INTRODUCTION

The use of beta-blockers has been shown to reduce morbidity and mortality in patients with coronary artery disease (CAD), and is therefore recommended for secondary prevention by the European Society of Cardiology. Patients with cardiovascular diseases with co-diagnosis of chronic obstructive disease (COPD) have a higher risk of hospitalization and mortality. Beta-blockers are less frequently prescribed in these patients due to concerns about deterioration of lung function or acute bronchospasm. Epidemiological studies from the UK and Sweden have shown an underuse of beta-blockers in this particular patient group. Multiple retrospective studies including a meta-analysis of observational studies support these findings.

Key terms: beta-blocker, CAD, COPD, drug utilization, mortality, pharmaco-epidemiology
Despite these concerns over pulmonary adverse effects, there is growing evidence that cardio-selective beta-blockers are beneficial in the treatment of patients with CAD and co-diagnosis of COPD. Previous studies have shown an improvement in overall mortality and, importantly, also a reduction in the frequency of obstructive pulmonary exacerbations. However, there is very little information available about the use of beta-blockers and the clinical impact in patients with CAD and COPD in Austria and in other European countries.

The aim of the present study was to investigate epidemiological data on beta-blocker use in patients hospitalized with CAD in Austria in 2006 and 2007. Furthermore, we aimed to study the association between beta-blocker use and overall mortality in patients with CAD and co-diagnosis of COPD. To this end, we utilized prescription, demographic data and information on hospital discharges with primary diagnoses coded by the International Classification of Diseases (ICD) system and disease-specific drugs coded by the Anatomical Therapeutic Chemical (ATC) Classification System.

2 | MATERIALS AND METHODS

2.1 | Study population

In Austria, data from medical services covered by the health insurance funds are stored in the respective databases. These include demographic data, information on hospital discharges with primary diagnoses coded using the ICD-system and reimbursed drug prescriptions. Each medication is described by the unique Austrian pharmaceutical registration number and linked to the ATC Classification System. We analyzed data from Austrian health insurance funds covering about 95% of the Austrian population in the years 2006 and 2007. The observation period was defined from January 1, 2006 until December 31, 2007. Data were pseudonymized to preserve patients’ privacy. Data storage and handling were in agreement with privacy laws. This study was approved by the Ethics Committee of the Medical University of Vienna. (EK #1131/2013).

All patients aged 18 years or older who were discharged from a hospital with the principal diagnosis of CAD were eligible for this study. Presence of CAD was defined as acute myocardial infarction (ie, I21 including sub-codes), subsequent myocardial infarction (ie, I22 including sub-codes), or chronic ischaemic heart disease (ie, I25 including sub-codes) by ICD-10. Among these patients, the co-diagnosis of COPD was identified by ICD-10 code J44 including sub-codes. Co-diagnosis of diabetes was defined by ICD-10 codes E10-E14 including sub-codes and ATC-codes as described in Rinner et al.

2.2 | Statistical analysis

Metric variables are described by median and interquartile ranges (IQR), and categorical variables by absolute and relative frequencies. As index hospitalization, we used the first data recorded for hospitalization in 2006 and excluded these data from the analysis of patients hospitalized in 2007. The duration of drug intake was defined as the time between the first and last recorded prescription. Based on this definition, drug survival was estimated using the product-limit method, censoring for death and end of data availability. The distribution of time to death was estimated using the product-limit method, censoring for end of data availability. As starting point for survival analyses, we used 30 days after the first prescription after index hospital discharge, whichever occurred later. For comparisons of nonparametric data between patients with and without COPD chi-square tests were used (Yates’ corrected chi-square for all 2 x 2 tables). We performed a multivariate analysis of survival using Cox’s model of the proportional hazards regression. The free statistic framework R was used for statistical analysis. All given P-values are 2-tailed and P-values < .05 were considered statistically significant.

3 | RESULTS

Patient data including sex, co-morbidity, and age for 2006 and 2007 are presented in Table 1. Beta-blocker use is illustrated by substance in patients with CAD with or without co-diagnosis of COPD in Table 2. In total patients had a mean number of 29 hospitalization days.

In 2006, 34923 patients (38% female, 62% male) were discharged with a diagnosis of CAD. Among these subjects, 16275 had a co-diagnosis of COPD, 8673 had diabetes, and 26669 received beta-blockers. Figure 1 illustrates patient diagnosis, beta-blocker treatment, and six months mortality in 2006. In total, 2130 (6.1%) patients died within 30 days after the index hospitalization and 3519 (10.1%) died during six months of observation. The six-month mortality of patients with and without COPD was similar with 10.5% and 9.7%, respectively.

Among patients with co-diagnosis of COPD, 6.9% of beta-blocker users and 22.6% of nonusers died within an observation period of six months. In the group of patients without COPD 5.4% of beta-blocker users and 23.1% of nonusers died within six months. Six-month mortality of patients with and without COPD and diabetes was 10.8% and 16.5%, respectively.

In 2007, 30 794 (37% female, 63% male) patients were discharged with a diagnosis of CAD. Among these subjects, 13 842 had a co-diagnosis of COPD, 7360 had diabetes, and 22 797 received beta-blockers. Figure 2 illustrates patient diagnosis, beta-blocker treatment, and six months mortality in 2007. In total, 1999 (6.5%) died within 30 days after the index hospitalization and 3241 (10.5%) died after six months of observation.

The six-month mortality of patients with and without COPD was with 12.5% and 8.9%, respectively.
Among patients with co-diagnosis of COPD, 9.6% of beta-blocker users and 21.4% of nonusers died within an observation period of six months. In the group of patients without COPD, 5.8% of beta-blocker users and 17.4% of nonusers died within six months. Six-month mortality of patients with and without COPD and diabetes was 13.4% and 16.5%, respectively.

The multivariate survival analysis revealed gender, age, co-diagnosis of diabetes, and COPD as independent predictors of survival (Tables 3 and 4). In 2006 and 2007, age over 60 years, and diabetes increased the risk of death \((P < .001)\). In 2006, co-diagnosis of COPD was positively associated with mortality \((P < .001)\) after 30 days and six months of observation period, but not in 2007.

### 4 | DISCUSSION

This retrospective, nationwide epidemiological study on beta-blocker utilization in patients with CAD and co-diagnosis of COPD reveals three major findings. Firstly, our results show that less than 80% of patients with CAD received beta-blockers. This underuse is similar to results obtained in 2003, when 72% of patients with acute myocardial infarction received beta-blockers in Austria. Likewise, the EUROASPIRE III survey has reported that beta-blockers were used in only 80% of patients with CAD in 2006 and 2007. This low utilization of beta-blockers continues in the EUROASPIRE IV survey, which was conducted from 2007 to 2012 and indicates that beta-blockers are still under-prescribed in European countries. In the present study, CAD was defined as acute myocardial infarction (ie, I21 including sub-codes), subsequent myocardial infarction (ie, I22 including sub-codes), or chronic ischaemic heart disease (ie, I25 including sub-codes) by ICD-10. We did not have further information on STEMI or NSTEMI diagnosis or on performed interventions. Compared to our retrospective cohort study, Campo et al investigated data from the selected group of patients with a diagnosis of ST-elevation...
myocardial infarction undergoing mechanical reperfusion (REAL registry). Seronde et al studied the mortality of patients with acute myocardial infarction (FAST-MI). This distinct discrepancy in our results may therefore be due to the selection of patients and diagnosis in these registry studies, when compared with our unselected retrospective cohort study of patients with CAD.

These lower numbers of beta-blocker utilization in patients with CAD are consistent with results obtained in patients with heart failure. The EuroHeart Failure Survey II reported that 61% of patients with heart failure had a beta-blocker prescription by the end of August 2005. In Austria, 70% of patients discharged with a diagnosis of heart failure between 2006 and 2010 received a prescription of a beta-blocker, but the adherence was low and in the range of 40%. In this group of patients, however, an increased beta-blocker prescription has been reported recently. Secondly, our results show a similar percentage of beta-blocker prescription in patients with CAD with or without co-diagnosis of COPD. This has also been reported in a Swedish study, and suggest that at least in some European countries a similar pattern of beta-blocker prescription is in use in patients with CAD and COPD. As expected, the prescription of nonselective beta-blockers was small compared to other medicines of this class (Table 2). The prescriptions of beta-blockers vary greatly across European countries, as indicated from a previous study in the UK, where less than 40% of patients with CAD and co-diagnosis of COPD received beta-blockers.

Thirdly, patients with CAD and beta-blocker prescription had a reduced mortality, which is in agreement with results from our previous study. This was also seen in patients with co-diagnosis of COPD with an almost linear reduction in cumulative overall mortality 30 days after index hospital discharge (Figure 3). This reduced mortality was similar across

**FIGURE 1** Patient diagnosis, beta-blocker prescription, and six-month mortality in 2006
patients with CAD with or without COPD (Figures 3 and 4). Multiple retrospective studies on beta-blockers support our findings. We have not explored whether this salutary effect of beta-blocker extends across all different chemical substances to a similar degree or can be considered as class effect.

An additional finding is that co-diagnosis of diabetes was found more often in COPD patients as compared to patients without COPD. This is in line with an epidemiological cardiovascular health study, which demonstrated that patients with COPD stage GOLD≥II had a higher risk of diabetes. The correlation of COPD and co-morbidity of diabetes and CV disease has been associated with systemic inflammation. However, comparing our results with similar previous studies, we found that diabetes was significantly more frequent in patients with COPD in Austria. The reason for this disproportionate occurrence of co-diagnosis of diabetes is unclear. Systemic steroid therapy had no impact in the incidence of co-diagnosis of diabetes.

4.1 Limitations

There are several limitations in our study. ICD-10 coding of hospital discharge diagnosis was used to identify CAD patients in the database. It has been reported that this approach may underestimate the number of patients with CAD. This is considered unlikely in our database as disease-specific drugs were also taken into account. One should note that more than 20% of CAD patients had no beta-blocker prescription. Confounding may also arise from limited information on co-morbidities from primary ICD diagnoses and disease-specific drugs. Another major limitation is the lack of data on COPD severity or measurements of pulmonary function, which are not included in the claims database of the health insurance funds. In addition, smoking prevalence and incidence is very high in Austria compared to other European countries and therefore a possible reason for the high incidence of COPD in our study. In addition, our data does not provide information on exacerbation frequency, which also has an important
### TABLE 3  Multivariate survival analysis for sex, co-diagnosis of COPD and diabetes in 2006

|                | After 30 days |            |            |                | After 6 months |            |            |
|----------------|--------------|------------|------------|----------------|----------------|------------|------------|
|                | HR           | 95% CI     | p-value    | HR             | 95% CI         | p-value    |
| Sex (female)   | .95          | (.87-1.04)  | .281       | .97            | (.91-1.04)     | .399       |
| COPD           | .72          | (.65-0.79)  | <.001      | .85            | (.78-0.91)     | <.001      |
| Diabetes       | 1.46         | (1.30-1.63) | <.001      | 1.44           | (1.32-1.57)    | <.001      |
| Age            |              |            |            |                |                |            |
| ≤39 years      | .58          | (.28-1.20)  | .143       | .57            | (.30-1.08)     | .085       |
| 40-49 years    | .77          | (.52-1.15)  | .203       | .77            | (.55-1.07)     | .123       |
| 50-59 years    | 1            |            |            |                |                |            |
| 60-69 years    | 1.59         | (1.27-2.00) | <.001      | 1.87           | (1.55-2.26)    | <.001      |
| 70-79 years    | 3.14         | (2.54-3.88) | <.001      | 3.69           | (3.10-4.40)    | <.001      |
| 80-89 years    | 6.33         | (5.14-7.80) | <.001      | 8.00           | (6.73-9.50)    | <.001      |
| >90 years      | 12.04        | (9.57-15.15)| <.001      | 16.32          | (13.49-19.74)  | <.001      |

Abbreviations: CI, confidence interval; HR, hazard ratio.

### TABLE 4  Multivariate survival analysis for sex, co-diagnosis of COPD and diabetes in 2007

|                | After 30 days |            |            |                | After 6 months |            |            |
|----------------|--------------|------------|------------|----------------|----------------|------------|------------|
|                | HR           | 95% CI     | p-value    | HR             | 95% CI         | p-value    |
| Sex (female)   | 1.05         | (.96-1.15)  | .302       | 1.02           | (.95-1.02)     | .48        |
| COPD           | .87          | (.79-0.97)  | .010       | 1.08           | (.99-1.17)     | .059       |
| Diabetes       | 1.66         | (1.49-1.86) | <.001      | 1.51           | (1.39-1.65)    | <.001      |
| Age            |              |            |            |                |                |            |
| ≤39 years      | .39          | (.12-1.25)  | .115       | .41            | (.15-1.11)     | .081       |
| 40-49 years    | .52          | (.31-0.88)  | .015       | .64            | (.42-0.96)     | .033       |
| 50-59 years    | 1            |            |            |                |                |            |
| 60-69 years    | 1.85         | (1.44-2.37) | <.001      | 1.99           | (1.62-2.45)    | <.001      |
| 70-79 years    | 3.19         | (2.52-4.03) | <.001      | 3.91           | (3.22-4.76)    | <.001      |
| 80-89 years    | 8.27         | (6.59-10.37)| <.001      | 10.15          | (8.38-12.30)   | <.001      |
| >90 years      | 14.27        | (11.10-18.34)| <.001     | 19.84          | (16.20-24.47)  | <.001      |

Abbreviations: CI, confidence interval; HR, hazard ratio.

**FIGURE 3** Overall survival of patients with CAD and without co-diagnosis of COPD grouped by use of beta-blockers during an observation period of six months (pooled data for 2006 and 2007)

**FIGURE 4** Overall survival of patients with CAD and with co-diagnosis of COPD grouped by use of beta-blockers during an observation period of six months (pooled data for 2006 and 2007)
impact on patient’s survival.15,26,33 Furthermore, we were not able to assess adherence to the medications for which prescriptions were filled. Our database only contains information about the first and last prescription of medication for each patient. Thus, two independent treatment periods are considered as one single, long treatment period, potentially resulting in an overestimation of the duration of treatment and proportion of days covered. For 2006, we did not have access to data of patients from 2005 and therefore could not adjust the number of patients to “match” for preexisting diagnosis of CAD.

5 | CONCLUSION

The results of this epidemiological study suggest that beta-blockers are under-prescribed in CAD patients in clinical practice. Patients with CAD and co-diagnosis of COPD had a similar percentage of beta-blocker prescription and this use is associated with reduced mortality. Patients with CAD and co-diagnosis of COPD more often present with diabetes co-medication.

ACKNOWLEDGMENT

We want to thank the Main Association of Austrian Social Security Institutions and especially Gottfried Endel for granting us access to their database.

CONFLICT OF INTEREST

All authors report no financial support or relationships that could be construed as a conflict of interest.

AUTHOR CONTRIBUTIONS

All authors discussed the results and contributed to the final manuscript.

Planning and conducting the study: Rezaei, Woltz
Wrote the paper with input from all authors: Rezaei
Data preparation: Rinner, Ratajczak, Grossmann
Performed statistical tests: Rinner, Ratajczak
Collected data: Ratajczak
Supervised statistical methods: Grossmann, Gall
Interpretation of the results: Grossmann, Gall
Supervised the project: Woltz

ETHICS

This study was approved by the Ethics Committee of the Medical University of Vienna (EK #1131/2013).

ORCID

Safoura Sheikh Rezaei http://orcid.org/0000-0002-1310-3151

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How to cite this article: Rezai SS, Rinner C, Ratajczak P, Grossmann W, Gall W, Wolzt M. Use of beta-blocker is associated with lower mortality in patients with coronary artery disease with or without COPD. Clin Respir J. 2018;12:2627–2634. https://doi.org/10.1111/crj.12968