

Tiotropium Respimat® vs. HandiHaler®: real-life usage and TIOSPIR trial generalizability

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- After the TIOSPIR trial, there were still some safety concerns regarding tiotropium Respimat® in, for example, cardiovascular patients.
- Comparing characteristics of patients receiving tiotropium Respimat® or HandiHaler® is crucial in identifying populations at risk.
- Up to now, generalizability of TIOSPIR trial results to a real-life population is unclear, hampering risk–benefit weighting.

AIM

Two inhaler devices (Respimat® and HandiHaler®) are available for tiotropium, a long acting anticholinergic agent. We aimed to analyze drug utilization, off-label usage and generalizability of the TIOSPIR trial results for both devices.

METHODS

Patients aged ≥18 years exhibiting at least one documented prescription of tiotropium in the database of the Association of Statutory Health Insurance Physicians, Bavaria, Germany, were included (years 2004–2008). Annual period prevalence rates (PPRs) were calculated stratified by age, gender and inhaler devices. Off-label usage (patients lacking a chronic obstructive pulmonary disease (COPD) diagnosis) and the proportion of patients meeting the inclusion and exclusion criteria of the TIOSPIR trial were analyzed.

RESULTS

Between 2004 and 2008, PPRs increased and varied between 49.2 and 74.5 per 10 000 persons for HandiHaler® and between 1.5 and 9.3 per 10 000 persons for Respimat®. Small differences regarding patient characteristics existed between the two inhaler devices. Only about 30% (HandiHaler® 32.1%, Respimat® 30.0%) of the database patients receiving tiotropium could be theoretically included in the TIOSPIR trial.

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WHAT THIS STUDY ADDS

- In a claims database covering 10.5 million patients, similar characteristics were found comparing patients receiving Respimat® or HandiHaler®.
- For both devices, only about 30% of patients receiving tiotropium could be potentially included in the TIOSPIR trial.
- Further studies examining safety concerns in 'real-life' patients receiving tiotropium are crucial.

CONCLUSIONS

Comparing the two tiotropium devices, no clinically relevant differences regarding patient and prescribing characteristics were revealed. Results of the TIOSPIR trial were generalizable only to a minority of our study patients, underlining the need for real-life data.

Introduction

Tiotropium, a long acting anticholinergic compound, is recommended as controller medication for patients suffering from chronic obstructive pulmonary disease (COPD) [1]. Two different tiotropium inhaler devices are available on the market, dry powder inhalation (DPI, HandiHaler®), which was authorized in the European Union in 2002 and Soft Mist™ inhaler (SMI, Respimat®), which was approved in 2007. The recommended daily dose for Respimat® is 5 µg compared with 18 µg for HandiHaler®, as the Respimat® aerosol contains a higher fraction of fine particles leading to higher pulmonary drug deposition. Comparing the systemic exposure in patients receiving tiotropium by Respimat® or HandiHaler®, pharmacokinetic data are somewhat conflicting [2–4]. In addition, safety data comparing both inhaler devices are also oppositional. In a cohort study, an increased risk of all-cause mortality and cardiovascular/cerebrovascular death was found for patients using Respimat® compared with HandiHaler®, particularly in patients exhibiting coexisting cardiovascular diseases [5]. Similarly, a meta-analysis revealed an increased risk of overall death for patients using Respimat® compared with HandiHaler®, with more evident risk increases for cardiovascular death in patients with severe COPD and at higher daily doses of tiotropium [6].

In contrast, in a recently published randomized controlled trial (RCT, i.e. TIOSPIR), two Respimat® dosages (2.5 µg or 5 µg once daily) were not inferior to HandiHaler® (18 µg once daily) regarding the mortality risk [7]. Nevertheless, an increased risk of adjudicated myocardial infarctions was detected when both Respimat® dosage groups were combined by conducting a re-analysis of the TIOSPIR trial [8]. In addition, the TIOSPIR trial's generalizability was critically discussed owing to, for example, excluding patients with renal impairment or cardiac comorbidities [9], but detailed analyses focusing on real-life population coverage are lacking [10].

The objectives of our study were twofold, first, to assess the real-life usage of both tiotropium devices and to identify patients potentially having an increased risk of safety issues by comparing patient characteristics of Respimat® or HandiHaler® users with regard to age, gender, indication (off-label use by indication), cardiovascular and respiratory comorbidities, and co-medication in a large German database and second, to assess the generalizability of the TIOSPIR trial by quantifying the proportion of database patients theoretically meeting the inclusion and exclusion criteria of the TIOSPIR trial.

Methods

Study design and data source

A drug utilization study was conducted including the years 2004–2008 in the database of the Association of Statutory Health Insurance Physicians, Bavaria, Germany ('Kassenärztliche Vereinigung Bayerns', KVB) [11]. This population-based database was established in 2001 and covers approximately 85% (i.e. 10.5 million people) of the Bavarian population (excluding those with private insurance). It contains all accounting information from Bavarian physicians including outpatient data on diagnoses, medical services performed and drug utilization of statutory health insurance patients. All diagnoses from general practitioners and specialists are recorded quarterly (i.e. the quarter but not the precise date is documented for each diagnosis or prescription). A patient is documented in the database only when consulting a physician. Pharmaceuticals are recorded only if they were prescribed and filled at the pharmacy. The German modification of the International Statistical Classification of Diseases and Related Health Problems (ICD-10-GM) was used for coding diagnoses and the Anatomical Therapeutic Chemical (ATC) classification system was used for coding drugs. All analyses were performed using anonymized data. Neither German law nor the professional code of conduct for physicians requires

an ethical review for research with routinely collected anonymized data.

Study population

Patients aged ≥ 18 years having at least one documented prescription of tiotropium HandiHaler® (central pharmaceutical numbers (CPN) 02286532, 01686873, 02286549, 03649221) or tiotropium Respimat® (CPN 04913588, 04913594, 04913625) within the study period were included in the analysis. The study entry date was defined as the quarter of the first tiotropium prescription in the study period.

Definition of off-label use, comorbidities and co-medication

Patients exhibiting at least one documented COPD diagnosis in the study period (irrespective of any other additional respiratory diagnoses) were considered as 'on-label' patients. Taking into account the labelling status of tiotropium during the study period, all other patients were considered as off-label users. Patients exhibiting a diagnosis coded with one-digit ICD-10-GM code 'I' in their medical history were considered as patients suffering from cardiovascular comorbidity. Additionally, patients with a documented diagnosis of heart failure (ICD-10-GM code I50), chronic ischaemic heart disease (I25) and arrhythmias including atrial fibrillation and flutter (I48), and other cardiac arrhythmias (I49) were defined as patients with a cardiovascular comorbidity of particular interest. Cardiovascular drugs (ATC one-digit: 'C') were analyzed stratified by therapeutic groups (ATC three digits). Drug classes were considered for respiratory co-medication as follows: selective β_2 -adrenoreceptor agonists (R03AC), adrenergics and other drugs for obstructive airway diseases (R03AK), anticholinergics (R03BB), systemic selective β_2 -adrenoreceptor agonists (R03CC), xanthines (R03DA), and xanthines and adrenergics (R03DB).

TIOSPIR trial

In the TIOSPIR trial, some seven inclusion and 29 exclusion criteria were applied to define the study population [12]. In total, 21 of these criteria were reproducible in our database. Lung function parameters, for example, remained undocumented in the Bavarian database, whereas other criteria (e.g. comorbidities) were available in most cases (e-Table 1). A sensitivity analysis was performed using additional ICD-10-GM codes for the exclusion criteria 'Myocardial infarction within the last 6 months' (I25.21), 'Hospitalization for cardiac failure (NYHA Class III or IV) during the last year' (I50.13) and 'Known significant symptomatic prostatic hyperplasia or bladder-neck obstruction. Subjects whose symptoms were controlled on treatment may have been included' (N40).

Statistical analysis

All metric and normally distributed variables were reported as mean $\pm$ standard deviation (SD). Non-normally distributed variables were presented as median (first quartile–third quartile). Categorical variables were presented as frequency and percentage. For the comparison of groups, the Mann–Whitney U-test was used for metric variables and the chi-square test or Fisher's exact test for categorical variables. *P* values < 0.05 were considered statistically significant.

Annual period prevalence rates (PPRs) were calculated using the number of patients with at least one prescription of interest during the year of interest (numerator) divided by the total number of compulsorily insured Bavarians at midyear of the year of interest (1 July; denominator). Annual PPRs per 10 000 persons were calculated stratified by age (10 year age groups [18–19 years, 20–29 years, 30–39 years [...], ≥ 90 years]), gender and inhaler device. As Respimat® was launched on the European market in 2007, analyses for this device are restricted to the years 2007 and 2008, whereas the HandiHaler® PPR-related analyses were conducted for the whole study period (2004–2008). Detailed analyses regarding for example comorbidities and co-medication were conducted for the year 2008 only.

Results

Drug utilization

In 2008, some 69 812 patients (approximately 0.7% of all insured people) were treated with tiotropium (Table 1). Almost 89% of these patients used tiotropium via HandiHaler®. Respimat® users were slightly younger (67.9 ± 12.3 years) than patients using HandiHaler® (69.5 ± 12.2 years; $P < 0.0001$). The proportion of females was higher in Respimat® compared with HandiHaler® users (46.9% vs. 44.6%; $P < 0.0001$). The highest PPRs were found in patients aged between 70 and 79 years (2004–2006) and 80 and 89 years (2007–2008) for HandiHaler® and between 80 and 89 years for Respimat® (2007–2008; e-Table 2).

PPR increase was revealed for both inhaler devices within the study period. The PPRs varied between 49.2 and 74.5 per 10 000 persons for HandiHaler® (2004–2008) and between 1.5 and 9.3 per 10 000 persons for Respimat® (2007–2008; e-Table 2). For both devices, PPRs for males were higher than those for females (Figure 1). Regarding age groups, the most prominent PPR increase for HandiHaler® was found in patients aged at least 80 years (80–89 years: +97.7%; ≥ 90 years: +154.1%) compared with Respimat® patients aged ≥ 90 years (+1217.2%; e-Table 2).

Comorbidities and co-medications

In 2008, the proportion of patients with at least one cardiovascular disease (ICD-10-GM code 'I') in their medical

Table 1

Baseline characteristics stratified for inhaler device (year 2008)

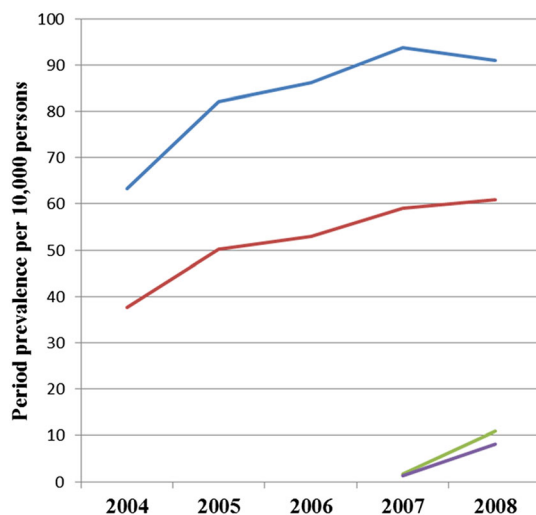
				HandiHaler®	RespiMat®
Patient characteristics					
Total (patients)				62 036	7776
Proportion of females (<i>n</i> [patients], %)				27 641 (44.6%)	3649 (46.9%)
Age (years) (mean ± SD)				69.5 ± 12.2	67.9 ± 12.3
Cardiovascular comorbidities					
Patients with at least one cardiovascular comorbidity (<i>n</i> [patients], %)				54 308 (87.5%)	6586 (84.7%)
Patients with at least one cardiovascular comorbidity of particular interest (<i>n</i> [patients], %)				32 632 (52.6%)	3679 (47.3%)
Five most frequent cardiovascular comorbidities (<i>n</i> [patients], %)				Essential (primary) hypertension (41 052 [75.6%])	Essential (primary) hypertension (4838 [73.5%])
				Chronic ischaemic heart disease (18 995 [35.0%])	Chronic ischaemic heart disease (2108 [32.0%])
				Heart failure (17 731 [32.6%])	Heart failure (1862 [28.3%])
				Varicose veins of lower extremities (10 209 [18.8%])	Varicose veins of lower extremities (1213 [18.4%])
				Atrial fibrillation and flutter (9357 [17.2%])	Other cardiac arrhythmias (1094 [16.6%])
Cardiovascular co-medication					
Patients with at least one cardiovascular co-medication (<i>n</i> [patients], %)				47 095 (75.9%)	5311 (68.3%)
Cardiovascular co-medication (<i>n</i> [patients], %)	Cardiac therapy (C01)			11 376 (18.3%)	1126 (14.5%)
	Antihypertensives (C02)			2611 (4.2%)	247 (3.2%)
	Diuretics (C03)			25 612 (41.3%)	2485 (32.0%)
	Peripheral vasodilators (C04)			935 (1.5%)	93 (1.2%)
	Vasoprotectives (C05)			1226 (2.0%)	135 (1.7%)
	β-adrenoceptor blocking agents (C07)			17 368 (28.0%)	1858 (23.9%)
	Calcium channel blockers (C08)			14 263 (23.0%)	1497 (19.3%)
	Agents acting on the renin–angiotensin system (C09)			31 557 (50.9%)	3413 (43.9%)
	Lipid modifying agents (C10)			15 001 (24.2%)	1517 (19.5%)
	Respiratory co-medication				
Patients with at least one respiratory co-medication (<i>n</i> [patients], %)				46 339 (74.7%)	5541 (71.3%)
Respiratory co-medication (<i>n</i> [patients], %) [at least 1% in one group]	Inhaled short acting β ₂ -adrenoceptor agonists	Salbutamol		14 384 (23.2%)	1889 (24.3%)
		Fenoterol		2736 (4.4%)	361 (4.6%)
	Inhaled short acting β ₂ -adrenoceptor agonist combinations	Fenoterol and cromoglicic acid		9551 (15.4%)	1352 (17.4%)
		Reproterol and cromoglicic acid		445 (0.7%)	78 (1.0%)
	Oral short acting β ₂ -adrenoceptor agonist combinations	Clenbuterol and ambroxol		1149 (1.9%)	168 (2.2%)
	Inhaled short acting anticholinergics	Ipratropium		3237 (5.2%)	490 (6.3%)
	Inhaled long acting β ₂ -adrenoceptor agonists	Salmeterol		832 (1.3%)	101 (1.3%)

(Continues)

Table 1

(Continued)

		HandiHaler®	Respimat®
Inhaled long acting β_2 -adrenoceptor agonist combinations	Formoterol	12 922 (20.8%)	1248 (16.0%)
	Salmeterol and fluticasone	10 595 (17.1%)	1251 (16.1%)
	Formoterol and beclometasone	2775 (4.5%)	612 (7.9%)
	Formoterol and budesonide	12 046 (19.4%)	1169 (15.0%)
Xanthines	Theophylline	12 975 (20.9%)	1413 (18.2%)
Leukotriene receptor antagonists	Montelukast	1222 (2.0%)	195 (2.5%)
Inhaled corticosteroids	Beclomethasone	1807 (2.9%)	282 (3.6%)
	Budesonide	7284 (11.7%)	783 (10.1%)

**Figure 1**

Period prevalence rates per 10 000 persons stratified by inhaler device and gender. — HandiHaler® males, — HandiHaler® females, —, Respimat® males, — Respimat® females

history was slightly higher in patients using HandiHaler® (87.5%) compared with Respimat® (84.7%; $P < 0.0001$; Table 1). Limiting the prevalence analysis to patients with at least one cardiovascular comorbidity of particular interest (heart failure, chronic ischaemic heart disease, atrial fibrillation and flutter, and other cardiac arrhythmias), the respective values were 52.6% (HandiHaler®) and 47.3% (Respimat®, $P < 0.0001$). For both patient

groups, essential hypertension, chronic ischaemic heart disease and heart failure were the most frequent cardiovascular diseases with higher prevalence rates in patients using HandiHaler®.

The proportion of patients receiving at least one cardiovascular co-medication was higher in HandiHaler® patients (75.9%) than in Respimat® patients (68.3%; $P < 0.0001$). For both devices, the most frequent cardiovascular compound was 'agents acting on the renin-angiotensin system' (HandiHaler® $n = 31\,557$ (50.9%); Respimat® $n = 3413$ (43.9%)), whereas the most frequently prescribed respiratory co-medications were salbutamol (HandiHaler® $n = 14\,384$ (23.2%); Respimat® $n = 1889$ (24.3%)) and theophylline (HandiHaler® $n = 12\,975$ (20.9%); Respimat® $n = 1413$ (18.2%); Table 1)).

Off-label use

The proportion of patients with off-label HandiHaler® prescriptions was highest in 2004 ($n = 5590$ patients (13.9%)) and lowest in 2006 ($n = 6077$ (10.9%); Table 2). A small increase in the proportion of patients with off-label prescriptions was revealed for Respimat® from 10.5% ($n = 130$) in 2007 to 14.0% ($n = 1086$) in 2008 (Table 2).

Regarding age groups, we found the highest proportion of patients receiving off-label prescriptions for HandiHaler® in the youngest age groups (18–19 years: 51.5–82.4%; 20–29 years: 46.6–53.0%), whereas the

Table 2

Number and proportion of patients with on-label and off-label prescriptions stratified by inhaler device

Year	HandiHaler® (n, %)		Respimat® (n, %)	
	On-label	Off-label	On-label	Off-label
2004	34 631 (86.1%)	5590 (13.9%)	—	—
2005	46 606 (87.8%)	6466 (12.2%)	—	—
2006	49 903 (89.1%)	6077 (10.9%)	—	—
2007	55 064 (89.0%)	6788 (11.0%)	1109 (89.5%)	130 (10.5%)
2008	54 880 (88.5%)	7156 (11.5%)	6690 (86.0%)	1086 (14.0%)

Table 3

Exclusion criteria stratified for inhaler device (multiple counting)

Category	Explicit criterion	Code category/unit used in KVB	Explicit code/threshold used in KVB	Not included/excluded HandiHaler®	Not included/excluded RespiMat®
Inclusion criteria	Gender	Male/female	Male/female	0	0
	Age	years	≥40	769 (1.8%)	169 (3.1%)
	Clinical diagnosis	ICD-10-GM	J44	7156 (17.0%)	1086 (20.0%)
Exclusion criteria	Concomitant cardiovascular disease	ICD-10-GM	I21, I22, I25.20	4535 (10.8%)	528 (9.7%)
	Myocardial infarction within the last 6 months	ICD-10-GM	I50.14	564 (1.3%)	62 (1.1%)
	Hospitalization for heart failure within 12 months	ICD-10-GM	I44.2, I45.9, I46, I47.0, I47.2, I49.0	1306 (3.1%)	158 (2.9%)
	Unstable or life threatening arrhythmia requiring intervention or change in drug therapy within 12 months	ICD-10-GM			
	Other significant lung diseases	ICD-10-GM	A15, A16, A17, A18, A19	1507 (3.6%)	200 (3.7%)
	Active tuberculosis	ICD-10-GM	J45, J46	23 701 (56.2%)	3140 (57.7%)
	Asthma	ICD-10-GM	E84	46 (0.1%)	3 (0.1%)
	Cystic fibrosis	ICD-10-GM	J47	712 (1.7%)	101 (1.9%)
	Clinically evident bronchiectasis (not excluded for radiographic evidence of bronchiectasis if they were not being treated for this condition)	ICD-10-GM			
	Interstitial lung disease	ICD-10-GM	J60-J70, J80, J82, J84	0	0
	Pulmonary thromboembolism	ICD-10-GM	I26	2159 (5.1%)	252 (4.6%)
Cancer	Malignancies (other than treated basal cell carcinoma) requiring therapy within the last 5 years (resection, radiation, chemotherapy or biological treatments)	ICD-10-GM	C00-C97 except C44	11 458 (27.2%)	1376 (25.3%)
Others	Known moderate to severe renal impairment (as judged by the investigator)	ICD-10-GM	N18.3, N18.4, N18.5	2592 (6.1%)	257 (4.7%)
	Drug abuse within 12 months	ICD-10-GM	F11.2, F12.2, F13.2, F19.0	261 (0.6%)	42 (0.8%)
	Alcohol abuse within 12 months	ICD-10-GM	F10, K70, Z72.0	3883 (9.2%)	521 (9.6%)
	Known narrow angle glaucoma	ICD-10-GM	H40.2	266 (0.6%)	34 (0.6%)
	Known hypersensitivity to anticholinergic drugs, lactose or other components of the HandiHaler® or RespiMat® inhalation solution delivery system	ICD-10-GM	E73.-	250 (0.6%)	34 (0.6%)
	Symptomatic bladder neck obstruction	ICD-10-GM	N32.0	523 (1.2%)	52 (1.0%)
	Child-bearing potential not on contraceptives	ATC Age	No G03A ≤ 45 years	856 (2.0%)	165 (3.0%)
Unstable COPD	Plans for lung transplantation or lung volume reduction surgery	ICD-10-GM	Z94.2, Z94.3, T86.3, T86.81, U55.2, U55.3	23 (0.1%)	5 (0.1%)
Total				42 151 (67.9%)	5443 (70.0%)

KVB, Kassenärztliche Vereinigung Bayerns database.

lowest proportion was found in patients aged between 60 and 69 years (8.5–11.6%, [percentage range between 2004 and 2008]). A similar age-related pattern was found for Respimat® (data not shown).

More than one-third of the off-label patients had a documented diagnosis of asthma (HandiHaler® $n = 2674$ (37.4%); Respimat® $n = 438$ (40.3%)). Other relevant off-label diagnoses were acute respiratory tract infections (e-Table 3).

TIOSPIR trial

Only approximately 30% (HandiHaler® 32.1%; Respimat® 30.0%) of our study patients theoretically met all the criteria for participating in the TIOSPIR trial. Between the two devices, no relevant differences were detected regarding exclusion criteria. Most patients were theoretically excluded because of a (concurrent) diagnosis of asthma (HandiHaler® $n = 23\,701$ (56.2%); Respimat® $n = 3140$ (57.7%)); Table 3; multiple counting of exclusion criteria). For both devices, patients potentially excluded/not included in the TIOSPIR trial were slightly younger than potentially included patients. There were no gender-related differences between potentially included or excluded patients for both inhaler devices (e-Table 4). In a sensitivity analysis considering additional comorbidities as exclusion criteria (ICD-10-GM codes I25.21, I50.13, and N40), the proportion of patients excluded from the TIOSPIR trial increased to 73.0% for patients using HandiHaler® and to 74.3% for patients using Respimat®.

Discussion

By analyzing a large population-based German claims database, we found an increase in prescriptions for HandiHaler® (years 2004–2008) and Respimat® devices (2007–2008), particularly in elderly patients. There were only minor differences regarding cardiovascular comorbidities and co-medications between patients receiving HandiHaler® or Respimat®. For both devices, a similar proportion of patients received tiotropium off-label with the highest rates in the youngest patients suffering from asthma. Of all patients documented in our database receiving tiotropium, only one-third theoretically met the criteria for participating in the TIOSPIR trial, underlining the highly selected patient samples of RCTs.

Drug utilization

In 2008, only 0.7% of all insured people received at least one tiotropium prescription (combined analysis for both devices). The prevalence of tiotropium estimated in our study seems to be reliable for three reasons: (i) focusing on the main indication, COPD, European prevalence estimates range between 2.1% and 26.1% depending on, for example, the country and included age groups [13], (ii)

the results of the BOLD study showed for a German region that almost half of patients with COPD are grouped into stage 2 or higher and (iii) the guidelines recommend tiotropium for COPD stage 2–4 [1, 14]. Similar to other studies focusing on COPD, we found the highest tiotropium prevalence estimates in elderly men [14, 15]. Nevertheless, differences in the methods used for defining COPD cases (e.g. questionnaires, spirometry data) limit the comparability of study results [13].

Currently, only limited device-related drug utilization data are available. In a cross-sectional analysis assessing patient preferences with inhaler technique and incorrect use of inhaler devices in Portuguese patients attending an outpatient clinic in 2013, HandiHaler® was used by 17% of patients, whereas Respimat® was used by only 4% of patients [16]. Similarly, in a multinational online survey conducted in 2010, most COPD patients were using HandiHaler® [17]. To sum up the available evidence, HandiHaler® is more widely used than Respimat®.

Comorbidities and co-medications

In our study focusing on cardiovascular comorbidities, we found that three-quarters of all patients receiving tiotropium had a concomitant diagnosis of hypertension, whereas one-third exhibited a diagnosis of chronic ischaemic heart disease or heart failure. Comparing patient characteristics for both devices, patients using Respimat® had slightly fewer cardiovascular comorbidities (all cardiovascular comorbidities and cardiovascular comorbidities of particular interest) than patients using HandiHaler®, a fact that might be related to a somewhat lower age. In a recently published review analyzing the burden of comorbidities in COPD patients, lower prevalence rates were reported for cardiovascular diseases compared with our study [18]. These differences might be related to including patients not receiving tiotropium in most studies (stage 1 according to GOLD), resulting in younger and healthier study populations compared with our study. In addition, differences regarding age groups, definitions of comorbidities or national regulations concerning documentation modalities may also contribute to different results.

Focusing on respiratory co-medication, the short acting β_2 -adrenoceptor agonist, salbutamol, and theophylline were the most frequently prescribed compounds. Whereas salbutamol is an effective bronchodilator and recommended according to the guidelines, the high proportion of patients receiving theophylline is a matter of concern due to a narrow therapeutic range, but similar drug utilization data for theophylline were also reported in an Italian study covering the years 2006–2008 [19]. Reflecting theophylline-related changes in COPD guidelines in recent years [1, 20], a 65% decrease in theophylline defined daily doses was found between 2004 and 2012 for Germany according to national drug

consumption data [21, 22]. From a general point of view, by co-prescribing beta-2-agonists and/or theophylline to patients receiving tiotropium, one cannot exclude an, for example, increased risk for cardiovascular side effects due to pharmacodynamic drug-drug interactions.

Off-label use

In our study, 10–14% of all patients received tiotropium off-label without relevant clinical differences between the two devices regarding off-label indications (e-Table 3). In both patient groups, asthma was the most frequent off-label indication. In recent years, evidence has accumulated for using tiotropium in asthmatic patients [23]. In particular, when tiotropium was added to inhaled corticosteroids [ICS]/salmeterol, relevant clinical endpoints (e.g. asthma exacerbations) were reduced [24]. Recently, tiotropium Respimat® has been approved by the European Medicines Agency (EMA) and the Federal Drug Administration (FDA) for the treatment of asthma. However, during the study period, using tiotropium in patients with asthma not having a concomitant diagnosis of COPD should be considered as off-label treatment taking into account formerly effective guidelines [25–27].

TIOSPIR trial

Of all patients receiving tiotropium, only approximately 30% were theoretically eligible for the TIOSPIR trial considering inclusion and exclusion criteria. Thus, the results of the TIOSPIR trial stating a similar mortality risk comparing HandiHaler® and Respimat® are not generalizable to two-thirds of patients receiving tiotropium under real-life conditions. In a recently published study, Scichilone *et al.* estimated the proportion of patients not meeting the inclusion and exclusion criteria of RCTs published up to the year 2012 based on the clinical records of COPD outpatients at 83% [10]. Similar to our results, concomitant lung diseases other than COPD were the most common exclusion criteria even in patients primarily diagnosed as COPD patients. In contrast to our study using claims data, Scichilone *et al.* were able to include additional parameters (e.g. lung function), explaining the slightly higher proportion of excluded patients compared with our results [10]. Nevertheless, in the sensitivity analysis using additional ICD codes to define a few exclusion criteria, a slightly higher proportion of excluded patients was found.

From a medical and methodological point of view, both inclusion and exclusion criteria limit the generalizability of RCTs regarding efficacy and safety [28, 29]. For tiotropium, which is (i) primarily renally excreted after pulmonary uptake and (ii) mainly used in elderly COPD patients frequently suffering from cardiovascular comorbidities, the exclusion of patients with cardiovascular and renal comorbidities might be justified with

regard to minimizing risks for the study participants. Nevertheless, the external validity of such trials is moderate taking into account the results from Scichilone *et al.* and our own study [10]. By excluding ‘real-life’ patients, as mentioned above, important research questions addressing risk estimates for special populations cannot be answered sufficiently, as shown by several replies made to the TIOSPIR trial [8, 9, 30]. Furthermore, absolute and relative contraindications covering, for example, comorbidities are neglected by physicians to a relevant extent under real-life conditions [31]. This fact underlines the urgent need to conduct pragmatic trials to get ‘the whole picture’ in terms of a realistic assessment of benefits and risks for patients with a potentially increased risk of adverse drug reactions [29].

Strengths and limitations

Lung function parameters were not documented in the claims database used in this study. Hence, we were unable to re-check whether a documented diagnosis of COPD was valid or whether a diagnosis of COPD was present but not documented in the database. As described previously, an accurate diagnosis of COPD is a crucial but often unmet need in clinical practice even if lung function parameters are available [32, 33]. Owing to the lack of lung function parameters, we were not able to stratify our analysis by the severity of COPD. For feasibility and validity reasons, we abstained from using surrogates (e.g. prescriptions of antibiotics) as estimates for COPD exacerbation rates. Second, we cannot exclude an underestimation of on-label usage in patients with a documented COPD diagnosis before 2004 because of the limited observation period of 5 years. Nevertheless, by using a 5 year study period, it seems reasonable that patients suffering from COPD were coded at least once as COPD patients. Third, our off-label analyses were focused on indication-related off-label usage, whereas other aspects (e.g. dose or age) remained not covered in this study. However, indication-related off-label usage is the most relevant off-label use even in children with a relevant age-related labelling [34, 35]. Fourth, several inclusion and exclusion criteria were not sufficiently covered in our database and, by using surrogates, we cannot completely exclude an under- or overestimation of the proportion of patients not meeting the TIOSPIR criteria. However surrogates were only used for a minority of criteria and the major criteria were covered in our study (e.g. respiratory diseases other than COPD). Underlining this assumption, similar results were found in a sensitivity analysis using additional ICD codes for some exclusion criteria. Fifth, a few time-dependent exclusion criteria (e.g. acute respiratory infection/acute exacerbation 4 weeks prior to randomization) were not applicable in our study due to the quarterly documentation in our database. Hence, we abstained from including these criteria, leading to an underestimation of potentially

excluded patients. As a major strength, we used a large German database (10.5 million people) covering 85% of the Bavarian population, allowing a comprehensive assessment of real-life prescribing for the two tiotropium devices.

In conclusion, our study analyzing claims data from 10.5 million patients between 2004 and 2008, we found an increase in prescriptions for two tiotropium devices (HandiHaler®, Respimat®). Despite some published reservations regarding the safety of the Respimat® device in particular patient groups, we revealed only slight differences between the two devices with regard to age, gender, cardiovascular and respiratory comorbidities, co-medication and off-label use in clinical practice. Of all patients receiving tiotropium, approximately 30% would theoretically meeting the inclusion and exclusion criteria of the TIOSPIR trial, limiting the generalizability of this trial to a relevant extent. Hence, further studies are urgently required to assess and compare the safety of both tiotropium devices in vulnerable, real-life patient populations.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work. SS reports personal fees from Rottapharm Madaus (Cologne, Germany) and travel costs for an investigator meeting were reimbursed by Bayer HealthCare AG (Leverkusen, Germany) outside the submitted work. PT reports personal fees from Rottapharm Madaus (Cologne, Germany) outside the submitted work. JF and RR belong to EFPIA (European Federation of Pharmaceutical Industries and Association) member companies in the IMI JU, and costs related to their part in the research were carried by the respective company as in-kind contributions under the IMI JU scheme.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

e-Table 1

Inclusion and exclusion criteria of the TIOspir trial

e-Table 2

Period prevalence per 10 000 persons stratified by age group and inhaler device

e-Table 3

Number and proportion of off-label indications (year 2008, multiple counting of off-label indications per prescription)

e-Table 4

Characteristics of patients potentially excluded/ not included in the TIOspir trial