitalisations was identified across databases (HR, 0.54; 95% CI 0.47 to 0.61), which persisted even within the first 30 days of follow-up (HR, 0.55; 95% CI 0.37 to 0.82). Results were similar across a variety of sensitivity analyses, including PS trimming, high dimensional-PS matching and restricting to high-risk patients.

**Conclusions:** This multinational study found a large inverse association between cardioselective BBs and short-term COPD hospitalisations. The persistence of this bias despite state-of-the-art

## Strengths and limitations of this study

- A growing body of observational studies suggests that  $\beta$  blockers (BBs) may decrease risk of mortality and chronic obstructive pulmonary disease (COPD) exacerbations in patients with COPD; most studies compared prevalent BB users to non-users.
- This study used an active comparator, new user cohort design to examine the association between BBs and clinical outcomes and to assess potential remaining unmeasured confounding using data from five claims databases in the USA, Italy and Taiwan.
- The study applied a variety of sensitivity analyses, including propensity score (PS) trimming, an high-dimensional PS matching technique and restricting to high-risk patients, to evaluate the consistency of results.
- Although this multinational study was conducted with a common protocol, the inherent variations in healthcare systems and data structures across countries necessitated certain database-specific modifications to the protocol.
- Owing to analytic flexibility, we conducted sensitivity analyses in the three US databases only.

pharmacoepidemiologic methods calls into question the ability of claims data to address confounding in studies of BBs in patients with COPD.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has profound health impacts worldwide<sup>1 2</sup> and usually coexists with cardiovascular (CV) morbidity.<sup>3-6</sup> CV risk reduction is

therefore a major focus in COPD management.  $\beta$  blockers (BBs) are a cornerstone treatment for improving survival and reducing CV morbidity in patients with coronary artery disease.<sup>7–10</sup> The cardioprotective benefits of BBs are expected to extend to patients with COPD. However, those with COPD have generally been excluded from randomised controlled trials evaluating the efficacy of BBs in patients experiencing myocardial infarction (MI).<sup>7–9</sup> In addition, while the targets of BBs in treating CV disease are  $\beta$ -1 receptors predominantly found in cardiac tissues, BBs can also block  $\beta$ -2 receptors in the respiratory system, causing bronchospasm and increasing the risk of COPD exacerbations.<sup>11</sup> Therefore, in clinical practice, physicians may be reluctant to prescribe BBs to patients with COPD.<sup>6–12</sup> One study found that, among patients hospitalised for acute MI, those with COPD had 56% lower odds of being treated with BBs as compared to those without COPD.<sup>12</sup>

Despite these safety concerns, a growing body of observational studies suggests that BBs may have cardioprotective effects in COPD patients.<sup>13–22</sup> One meta-analysis of observational studies reported a 36% reduction in all-cause mortality associated with BB use in patients with coronary heart disease and COPD.<sup>23</sup> However, these studies have important methodological limitations. In particular, most of these studies focused on prevalent users of BBs<sup>13–22</sup> and used non-users of BBs as the comparator group.<sup>13–21</sup> Patients who remain on BB treatment for a long time may be less susceptible to an outcome of interest as compared to those just starting the drug. The prevalent user design is therefore vulnerable to biases due to depletion of susceptible patients.<sup>24–25</sup> Treated patients may also differ from untreated patients in important ways, which can create strong confounding, especially when the indication for treatment is a risk factor for the outcome(s) of interest.<sup>24</sup> The non-user comparator approach is also vulnerable to immortal time bias.<sup>26</sup> These methodological issues may explain the paradoxical COPD hospitalisation findings reported in these studies and perhaps even the reported survival advantage.

Drug safety and comparative effectiveness studies are increasingly using multiple databases across various countries.<sup>27–29</sup> The larger sample size afforded by multi-databases studies facilitates the application of robust study designs and, by using a common protocol, such studies enable investigators to leverage differences in the healthcare systems in the assessment of unmeasured confounding, treatment effect heterogeneity and generalisability across diverse populations, while holding constant the design and analytic approach. In the present study, we used multiple databases from three countries to: (1) address important shortcomings of prior studies by comparing the effectiveness and safety of BBs in patients with acute coronary syndromes (ACS) and COPD using a propensity score (PS)-matched, active comparator, new user cohort design; and (2) assess for potential remaining unmeasured confounding by examining a short-term COPD hospitalisation outcome.

## METHODS

### Data source

We identified eligible cohorts from five databases in the USA, Italy and Taiwan: (1) the Optum Research Database (Optum); (2) pharmacy claims data from the Pharmaceutical Assistance Contract for the Elderly program (PACE) in Pennsylvania linked to Medicare claims data; (3) pharmacy claims data from the Pharmaceutical Assistance for the Aged and Disabled program in New Jersey (PAAD) linked to Medicare claims data; (4) the population-based Regione Emilia-Romagna, Italy, database (RER) and (5) the population-based Taiwan National Health Insurance database (NHI). These databases contain demographic and enrolment records, hospital admissions, outpatient visits (except in RER), outpatient pharmacy dispensing claims and death information. These five databases cover the period from 1994 through the end of 2013 and represent diverse source populations across countries with different health insurance programmes (see the online supplementary materials for details).

### Study population and study drugs

From each database, we identified patients who were hospitalised for ACS, had a COPD diagnosis before the ACS hospitalisation discharge date and initiated a cardioselective BB or non-dihydropyridine calcium channel blocker (non-DHP CCB) within 90 days following hospital discharge (see the online supplementary materials for details). Codes used to identify study drugs are provided in online supplementary table S1. The index date was defined as the date of the first postdischarge prescription of a study drug. To focus on initiators, patients with any use of these drugs before the first postdischarge prescription were excluded. Cardioselective BBs were chosen as the exposure of interest in alignment with prior studies.<sup>13–22</sup> Initiators of non-DHP CCBs were selected as the referent group since guidelines recommend non-DHP CCB treatment in patients with ACS who have a contraindication to BBs and have no other contraindications (eg, severe left ventricular dysfunction).<sup>30–31</sup>

We excluded patients without continuous enrolment for at least 180 days before the ACS hospitalisation admission date (see the online supplementary materials for details), those with age <20 years (Optum, RER, NHI) or 65 years (PACE, PAAD) or more than 120 years, and those who simultaneously initiated study drugs from both exposure groups on the index date.

### Outcomes and follow-up

We selected all-cause mortality and CV hospitalisations as outcomes of interest. CV hospitalisations were defined as first hospitalisation for a composite CV event, including acute MI, unstable angina and congestive heart failure (CHF) following the index date. We conducted analyses for the composite CV event and individual components of the outcomes separately. We also examined

hospitalisation for COPD as an outcome. CV and COPD hospitalised events were defined using validated claims-based algorithms with positive predictive values of 80% for acute MI,<sup>32</sup> 88–94% for CHF<sup>33</sup> and 86% for COPD<sup>34</sup> (see the online supplementary materials for outcome ascertainment; all outcomes were based on primary inpatient diagnoses). While animal models have suggested that chronic BB use may upregulate  $\beta$ -2 adrenoreceptors and attenuate pulmonary inflammation,<sup>35</sup> <sup>36</sup> meta-analyses of randomised trials have found that there is no significant effect of cardioselective BB on pulmonary function in the short term (single dose to 4 months).<sup>37</sup> <sup>38</sup> We therefore assessed for the presence of bias by using a short-term COPD hospitalisation outcome as a negative control, defined as a COPD hospitalisation within 30 days following the index date. We assumed that, even if BBs improve COPD in the long term, a large apparent protective association in the short term would not be causal and would reflect bias, such as confounding due to unmeasured baseline differences between treatment groups.

In the primary 'first exposure carried forward' analysis, we followed patients from the index date to the earliest of outcome occurrence, death, disenrollment from the health insurance programme or the end of study. In the secondary 'as-treated' analysis, follow-up ended on the first of treatment discontinuation or change, outcome occurrence, death, disenrollment from the health insurance programme or the end of study. Treatment discontinuation was defined using a grace period of up to 14 days between the end of one prescription and the date of the next prescription, if any. Treatment change was defined as a dispensation of a drug in the other exposure group. Given the absence of information on days supply in the RER database, we assigned a proxy based on the WHO's Defined Daily Dose methodology (online supplementary table S1). This approach has shown good concordance with days supply for chronically used medications.<sup>39</sup>

### Covariates

Information on potential confounders included demographic data, year of index date, enrolment duration, resource utilisation, comorbidities and other medication use. Resource utilisation was evaluated during the 180-day baseline period preceding the index date. CV-related comorbidities and medication use were assessed in two separate periods: a chronic phase before the ACS hospitalisation admission date (data were traced back as far as possible within each database); and an acute phase between the ACS hospitalisation date and the index date. Non-CV comorbidities and medication use were evaluated using all available data prior to the index date. Using all available claims information has been found to better reduce bias under most conditions as compared to a fixed look-back period.<sup>40</sup> <sup>41</sup> Details on covariate ascertainment are provided in online supplementary tables S2 and S3.

### Statistical analysis

Using the predefined covariates described above, we estimated baseline PSs using logistic regression models to predict the probability of receiving cardioselective BBs versus non-DHP CCBs. Non-categorical covariates (eg, age) were included in the PS model as linear terms. Since we had many more cardioselective BB initiators than non-DHP CCB initiators, we conducted variable-ratio matching (up to 10 cardioselective BB users to each non-DHP CCB user) using a nearest-neighbour algorithm with a maximum matching caliper of 0.01 on the PS scale.<sup>42</sup>

Variable-ratio matching produces covariate balance within matched sets but not marginally in the overall matched population.<sup>42</sup> We therefore randomly sampled one cardioselective BB user from each set of patients matched to each non-DHP CCB user and examined whether adequate balance in covariates was achieved between treatment groups using standard differences<sup>43</sup> among this sample (1:1 random-sample matched cohort). We used Cox proportional hazard models to estimate HRs and 95% CIs. To account for the variable-ratio matching, the Cox model was stratified on PS-matched sets.

We identified study cohorts, extracted information on variables, fit PS models and performed PS matching separately within each database. We computed standardised differences across the databases for each variable using pooled means and SDs. The random-effects meta-analysis was used to generate summary estimates across all databases. Statistical heterogeneity across databases was quantified using the  $I^2$  statistic.

### Sensitivity and subgroup analyses

To mitigate potential unmeasured confounding, four sensitivity analyses were performed in the US databases. First, the maximum matching caliper was reduced to 0.005. Second, before PS matching, asymmetric PS trimming<sup>44</sup> was applied to exclude those with PS values less than the 2.5th centile or greater than the 97.5th centile of the PS distribution in cardioselective BB users and non-DHP CCB users, respectively. Third, high-dimensional PSs (hd-PSs) were used to identify and include an additional 100 empirically identified variables in the PS model.<sup>42</sup> <sup>45</sup> Finally, we restricted to high-risk patients, defined as those with COPD hospitalisations and use of bronchodilators or inhaled corticosteroids in the window between 180 days before the index hospital admission date and the index date. To examine the influence of prescribing patterns and treatment strategies over time, we also conducted subgroup analyses by year of the index date.

## RESULTS

### Patients

Among 22 985 eligible patients, 18 406 initiated cardioselective BBs (80.1%) and 4579 initiated non-DHP CCBs



(18.9%) (figure 1 and see online supplementary table S4). Most patients (>80%) started treatment within 30 days after the ACS hospitalisation discharge. The mean age of the cohort was 71 years and 59% were men. In general, non-DHP CCB initiators were older and had a longer length of stay for the index ACS hospitalisation, a longer history of COPD and higher resource utilisation. Cardioselective BB initiators were more likely to have received coronary revascularisation procedures, have had a diagnosis of MI, peripheral vascular disease and hyperlipidaemia and have used ACE inhibitors, fibrates and statins. Non-DHP CCB initiators were more likely to have had a diagnosis of angina, arrhythmia and CHF and taken antihypertensive agents, nitrates, antiarrhythmic agents and antiplatelet agents. Non-DHP CCB initiators were also more likely to have had asthma and used bronchodilators or corticosteroids (table 1 and see online supplementary table S5a–S5e).

The PS-matched cohort included 11 479 cardioselective BB initiators and 3588 non-DHP CCB initiators (66% of the total study cohort). Most, but not all, covariates had standardised differences of <0.1 in the matched

cohort with random sampling of comparator patients (table 1 and see online supplementary table S5a–S5e). Summaries of the PS distributions across study drugs and databases are provided in online supplementary table S6.

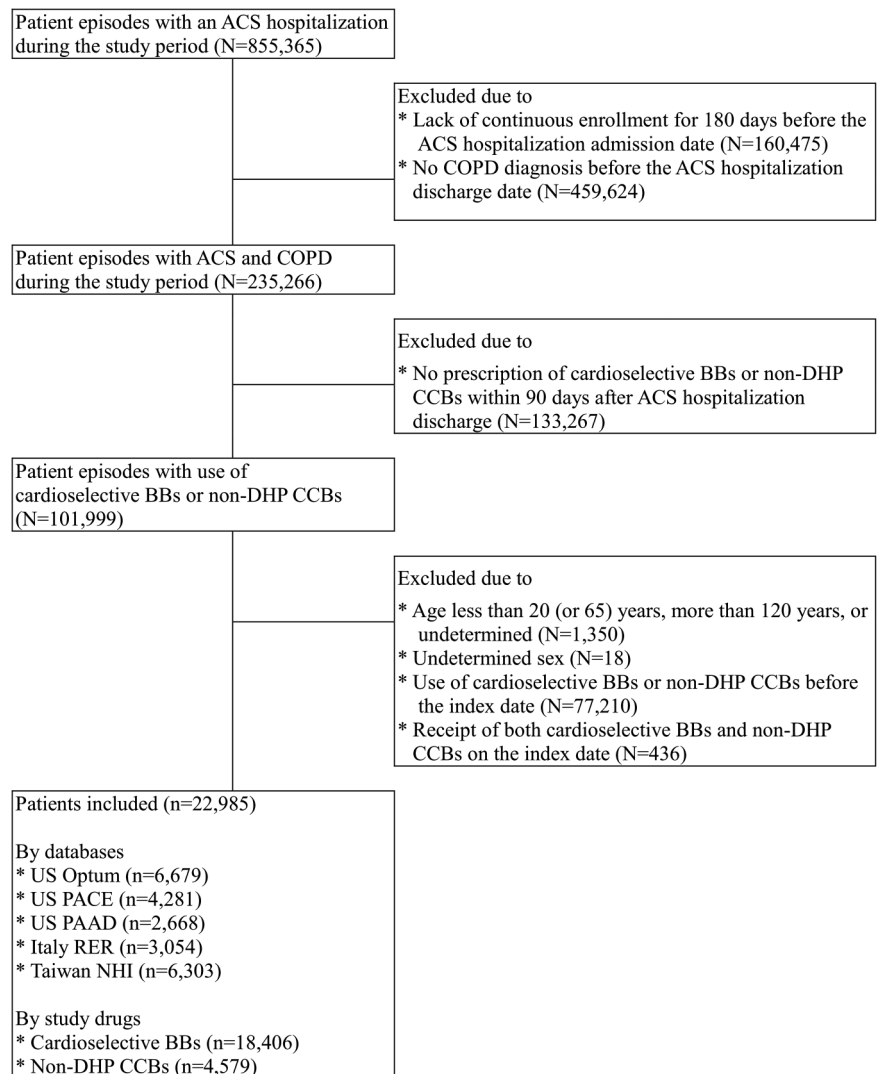
### Follow-up and incidence rates

The mean follow-up duration ranged from 1.9 to 3.5 years across databases, with 7489 death, 4970 CV hospitalisation and 1829 COPD hospitalisation events. Incidence rates of individual outcomes for each treatment group are presented in table 2 and online supplementary table S7.

### All-cause mortality and CV hospitalisations

In the primary analysis considering first exposure carried forward, the crude HRs comparing cardioselective BBs to non-DHP CCBs on all-cause mortality and CV hospitalisations were 0.73 (95% CI 0.65 to 0.83) and 0.98 (95% CI 0.84 to 1.14), respectively. After PS matching, the adjusted HRs were 0.90 (95% CI 0.78 to 1.02) for mortality and 1.06 (95% CI 0.91 to 1.23) for CV

**Figure 1** Flow chart of the study cohort assembly. ACS, acute coronary syndromes; BBs,  $\beta$  blockers; COPD, chronic obstructive pulmonary disease; DHP CCBs, dihydropyridine calcium channel blockers. N and n represented number of patient episodes and number of patients remained and excluded in each step.





**Table 1** Selected baseline demographics, resource utilisation, comorbidities and medication use between cardioselective BB or non-DHP CCB initiators\*

	Before matching			After matching		
	Total study cohort (n=22 985)			1:1 Random-sample† matched cohort (n=7176)		
	Cardioselective BBs (n=18 406)	Non-DHP CCBs (n=4579)	STD	Cardioselective BBs (n=3588)	Non-DHP CCBs (n=3588)	STD
Age, mean (SD)	70.4 (9.9)	73.8 (10.2)	-0.34	73.7 (10.2)	73.5 (10.4)	0.02
Male, %	59.6	55.4	0.09	56.1	55.7	0.01
Length of stay of ACS hospitalisation, day, mean (SD)	8.6 (7.9)	10.5 (12.6)	-0.18	10.0 (11.4)	10.2 (12.4)	-0.02
COPD duration, day, mean (SD)	998.1 (773.7)	1374.0 (967.6)	-0.43	1384.4 (962.9)	1367.2 (988.1)	0.02
<i>Resource utilisation</i>						
Number of hospitalisation due to any episodes, mean (SD)	1.4 (0.8)	1.6 (1.0)	-0.25	1.6 (1.0)	1.6 (1.0)	0.01
Number of outpatient visits due to any episodes, mean (SD)	8.2 (6.2)	14.5 (9.6)	-0.78	14.0 (9.2)	13.9 (9.4)	0.02
Number of outpatient visits due to CV episodes,‡ mean (SD)	3.9 (4.3)	5.2 (4.9)	-0.29	5.4 (4.8)	5.3 (4.9)	0.02
Number of outpatient visits due to pulmonary-related episodes,§ mean (SD)	1.2 (2.6)	2.7 (3.9)	-0.44	2.0 (3.6)	2.1 (3.2)	-0.01
Number of drugs, mean (SD)	14.4 (6.7)	21.0 (9.4)	-0.81	20.4 (9.3)	20.1 (9.0)	0.03
<i>Comorbidities, %</i>						
Before the ACS admission date						
MI	17.3	17.1	0.01	18.3	17.5	0.02
PTCA	4.7	6.6	-0.09	7.0	7.0	<0.01
Stent	3.0	2.4	0.04	2.6	2.8	-0.01
CABG	1.1	1.0	0.01	1.2	1.1	0.01
Haemorrhagic stroke	1.8	2.8	-0.07	2.8	2.8	<0.01
Ischaemic stroke	12.5	14.3	-0.06	14.8	14.7	<0.01
TIA	10.3	12.1	-0.06	12.2	12.2	<0.01
Between the ACS admission date and the index date						
MI	76.3	58.2	0.40	62.2	62.8	-0.01
PTCA	44.0	25.9	0.41	29.1	30.4	-0.03
Stent	37.0	16.0	0.52	17.9	18.3	-0.01
CABG	17.3	7.8	0.30	8.7	9.1	-0.01
Haemorrhagic stroke	0.5	0.6	-0.01	0.5	0.6	-0.02
Ischaemic stroke	4.7	4.5	0.01	5.0	4.5	0.02
TIA	2.3	1.7	0.04	1.6	2.0	-0.02
Before the index date						
Hypertension	82.0	81.0	0.03	83.0	82.3	0.02
Angina	52.1	62.8	-0.22	60.7	59.8	0.02
Ischaemic heart disease	86.1	84.2	0.06	84.9	84.5	0.01
Cardiac dysrhythmia	44.1	50.8	-0.14	49.7	48.9	0.02
Atrial fibrillation	19.1	25.7	-0.17	25.4	24.4	0.02
CHF	45.3	53.7	-0.18	53.8	53.7	<0.01
Cerebrovascular disease	36.9	38.8	-0.04	39.4	39.5	<0.01
PVD	18.4	12.7	0.21	13.3	13.1	0.01
Disorders of lipid metabolism	65.5	52.9	0.27	56.9	56.1	0.02
Diabetes mellitus	41.1	42.4	-0.03	44.3	43.6	0.01
Asthma	23.3	40.5	-0.40	37.0	35.9	0.02

Continued



Table 1 Continued

	Before matching			After matching		
	Total study cohort (n=22 985)			1:1 Random-sample† matched cohort (n=7176)		
	Cardioselective BBs (n=18 406)	Non-DHP CCBs (n=4579)	STD	Cardioselective BBs (n=3588)	Non-DHP CCBs (n=3588)	STD
<i>Medication use, %</i>						
Before the ACS admission date						
ACEIs/ARBs/renin inhibitors	51.6	56.5	-0.10	58.2	57.6	0.01
Non-cardioselective BBs	19.0	32.2	-0.37	33.9	32.7	0.03
DHP CCBs	35.4	46.0	-0.24	47.5	47.1	0.01
Diuretics	44.8	56.0	-0.23	56.2	55.3	0.02
Other antihypertensive agents	15.9	24.9	-0.26	25.3	25.0	0.01
Nitrates	30.2	46.8	-0.36	45.9	45.8	<0.01
Antiarrhythmic agents	7.2	11.3	-0.14	10.5	10.3	<0.01
Digoxin	9.3	16.6	-0.23	14.7	15.0	-0.01
Antiplatelet agents	33.1	51.1	-0.48	50.9	50.7	0.01
Anticoagulants	7.0	7.6	-0.02	8.5	7.5	0.04
Fibrates/statins	37.2	32.8	0.10	35.7	35.1	0.01
Between the ACS admission date and the index date						
ACEIs ARBs/renin inhibitors	48.5	36.2	0.26	41.9	40.3	0.03
Non-cardioselective BBs	4.2	8.7	-0.23	9.2	8.7	0.02
DHP CCBs	11.6	8.8	0.10	10.7	10.3	0.01
Diuretics	27.1	29.4	-0.05	30.9	30.0	0.02
Other antihypertensive agents	3.3	4.2	-0.06	4.1	4.4	-0.01
Nitrates	47.5	59.7	-0.25	59.2	59.0	<0.01
Antiarrhythmic agents	6.2	7.1	-0.04	6.9	7.0	<0.01
Digoxin	6.1	10.5	-0.17	9.0	9.4	-0.02
Antiplatelet agents	60.6	56.9	0.10	59.5	59.8	-0.01
Anticoagulants	6.1	6.6	-0.02	7.2	6.6	0.03
Fibrates/statins	48.2	25.6	0.51	29.4	29.4	<0.01
Before the index date						
Antidiabetic agents	27.1	27.2	<0.01	29.4	29.3	<0.01
Short-acting bronchodilators	34.3	49.8	-0.32	45.7	44.2	0.03
Long-acting bronchodilators	19.6	27.7	-0.21	24.9	23.6	0.03
ICS	23.8	34.3	-0.25	30.8	29.6	0.03
Oral corticosteroids	44.6	64.4	-0.45	61.4	61.4	<0.01
Oral bronchodilators	25.8	61.7	-1.16	57.0	56.7	0.01

\*Presenting as summary estimates for mean, SD and STD across databases.

†One randomly sampled cardioselective BBs user: 1 non-DHP CCBs user in each matched subset.

‡CV episodes included: MI, coronary revascularisation (PTCA, stent, CABG), haemorrhagic stroke, ischaemic stroke, TIA, hypertension, angina, IHD, cardiac dysrhythmia, atrial fibrillation, CHF, cerebrovascular disease and PVD.

§Pulmonary-related episodes included COPD, asthma, pneumonia, influenza and acute bronchitis.

ACEIs, ACE inhibitors; ACS, acute coronary syndromes; ARBs, angiotensin II receptor blockers; BBs,  $\beta$  blockers; CABG, coronary artery bypass graft surgery; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; Cox, cyclooxygenase; CV, cardiovascular; DHP CCBs, dihydropyridine calcium channel blockers; ICS, inhaled corticosteroids; IHD, ischaemia heart disease; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; STD, standardised differences; TIA, transient ischaemic attack.

hospitalisations. We observed substantial statistical heterogeneity across databases, with HRs and 95% CIs for mortality below one in the PACE and RER databases. In the as-treated analysis, the adjusted HRs for mortality and CV hospitalisations were 0.80 (95% CI 0.67 to 0.96) and 1.07 (95% CI 0.85 to 1.36), respectively. We did not

observe statistical heterogeneity for mortality, although the HR in the Taiwan NHI database was statistically significantly <1 (0.70; 95% CI 0.67 to 0.96) (table 3). HRs for CV hospitalisations due to acute MI, unstable angina and CHF were similar to those for the composite outcomes (see online supplementary table S8).

**Table 2** Follow-up and outcome event rates for cardioselective BB or non-DHP CCB initiators

Database	Cardioselective BBs (n=18 406)				Non-DHP CCBs (n=4579)			
	Number of patients	Number of events	Follow-up person-years	Crude incidence (per 1000 person-years)	Number of patients	Number of events	Follow-up person-years	Crude incidence (per 1000 person-years)
All-cause mortality*								
US Optum	6383	384	12 298	31.2 (28.3 to 34.5)	296	35	445	78.7 (56.5 to 109.5)
US PACE	3372	1909	11 616	164.3 (157.1 to 171.9)	909	717	3301	217.2 (201.9 to 233.7)
US PAAD	2108	957	6264	152.8 (143.4 to 162.8)	560	353	2128	165.9 (149.4 to 184.1)
Italy RER	2489	989	8042	123.0 (115.6 to 130.9)	565	352	2181	161.4 (145.4 to 179.2)
Taiwan NHI	4054	1003	11 403	88.0 (82.5 to 93.4)	2249	790	6491	121.7 (113.2 to 130.2)
Summary estimate				96.9 (61.9 to 151.8)				145.0 (111.1 to 189.3)
CV hospitalisations*								
US Optum	6383	476	11 534	41.3 (37.7 to 45.2)	296	27	402	67.2 (46.1 to 97.9)
US PACE	3372	1144	9155	125.0 (117.9 to 132.4)	909	312	2582	120.9 (108.2 to 135.0)
US PAAD	2108	633	4986	127.0 (117.4 to 137.2)	560	169	1724	98.0 (84.3 to 114.0)
Italy RER	2489	761	6267	121.4 (113.1 to 130.4)	565	225	1608	139.9 (122.8 to 159.4)
Taiwan NHI	4054	816	10 055	81.2 (75.6 to 86.7)	2249	407	5763	70.3 (63.4 to 77.1)
Summary estimate				91.7 (63.4 to 132.5)				96.8 (72.1 to 129.9)
COPD hospitalisations*								
US Optum	6383	192	12 035	15.95 (13.9 to 18.4)	296	35	395	88.5 (63.6 to 123.3)
US PACE	3372	274	11 023	24.9 (22.1 to 28.0)	909	214	2808	76.2 (66.7 to 87.1)
US PAAD	2108	155	5938	26.1 (22.3 to 30.6)	560	146	1823	80.1 (68.1 to 94.2)
Italy RER	2489	240	7529	31.9 (28.1 to 36.2)	565	145	1804	80.4 (68.3 to 94.6)
Taiwan NHI	4054	154	11 145	13.8 (11.6 to 16.0)	2249	274	6022	45.5 (40.1 to 50.9)
Summary estimate				21.5 (15.9 to 29.1)				71.5 (54.6 to 93.6)

BBs,  $\beta$  blockers; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DHP CCBs, dihydropyridine calcium channel blockers; NHI, National Health Insurance; PAAD, Pharmacy Assistance for the Aged and Disabled; PACE, Pharmacy Assistance Contract for the Elderly; RER, Emilia-Romagna Region.

\*Based on the analysis that considered first exposure carried forward.



**Table 3** Risk of all-cause mortality, CV hospitalisations and COPD hospitalisations comparing cardioselective BB versus non-DHP CCB initiators

Database	Crude HR (95% CI)	HR after PS matching (95% CI)	Crude HR (95% CI)	HR after PS matching (95% CI)
	First exposure carried forward		As-treated analysis	
<b>All-cause mortality</b>				
US Optum	0.42 (0.30 to 0.60)	1.05 (0.65 to 1.68)	0.71 (0.31 to 1.61)	1.23 (0.47 to 3.20)
US PACE	0.76 (0.69 to 0.82)	0.86 (0.76 to 0.98)	0.70 (0.57 to 0.87)	0.90 (0.64 to 1.27)
US PAAD	0.91 (0.81 to 1.03)	1.12 (0.93 to 1.36)	0.94 (0.69 to 1.30)	0.93 (0.58 to 1.52)
Italy RER	0.74 (0.66 to 0.84)	0.74 (0.64 to 0.85)	0.86 (0.68 to 1.11)	0.74 (0.52 to 1.05)
Taiwan NHI	0.71 (0.65 to 0.78)	0.90 (0.80 to 1.02)	0.63 (0.51 to 0.78)	0.70 (0.51 to 0.96)
Summary estimate	0.73 (0.65 to 0.83)	0.90 (0.78 to 1.02)	0.75 (0.64 to 0.87)	0.80 (0.67 to 0.96)
$I^2$ , %	81.9	68.5	35.1	0.0
P for heterogeneity	<0.001	0.013	0.187	0.649
<b>CV hospitalisations</b>				
US Optum	0.70 (0.47 to 1.02)	0.96 (0.59 to 1.56)	0.76 (0.41 to 1.39)	0.84 (0.41 to 1.71)
US PACE	1.01 (0.89 to 1.14)	1.03 (0.87 to 1.22)	0.96 (0.81 to 1.13)	1.09 (0.85 to 1.39)
US PAAD	1.16 (0.97 to 1.37)	1.30 (1.03 to 1.65)	1.27 (0.97 to 1.67)	1.41 (0.95 to 2.11)
Italy RER	0.80 (0.69 to 0.93)	0.86 (0.73 to 1.01)	0.77 (0.59 to 0.99)	0.75 (0.56 to 1.02)
Taiwan NHI	1.12 (1.00 to 1.26)	1.17 (1.00 to 1.36)	1.06 (0.87 to 1.29)	1.31 (1.00 to 1.71)
Summary estimate	0.98 (0.84 to 1.14)	1.06 (0.91 to 1.23)	0.98 (0.83 to 1.15)	1.07 (0.85 to 1.36)
$I^2$ , %	78.2	63.8	51.0	59.5
P for heterogeneity	0.001	0.026	0.086	0.043
<b>COPD hospitalisations</b>				
US Optum	0.19 (0.13 to 0.27)	0.54 (0.37 to 0.87)	0.16 (0.09 to 0.31)	0.53 (0.19 to 1.47)
US PACE	0.32 (0.27 to 0.39)	0.51 (0.39 to 0.67)	0.22 (0.17 to 0.29)	0.54 (0.34 to 0.86)
US PAAD	0.30 (0.24 to 0.38)	0.45 (0.32 to 0.62)	0.23 (0.15 to 0.34)	0.54 (0.30 to 0.98)
Italy RER	0.38 (0.31 to 0.48)	0.56 (0.44 to 0.73)	0.29 (0.19 to 0.46)	0.40 (0.20 to 0.77)
Taiwan NHI	0.30 (0.25 to 0.37)	0.60 (0.47 to 0.78)	0.24 (0.16 to 0.34)	0.65 (0.38 to 1.13)
Summary estimate	0.30 (0.26 to 0.36)	0.54 (0.47 to 0.61)	0.23 (0.19 to 0.27)	0.54 (0.41 to 0.70)
$I^2$ , %	62.0	0.0	0.0	0.0
P for heterogeneity	0.030	0.721	0.639	0.877

BBs,  $\beta$  blockers; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DHP CCBs, dihydropyridine calcium channel blockers; NHI, National Health Insurance; PAAD, Pharmacy Assistance for the Aged and Disabled; PACE, Pharmacy Assistance Contract for the Elderly; PS, propensity score; RER, Emilia-Romagna Region.

### COPD hospitalisation outcome

In the first exposure carried forward and as-treated analyses, the crude HRs comparing cardioselective BBs to non-DHP CCBs for COPD hospitalisations were 0.30 (95% CI 0.26 to 0.36) and 0.23 (95% CI 0.19 to 0.27), respectively. After PS matching, HRs were still substantially <1: 0.54 (95% CI 0.47 to 0.61) for the first exposure carried forward analysis and 0.54 (95% CI 0.41 to 0.70) for the as-treated analysis (table 3). The adjusted HR for COPD hospitalisations restricted to the first 30 days of follow-up was 0.55 (95% CI 0.37 to 0.82) (table 4).

### Sensitivity and subgroup analyses

Sensitivity analyses applying a narrower PS caliper, asymmetric PS trimming, hd-PS matching and restricting to high-risk patients did not materially change the primary analysis results. The hd-PS sensitivity analysis yielded an estimate for COPD hospitalisations that was closest to the null at 0.62 (95% CI 0.51 to 0.76) (table 5). See online supplementary table S9a–S9c for baseline characteristics of patients in sensitivity analyses. The association of cardioselective BBs and each outcome was

similar across periods before 2000, between 2001–2005 and after 2006 (see online supplementary table S10).

### DISCUSSION

This large-scale, multinational study employed state-of-the-art pharmacoepidemiologic methods, including an active comparator, new user cohort design, PS trimming and hd-PS matching, and found potential evidence of bias when comparing cardioselective BBs and non-DHP CCBs in patients with ACS and COPD as reflected by an apparent large protective effect of cardioselective BBs on a short-term COPD hospitalisation outcome. The observed association was highly consistent across different methods used to address confounding and across the five databases encompassing diverse populations from different health systems. Cardioselective BBs were not associated with reduced risk of mortality or CV hospitalisations, although statistical heterogeneity was observed across data sources.

While there may be several reasons for the apparent large protective effect of cardioselective BBs on a short-term COPD hospitalisation outcome, we believe bias due

to unmeasured confounding is a major contributor. We cannot exclude the possibility that CCBs may worsen oxygenation and lead to an increased risk of COPD hospitalisations.<sup>46 47</sup> However, this likely would not fully explain the observed association. In addition, this large finding is not likely to be due to chance given that we observed consistent point estimates across databases and

statistical approaches and the CIs around the estimates were narrow. In expectation, if there is non-differential exposure or outcome misclassification, it would lead to bias towards the null and therefore it is unlikely to explain the observed findings. Moreover, our finding is unlikely to be explained by surveillance bias because healthcare professionals or patients themselves may be more attuned to respiratory-related effects when cardio-selective BBs are given. Any resulting bias would be in the opposite direction of the observed association. It is possible that, since clinicians are more likely to prescribe CCBs than BBs to patients with more severe COPD, an anchoring bias<sup>48</sup> could occur where CCB-treated patients may be more closely monitored for respiratory function and COPD exacerbations. However, our study outcomes were all defined by requiring hospitalisation, reducing the likelihood that such differential surveillance could fully explain the results. We did observe important differences between cardioselective BB and non-DHP CCB initiators at baseline. As compared to non-DHP CCB initiators, cardioselective BB initiators were younger, had less health resource utilisation and had less prior COPD medication use. While we were able to account for these differences in measured factors, we suspect that other important unmeasured risk factors for COPD hospitalisation remained imbalanced, such as differences in COPD severity and

**Table 4** Results for 30-day COPD hospitalisations comparing cardioselective BB versus non-DHP CCB initiators\*

Database	Crude HR (95% CI)	HR after PS matching (95% CI)
US Optum	0.28 (0.06 to 1.23)	1.33 (0.17 to 10.70)
US PACE	0.27 (0.15 to 0.47)	0.70 (0.31 to 1.54)
US PAAD	0.19 (0.09 to 0.37)	0.43 (0.18 to 0.99)
Italy RER	0.22 (0.10 to 0.48)	0.37 (0.16 to 0.84)
Taiwan NHI	0.28 (0.15 to 0.51)	0.67 (0.32 to 1.38)
Summary estimate	0.25 (0.18 to 0.34)	0.55 (0.37 to 0.82)

\*Based on the analysis that considered first exposure carried forward.

BBs,  $\beta$  blockers; COPD, chronic obstructive pulmonary disease; DHP CCBs, dihydropyridine calcium channel blockers; NHI, National Health Insurance; PAAD, Pharmacy Assistance for the Aged and Disabled; PACE, Pharmacy Assistance Contract for the Elderly; PS, propensity score; RER, Emilia-Romagna Region.

**Table 5** Results of sensitivity analyses comparing cardioselective BB versus non-DHP CCB initiators in three US databases\*

Type of analysis Database	Main analysis†	Sensitivity analysis			
		PS matching caliper of 0.005	Asymmetric PS trimming	hd-PS with additional 100 empirical covariates	Restricting to high-risk patients
HR after PS matching (95% CI)					
All-cause mortality					
US Optum	1.05 (0.65 to 1.68)	1.06 (0.65 to 1.73)	0.92 (0.54 to 1.56)	1.02 (0.61 to 1.72)	1.11 (0.53 to 2.33)
US PACE	0.86 (0.76 to 0.98)	0.85 (0.75 to 0.97)	0.85 (0.74 to 0.97)	0.86 (0.76 to 0.99)	0.91 (0.73 to 1.14)
US PAAD	1.12 (0.93 to 1.36)	1.13 (0.93 to 1.36)	1.00 (0.82 to 1.23)	1.16 (0.95 to 1.40)	1.02 (0.73 to 1.42)
Summary estimate	0.98 (0.80 to 1.21)	0.98 (0.78 to 1.23)	0.90 (0.80 to 1.00)	0.99 (0.78 to 1.26)	0.95 (0.80 to 1.14)
CV hospitalisations					
US Optum	0.96 (0.59 to 1.56)	0.92 (0.56 to 1.49)	0.81 (0.48 to 1.38)	0.99 (0.60 to 1.65)	0.70 (0.31 to 1.62)
US PACE	1.03 (0.87 to 1.22)	1.03 (0.86 to 1.22)	1.02 (0.85 to 1.23)	1.01 (0.84 to 1.21)	1.03 (0.76 to 1.39)
US PAAD	1.30 (1.03 to 1.65)	1.33 (1.04 to 1.69)	1.31 (1.01 to 1.69)	1.10 (0.86 to 1.43)	1.31 (0.82 to 2.10)
Summary estimate	1.11 (0.94 to 1.32)	1.11 (0.91 to 1.36)	1.08 (0.87 to 1.35)	1.04 (0.90 to 1.19)	1.06 (0.83 to 1.35)
COPD hospitalisations					
US Optum	0.54 (0.37 to 0.87)	0.59 (0.35 to 0.97)	0.67 (0.37 to 1.23)	0.77 (0.44 to 1.34)	0.61 (0.30 to 1.22)
US PACE	0.51 (0.39 to 0.67)	0.52 (0.40 to 0.67)	0.50 (0.37 to 0.66)	0.61 (0.46–0.80)	0.56 (0.39 to 0.81)
US PAAD	0.45 (0.32 to 0.62)	0.46 (0.33 to 0.64)	0.36 (0.25 to 0.51)	0.59 (0.41 to 0.84)	0.52 (0.31 to 0.88)
Summary estimate	0.50 (0.41 to 0.69)	0.51 (0.42 to 0.61)	0.47 (0.35 to 0.64)	0.62 (0.51 to 0.76)	0.56 (0.42 to 0.73)

\*Based on the analysis that considered first exposure carried forward.

†Main analysis used maximum PS matching caliper of 0.01, no PS trimming and a predefined PS model.

BBs,  $\beta$  blockers; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DHP CCBs, dihydropyridine calcium channel blockers; hd, high dimensional; NHI, National Health Insurance; PAAD, Pharmacy Assistance for the Aged and Disabled; PACE, Pharmacy Assistance Contract for the Elderly; PS, propensity score; RER, Emilia-Romagna Region.

smoking status, which therefore led to a bias due to unmeasured confounding. However, since these variables are not captured in claims data, we cannot verify this.

In terms of pharmacological effects of BB treatment, animal models and meta-analyses of published randomised trials do not support the notion that BB treatment can have such a large and immediate effect on respiratory function.<sup>35–38</sup> A prior study did not observe significant differences in pulmonary function or symptoms of wheezing or dyspnoea after acute administration of BB treatment in patients with cardiac disease and COPD.<sup>49</sup> Our study, however, showed an apparent 45% reduction in COPD exacerbations comparing cardioselective BB to non-DHP CCB, which is similar to the 40% reduction observed in other observational studies in which BB use was compared to non-BB use.<sup>12 15 17 18 20 21 23</sup> This apparent benefit associated with BB treatment is even considerably larger than that conferred by the most effective known treatment—long-acting bronchodilators—which reduce COPD hospitalisations by only 14–17%.<sup>50 51</sup> An ongoing randomised, double-blind, placebo-controlled trial is examining whether BB treatment can prevent COPD exacerbations.<sup>52</sup> The results will help determine the extent to which the observed association between BB treatment and reduced COPD hospitalisation is due to actual clinical benefits of BBs versus bias in observational studies. Our study suggests the latter to be a major contributor.

A prior meta-analysis of observational studies suggested that BB use was associated with a 36% reduction in mortality in patients with coronary diseases and COPD.<sup>23</sup> However, our PS-matched as-treated analysis of mortality yielded an HR of 0.80 (95% CI 0.67 to 0.96) and our PS-matched first exposure carried forward analysis yielded an HR of 0.90 (95% CI 0.78 to 1.02). Our results also suggested no benefit of cardioselective BBs on CV hospitalisations. These findings were similar to a recent population-based observational study that included 107 902 patients with COPD (only 3% of whom having concomitant MI diagnosis) and found no difference in CV hospitalisations (HR, 0.98 (95% CI 0.94 to 1.03)) and CV mortality (HR, 1.05 (95% CI 0.97 to 1.13)) between cardioselective BBs and non-DHP CCBs.<sup>53</sup> An important difference between our study and most prior studies is that we used an active comparator group of non-DHP CCB initiators whereas most other studies compared BB users to non-users. To the best of our knowledge, only one published randomised trial has compared the efficacy of cardioselective BBs and non-DHP CCBs in patients with MI, who also had hypertension, and found similar results for mortality (HR, 1.01 (95% CI 0.87 to 1.16)) and MI (HR, 0.97 (95% CI 0.80 to 1.18)).<sup>54</sup> Our mortality and CV hospitalisation results are in line with comparable bradycardic effects between cardioselective BBs and non-DHP CCBs and are similar to those of the trial; however, given the potential unmeasured confounding observed for the short-term

COPD hospitalisation outcome, our results are likely biased downward to the extent that COPD severity and smoking status, if imbalanced between treatment groups, are also risk factors for mortality and CV hospitalisations.<sup>5 55</sup>

A strength of our multinational study is that it permits examination of heterogeneity in results across databases and across countries. While the overall summary estimate did not indicate a survival benefit comparing cardioselective BBs to non-DHP CCBs, the database-specific HRs for mortality in the US PACE and Italy RER databases were 0.86 (95% CI 0.76 to 0.98) and 0.74 (95% CI 0.64 to 0.85), respectively. These findings are similar to those of some prior observational studies.<sup>14 16</sup> While it is possible that this variation in results may be due to true heterogeneity in treatment effects across databases and populations, publication of these results in isolation could have led to very different and potentially misleading conclusions. The multidatabase approach protects against this potential problem. As prescribing patterns and patient characteristics vary across different health systems and geographical areas, true treatment effects and confounding can also vary across databases. Results can also vary across studies due to differences in design and analytic choices. In contrast to meta-analyses, which usually combine results from various study designs, our approach using a common protocol eliminates differences in design and analytic choices as an explanation for differences in results across databases.

Our study had several additional limitations. First, while we used a common protocol to implement our study across databases, the inherent variations in health-care systems and data structures across countries necessitated certain database-specific modifications to the protocol. For example, some databases required different definitions for continuous enrolment and different coding methods for ascertainment of drug use. Also, we could only access information on inpatient diagnoses in the RER database, which likely resulted in the identification of a more severe COPD population than in the other databases. Moreover, information on drug days supply was not available in the RER database, which we inferred based on the defined daily dose. Second, as drug data during hospitalisation are usually not available in healthcare claims databases, we could not accurately capture inpatient drug information in all five databases. Also, patients may not fully adhere to their index drugs and may add or switch medications during follow-up. However, our first exposure carried forward and as-treated analyses yielded similar results, which partially mitigates concerns about exposure misclassification. Third, owing to analytic flexibility, we conducted sensitivity analyses in the three US databases only. However, results restricted to these three databases were similar to the main analyses, which also included the RER and Taiwan NHI databases. In addition to COPD severity and smoking status, we could not rule out the influence of unmeasured confounding from other clinical parameters, such as cardiac function. Finally, previous

research suggests that non-DHP CCBs may increase the risk of CHF in patients experiencing acute MI,<sup>56</sup> which may limit non-DHP CCBs as a comparison group.

In conclusion, this multinational study found a strong inverse association between cardioselective BB use and COPD hospitalisations, even in the first 30 days of follow-up, suggestive of bias likely due to unmeasured confounding. This apparent bias persisted across diverse populations and health systems and could not be fully removed by state-of-the-art design and analysis methods. This finding calls into question the validity of prior observational studies of the effectiveness of BBs and also the ability of claims data, in general, to address questions related to outcomes of BBs in COPD patients. Data from randomised trials are needed to elucidate the benefits and risks of BBs in patients with COPD.

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**Contributors** Y-HD, MA, VM, C-HC, M-SL and JJG designed the study. VM, M-SL and JJG acquired data. Y-HD, MA, JL, ML and L-CW analysed data. Y-HD, MA, VM, C-HC, M-SL and JJG interpreted data. Y-HD and JJG drafted the manuscript. MA, VM, JL, ML, L-CW, C-HC and M-SL provided critical suggestion on the manuscript.

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