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REVIEW

Inhaled beta-2-agonists/muscarinic antagonists and acute myocardial infarction in COPD patients

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KEYWORDS
Beta-2-agonists;
Muscarinic antagonists;

Summary
Objective: Empirical results indicate an increased risk for cardiovascular (CV) adverse drug events (ADE) in chronic obstructive pulmonary disease (COPD) patients treated with beta-2-agonists (B2A) and muscarinic antagonists (MA). A systematic review (including a meta-analysis for drug classes with sufficient sample size) was conducted assessing the association between B2A or MA and acute myocardial infarctions (MI) in COPD patients.

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Acute myocardial infarction;
Systematic review;
Chronic obstructive pulmonary disease

Methods: Comprehensive literature search in electronic databases (MEDLINE, Cochrane database) was performed (January 1, 1946—April 1, 2013). Results were presented by narrative synthesis including a comprehensive quality assessment. In the meta-analysis, a random effects model was used for estimating relative risk estimates for acute MI.
Results: Eight studies (two systematic reviews, two randomized controlled trials, and four observational studies) were comprised. Most studies comparing tiotropium vs. placebo showed a decreased MI risk for tiotropium, whereas for studies with active control arms no clear tendency was revealed. For short-acting B2A, an increased MI risk was shown after first treatment initiation. For all studies, a good quality was found despite some shortcomings in ADE-specific criteria. A meta-analysis could be conducted for tiotropium vs. placebo only, showing a relative risk reduction of MI (0.74 [0.61—0.90]) with no evidence of statistical heterogeneity among the included trials ($I^2 = 0\%$; $p = 0.8090$).
Conclusions: An MI-protective effect of tiotropium compared to placebo was found, which might be attributable to an effective COPD treatment leading to a decrease in COPD-related cardiovascular events. Further studies with effective control arms and minimal CV risk are required determining precisely tiotropium's cardiovascular risk.

Contents

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic airway diseases in Western countries. A stepwise treatment using several drug classes is recommended to reduce symptoms, improve lung function, and prevent risk of exacerbation. According to current guidelines (e.g., Global Initiative for Chronic Obstructive Lung Disease [GOLD]) [1], beta-2-adrenoceptor agonists (B2A) are therapeutic mainstays of COPD treatment because of their bronchodilative effects. This drug class consists of two types: short-acting B2A (SABA) prescribed as reliever medication and long-acting B2A (LABA) used as maintenance/control medication. Widely taken SABA products with a short half-life are salbutamol, fenoterol, and terbutalin. Formoterol and salmeterol are the most frequently used LABA products that have a recommended twice-daily usage.

A second bronchodilative drug class that acts on the cholinergic system (muscarinic antagonists [MA]) is also

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recommended to treat COPD. Similarly to B2A, these MA drugs can be classified in short-acting MA (SAMA) and long-acting MA (LAMA) according to their half-life period. Currently available products in these classes are ipratropium (SAMA) and tiotropium or oxitropium (LAMA).

Focussing on adverse drug events (ADE) of B2A, stimulation of cardiac beta-adrenoceptors by B2A and anticholinergic effects by MA have been related to cardiovascular ADE, particularly in patients exhibiting cardiac risk factors [2]. For example, tachycardia and arrhythmias are well-known side effects for both drug classes [2,3].

Both randomised controlled trials and observational studies have been performed to assess the association between the usage of inhaled B2A and the occurrence of MI [4—6] resulting in conflicting evidence. Potential reasons for these differences may be misclassification of potential cardiac vs. airway-related events due to similar clinical complaints, differing baseline risk of MI in B2A users and non-users, different measurement of drug exposure, and a small number of events resulting in poor precision of risk estimates.

To contribute on this area of research, we performed an independent systematic review to assess the association between B2A or MA and MI (fatal and non-fatal) in COPD populations. In addition, after finishing the narrative synthesis, a meta-analysis was conducted for those drug classes the sample sizes were sufficient.

Methods

Literature search

In a first step, in order to analyze the current status of research, both meta-analyses and existing systematic reviews dealing with the association between B2A or MA and MI were searched for in different databases (Fig. 1). Hence, a comprehensive computer-based literature search using a

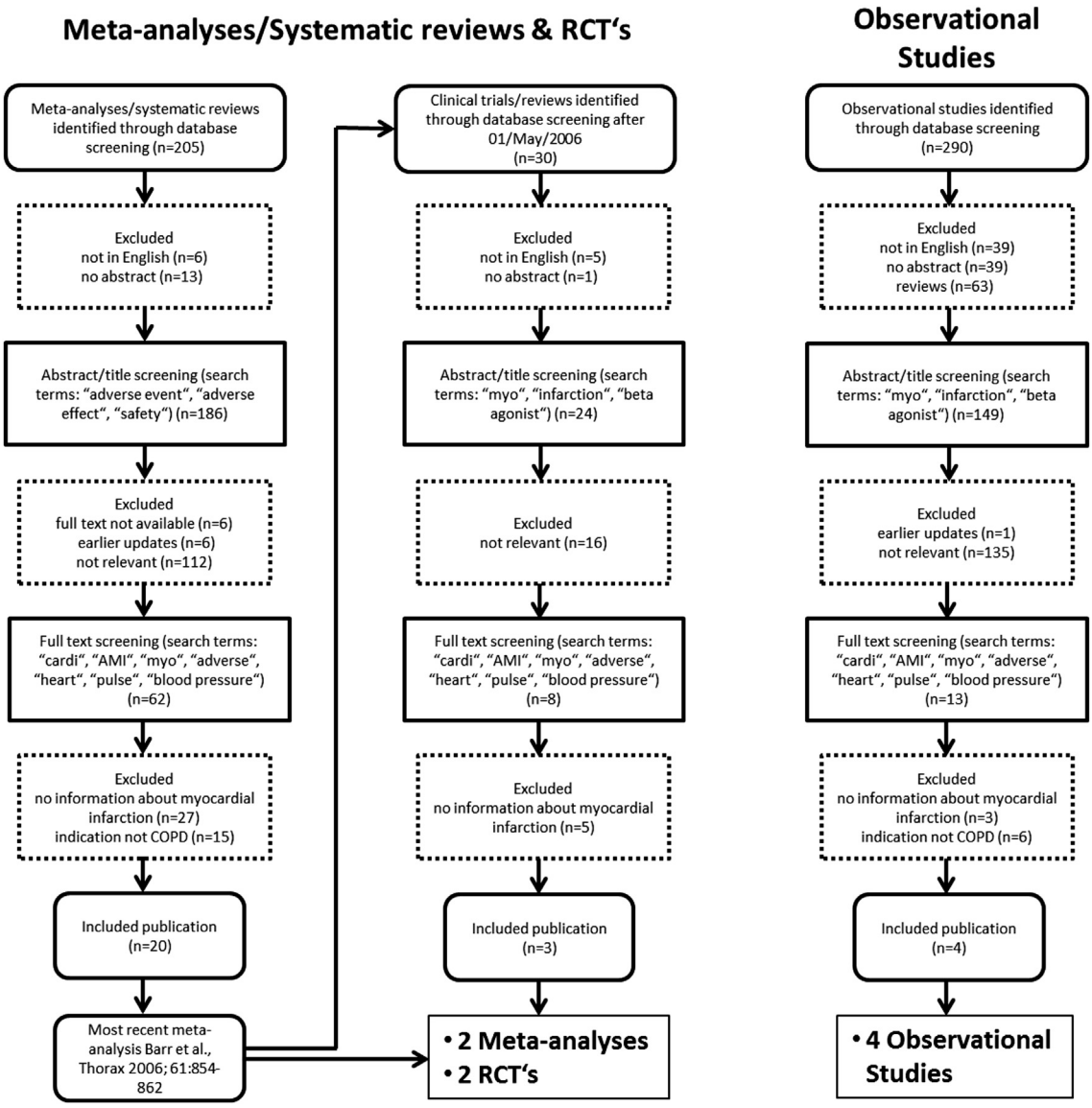

Figure 1 Literature search (flow chart, RCT: Randomised controlled trial).

predefined set of keywords was conducted in electronic databases (MEDLINE, Cochrane database) aiming to identify manuscripts dealing with the drug–adverse effect pair "B2A" or "MA" and "acute myocardial infarction". The full search term expression is presented in Appendix 1. Acute myocardial infarctions caused by B2A or MA are very rare adverse events (AE). Therefore, the term "acute myocardial infarction" is not expected to be contained in neither the publications' abstracts nor keyword lists. Hence, to deal with this problem and to retrieve all relevant publications, the search terms for the adverse event remained very unspecific to achieve an optimal coverage. All stages of publications (early view, in press, or published) were considered relevant for publication. Only English language articles were considered relevant in further analysis. Results were limited to the years January 1, 1946–April 1, 2013. Further publications were found by bibliographic hand search in key articles, key journals, and by citation tracking.

In a second step, the most recent high-quality systematic review or meta-analysis was identified (i.e., *Barr* et al. [7]). Our search of published clinical trials started beginning with the end of the study period of the systematic review by *Barr* et al. (May 1, 2006) and was conducted in electronic databases (MEDLINE, Cochrane database, ClinicalTrials.gov). In a third step, we performed a search for observational studies (starting May 1, 2006).

The specific inclusion criteria for the systematic review or meta-analysis were: 1) patients suffering from COPD; 2) outcome: acute myocardial infarction (fatal or non-fatal); 3) exposure: B2A or MA; 4) control arm: active or placebo; and 5) type of study: clinical trial or any kind of observational study (OS).

Data extraction and quality assessment

All titles, abstracts, citations, and full texts included were analysed by two independent reviewers who extracted the data based on a standardized taxonomy. The taxonomy covered the following 6 domains consisting of 42 items: i) study identification characteristics (i.e., author, title, reference, country of origin, publication year, source of funding); ii) study characteristics (i.e., primary objective and/or further objectives, setting); iii) participants' characteristics (i.e., age, gender, ethnicity, socio-economic status, disease severity, duration of disease, co-morbidities, co-treatments); iv) exposure (i.e., drug or drug class studies, dosage, route of administration, duration of treatment, index date, time window of exposure, description of comparator, indication of use); v) adverse effects/outcome (i.e., definition of reported AE, methodology of AE monitoring, AE frequency, study design/number of included studies for meta-analysis or systematic review, inclusion criteria, exclusion criteria, time during the study at which the AE is recorded, methodology of causality assessment, total number of withdrawals/drop-outs, reason for withdrawals/drop-outs, number of withdrawals/drop-outs due to AE, number of participants with AE by drug and indication, total number of AE); and vi) key results (i.e., statistical techniques, length of follow-up, number of participants included in the analysis, type of analysis, type of risk estimate, pooled risk estimates of AE and 95% confidence interval (CI), sources and magnitude (I^2) of statistical heterogeneity).

The quality of each study included was assessed based on a standardized questionnaire (developed under the supervision of the co-author LI) containing 31 questions applicable to randomized controlled trials, observational studies, and systematic reviews (Appendix 2). The checklist is divided into two parts reflecting a variety of issues: definition and severity of AE, validity of study design, and statistical methods (part 1); methods for AE identification, reporting frequency in randomized controlled trials, and for assessing causality in both OS and randomized controlled trials (part 2). For each item contained in the questionnaire one point was awarded by two independent reviewers (any disagreement was resolved by consensus). The maximum scores were determined for each study type as follows: systematic reviews or meta-analysis 8 points, RCTs 17 points, cohort studies 12 points, and case–control studies 10 points. For all study designs the following categories were applied: "very good" ($\geq$85% of maximum score), "good" ($<$85%–$\geq$70%), "satisfactory" ($<$70%–$\geq$55%), "inadequate" ($<$55%).

Statistical analysis

A meta-analysis was conducted for those drug classes the sample sizes were most sufficient. Summarising the relative risk (RR) estimates, a random effects model was applied. The "metafor" package (version 1.6.0) of the statistical software package R (version 2.14.1) was used for pooling the logarithms of the single relative risks. Statistical heterogeneity for the group of studies was analysed using the I^2 statistic. A p-value <0.05 was considered to indicate statistical significance. If sample size was insufficient for a meta-analysis, the results of these studies were summarized using a narrative synthesis.

Results

In total, eight relevant studies and systematic reviews (Table 1) were identified in the literature search process: two systematic reviews [7,8], two randomized controlled trials [9,10], and four observational studies (including one population-based cohort study, one cohort study, and two nested case–control studies) [5,11–13]. Three studies compared tiotropium vs. placebo treatment [7–9], whereas one study compared tiotropium vs. salmeterol [10]. In contrast, the scope of observational studies was wider covering tiotropium vs. non-tiotropium use [11], inhaled beta-2 agonists ("no", "any", "new", and "first use") [5], tiotropium vs. LABA [13], and new users of tiotropium vs. new users of LABA monotherapy [12]. Risk estimates from the selected studies for the comparison of tiotropium and placebo ($n = 3$) were pooled in a meta-analysis. The remaining five studies were highly heterogeneous concerning both the control arm and the study design. Therefore, it was impossible to pool the results of these studies based on a random effects model. Almost all studies ($n = 7$) focused on a combination of primary and secondary endpoints including various clinical and/or composed

Table 1 Summary of study characteristics.

First author	Study design	Number of studies/ number of centres/ database	Treatment	Number of patients	Age (years)	Male (%)	COPD severity
Barr [7]	Systematic review	4 trials	Tiotropium vs. placebo, or ipratropium	Tiotropium 1808; ipratropium 179; placebo 1281	Casaburi: tiotropium 65 ± 9, placebo 65 ± 9 Dusser: tiotropium 64.5 ± 9.1, placebo 65.0 ± 9.5 Brusasco: tiotropium 63.8 ± 8.0, placebo 64.6 ± 8.6 Vincken: tiotropium 63.6 ± 8.2, ipratropium 64.5 ± 8.1	Casaburi: tiotropium 66.5%, placebo 62.8% Dusser: tiotropium 89%, placebo 87% Brusasco: tiotropium 77.4%, placebo 76.3% Vincken: tiotropium 84%, ipratropium 86%	Not reported
Celli [8]	Systematic review	30 trials	Tiotropium vs. placebo	Tiotropium 10,846; placebo 8699	Tiotropium 65 ± 9; placebo 65 ± 9	Tiotropium 76%, placebo 76%	Tiotropium GOLD II: 26%, III: 49%, IV: 24% placebo GOLD II: 25%, III: 50%, IV: 24%
Tashkin [9]	RCT	490 centres	Tiotropium 18 μg (HandiHaler®) vs. placebo	Tiotropium 2986; placebo 3006	Tiotropium 64.5 ± 8.4; placebo 64.5 ± 8.5	Tiotropium 75.4%, placebo 73.9%	Tiotropium GOLD II: 46%, III: 44%, IV: 8% placebo GOLD II: 45%, III: 44%, IV: 9%
Vogelmeier [10]	RCT	725 centres	Tiotropium 18 μg (HandiHaler®) vs. salmeterol 50 μg	Tiotropium 3707; salmeterol 3669	Tiotropium 62.9 ± 9.0; salmeterol 62.8 ± 9.0	Tiotropium 74.4%, salmeterol 74.9%	Tiotropium GOLD II: 48%, III: 43%, IV: 9% salmeterol GOLD II: 50%, III: 42%, IV: 8%
de Luise [11]	Population-based cohort study	National health services, residents of North Jutland, Aarhus and Viborg counties in Denmark	Periods of tiotropium use vs. periods of non-tiotropium use	Tiotropium 2870; non-user 7733	40–59: tiotropium $n = 700$ (24.4%), non-user $n = 2011$ (26.0%) 60–74: tiotropium $n = 1564$ (54.5%), non-user $n = 3431$ (44.4%) 75+: tiotropium $n = 606$ (21.1%), non-user $n = 2291$ (29.6%)	Tiotropium 47.2%, non-user 48.1%	Not reported
Suissa [5]	Nested case–control study	Saskatchewan Health Services	SABA (no use vs. any use vs. new use vs. first use)	Cases 1127; controls 10,766	Cases 77 ± 8.3, controls 77 ± 8.0	Cases 69%, controls 55%	Not reported
Verhamme [13]	Nested case–control study	Integrated Primary Care Information project	Tiotropium vs. LABA	Tiotropium 1048; LABA 3214	40–59: tiotropium $n = 225$ (21.5%); LABA $n = 863$ (26.9%) 60–69: tiotropium $n = 278$ (26.5%); LABA	Tiotropium 61.0%, LABA 56.9%	Tiotropium (GOLD classification) mild: 23%, moderate: 47%, severe: 29%, very severe: 2%

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Table 1 (*continued*)

First author	Study design	Number of studies/ number of centres/ database	Treatment	Number of patients	Age (years)	Male (%)	COPD severity
					$n = 828$ (25.8%) 70+: tiotropium $n = 545$ (52.0%); LABA $n = 1523$ (47.3%)		LABA mild: 24%, moderate: 47%, severe: 27%, very severe: 2%
Jara [12]	Cohort study	The Health Improvement Network (THIN)	New users of tiotropium (HandiHaler®) vs. new users of LABA monotherapy	Tiotropium 4767; LABA 6073	40–49: tiotropium $n = 149$ (3%); LABA $n = 362$ (6%) 50–59: tiotropium $n = 641$ (13%); LABA $n = 943$ (16%) 60–69: tiotropium $n = 1391$ (29%); LABA $n = 1730$ (28%) 70–79: tiotropium $n = 1759$ (37%); LABA $n = 1991$ (33%) 80–89: tiotropium $n = 769$ (16%); LABA $n = 976$ (16%) 90+: tiotropium $n = 58$ (1%); LABA $n = 71$ (1%)	Tiotropium 57%, LABA 51%	Not reported

RCT: randomised controlled trial; SABA: short-acting beta-2-agonists; LABA: long-acting beta-2-agonists.

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endpoints. The most frequent endpoints were as follows: myocardial (adverse) events ($n = 7$), all-cause mortality ($n = 6$), and COPD-related hospitalization ($n = 5$). Two studies compared health-related quality of life only (Table 2). In addition, the limitations of all included studies were comparable and mostly associated with the known boundaries of systematic reviews and meta-analyses, e.g., differences in study design or publication, selection and reporting biases (Table 2).

Quality assessment

All studies were evaluated according to the standardized questionnaire described above. Quality in both systematic reviews was either assessed as "good" or "very good", with only minor shortcomings concerning the precise presentation of the criterion "severity of the adverse event" (question 2) [7,8]. In general, the two randomized clinical trials were of good quality, however, slight weaknesses concerning the precision of ADE definition, details on ADE severity description, and causality assessment existed [9,10]. Quality of the two cohort studies [11,12] was assessed as "good" to "very good" and "very good" for the two nested case–control studies [5,13]. To sum up, from a methodological point of view, all studies have been analyzed their endpoints accurately (Table 3).

Tiotropium overall

Sample size was large in all studies, with tiotropium patients ranging from 1048 to 10,846 cases. Age distribution in all studies was similar starting at the age of 40 years (due to the studies' inclusion criteria), with a large proportion of participants being older than 60 years. All studies had a predominance of male patients (tiotropium 57–89% vs. comparators 51–87%), except for the study by *de Luise* et al. [11] which included more females (tiotropium 53% vs. non-users 52%). Reporting of COPD severity (based on the GOLD grading system [1]) was heterogeneous between all studies: it remained totally unmentioned in four studies [5,7,11,12]. In the study by *Celli* et al. patients with "severe" and "very severe" COPD (stages III and IV) were predominant [8], whereas "mild" to "severe" patients (stages I–III) were the largest group in the study by *Verhamme* et al. [13]. Almost 90% of patients were "moderate" (stage II) or "severe" (stage III) in the studies by *Tashkin* et al. [9] and *Vogelmeier* et al. [10].

Tiotropium vs. placebo or periods of non-tiotropium use

One publication by *de Luise* et al. [11] analysed the incidence of MI during the use of tiotropium vs. periods of non-tiotropium therapy resulting in an adjusted incidence rate ratio of 1.05 (0.69–1.60, Table 3). The majority of studies compared treatment with tiotropium vs. placebo resulting in heterogeneous effects concerning the risk estimator: the study by *Barr* et al. [7] reported a neutral effect (1.0 [0.2–3.9]), whereas *Celli* et al. [8] and *Tashkin* et al. [9] revealed a lower risk of MI among tiotropium patients (0.78 [0.59–1.02] and 0.71 [0.52–0.99], Table 3). Finally, we pooled the results of the three studies [7–9] for the calculation of a pooled risk estimator. In total, 15,467 tiotropium patients suffered from 183 MI events, whereas in the placebo-controlled arm 217 MI events were detected in 13,092 patients (Fig. 2). The calculated pooled relative risk based on a random effects model was 0.74 (0.61–0.90) indicating a reduction of MI in tiotropium patients compared to placebo patients. There was no evidence of statistical heterogeneity among the included trials ($I^2 = 0\%$; $p = 0.8090$).

Tiotropium vs. active control arm

Comparing tiotropium with an active control arm, the studies by *Barr* et al. [7] focussing on ipratropium (odds ratio of 1.5 [0.2–15]) and *Vogelmeier* et al. [10] focussing on salmeterol (incidence rate ratio/100 person years of 1.50 [0.74–3.02]) indicated an increased risk of MI in tiotropium users (Table 3). Two other relatively small studies compared tiotropium against LABA use and found conflicting evidence [12,13]. *Verhamme* et al. [13] calculated an adjusted odds ratio of 0.67 (0.22–2.00), whereas, in contrast, the study by *Jara* et al. [12] resulted in an adjusted hazard ratio (aHR) of 1.26 (0.72–2.21, Table 3). However, there was heterogeneity in study specifications (e.g., exposure definition and confounding variables) and results were non-significant with wide confidence intervals.

Short-acting inhaled beta-2 agonists

Finally, the study by *Suissa* et al. [5] compared a variety of combinations associated with the treatment of short-acting beta-2 agonists. In summary, every kind of usage (any (current), new, or first time use) resulted in minor, non-significant increases of the rate ratios (range 1.06–1.12, Table 3) compared to non-usage.

Discussion

The aim of our study was to contribute on the evidence of MI associated with the utilization of B2A or MA in COPD patients. To sum up the eight studies of the literature review, an MI-protective effect of tiotropium could be found in studies comparing tiotropium vs. placebo. This beneficial effect has been attributed to an effective COPD treatment leading to a reduced number of cardiovascular events due to e.g. a decreased rate of COPD exacerbations [14–17]. On the other hand, in studies comparing tiotropium with active control (e.g., salmeterol, ipratropium) assuming an effective treatment in both treatment arms, an increased MI risk for patients treated with tiotropium was detected in some studies. Observational studies revealed an increased risk in the initial period after tiotropium or short-acting B2A was ingested for the first time (Table 3). All studies were assessed as having at least "good" quality. However, shortcomings in ADE-specific criteria, particularly ADE definition, severity classification, and causality assessment were revealed.

In our meta-analysis, we confirmed an earlier reported [7–9] decrease of MI risk in patients receiving tiotropium vs. placebo (0.74 [0.61–0.90]) based on the random effects

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Table 2 Endpoints, duration and study limitations.

First author	Endpoints	Duration	Limitations
Barr [7]	PE: COPD exacerbations and related hospitalisations, all-cause mortality SE: disease specific mortality, health-related QoL (SGRQ), symptom scores (TDI), multidimensional measure of breathlessness, FEV_1 change and forced FVC (from baseline and from steady state 8—15 days after randomization), adverse events (i.e., dry mouth, constipation, urinary infection and obstruction, chest pain, MI, arrhythmias, congestive heart failure)	RCTs between 12 weeks and 12 months	Double counting of patients randomised to tiotropium or of patients from overlapping publications, publication and reporting biases, selection bias (differential inclusion of available trials), selective reporting of secondary endpoints and of non-intention -to- treat reports in publications
Celli [8]	PE: all-cause mortality, selected CV events (composite CV endpoint encompassing CV deaths, nonfatal MI, nonfatal stroke, sudden death, sudden cardiac death, and cardiac death)	RCTs between 4 weeks and 4 years	Integration of placebo-controlled trials with active controlled trials, differential discontinuation, differences in exposure, selection bias (most evidence based on Health Lung Study), incomplete AE reporting of included studies, higher premature discontinuation in controls compared with tiotropium group; meta-analysis limitations: differences in populations, study design, duration of trials, collection of data, and adjustment for differences in exposure, susceptibility for different diagnostic reportings
Tashkin [9]	PE: annual rate of decline in mean FEV_1 before and after use of a study drug and short-acting bronchodilators in the morning (prebronchodilator) and after the use of a study drug (postbronchodilator) beginning on day 30 SE: rate of decline in the mean FVC and SVC, health-related QoL (SGRQ), COPD exacerbations and related hospitalizations, mortality from any cause and from lower conditions	4-year RCT	All respiratory therapies (exceptional other inhaled anticholinergic agents) allowed by study design, very low proportion of smokers at baseline (30%)
Vogelmeier [10]	PE: time to first COPD exacerbation (defined as "an increase in or new onset of more than one symptom of COPD (cough, sputum, wheezing, dyspnea, or chest tightness), with at least one symptom lasting 3 days or more and leading the patient's attending physician to initiate treatment with systemic glucocorticoids, antibiotics, or both (criterion for moderate exacerbation) or to hospitalize the patient (criterion for severe exacerbation)")	1-year RCT (2 weeks run in, 12 months study period, 30 days follow-up SAEs)	n/r

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Table 2 (*continued*)

First author	Endpoints	Duration	Limitations
	SE: time to following first event: • COPD exacerbation leading to hospitalization • moderate COPD exacerbation • premature discontinuation of trial medication • COPD exacerbation or time to discontinuation of study medication because of worsening of underlying disease • COPD exacerbation treated with systemic steroids • COPD exacerbation treated with antibiotics • COPD exacerbation treated with systemic steroids and antibiotics number of patients with events (occurrence): • at least 1 COPD exacerbation • at least 1 COPD exacerbation leading to hospitalization • premature discontinuation of trial medication number of events: • COPD exacerbations • COPD exacerbations leading to hospitalization • moderate COPD exacerbations • COPD exacerbations treated with systemic steroids and/or antibiotics pre-dose morning peak expiratory flow rate measured by patients at home during first 4 months of randomized treatment safety endpoints: • serious AE • AE leading to treatment discontinuation • treatment-related AE • major adverse cardiovascular events during treatment (fatal CV disorders, sudden (cardiac) death, cardiac death, serious AE (fatal and non-fatal) from MI, stroke) • all-cause mortality with onset of fatal AE during treatment with study medication + 30 days all-cause mortality including follow-up of vital status from patients who prematurely discontinued treatment and date of death within 360 days		
de Luise [11]	Hospitalization for any reason, hospitalization with cardiac discharge diagnoses (atrial fibrillation or atrial flutter, supraventricular tachycardia, angina, MI, congestive heart failure,	Hospitalized patients from January 1, 1977 to December 31, 2003 (Aarhus and Viborg) and from January 1, 1980 to December 31, 2003 (North	Misclassification of COPD and MI discharge diagnoses in medical record databases, missing random treatment assignment as therapy was

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Table 2 (*continued*)

First author	Endpoints	Duration	Limitations
	ventricular arrhythmia), hospitalization for COPD mortality endpoints: death from any cause or due to sudden death, cardiac arrest, MI, heart failure or other cardiac cause, non-cancer respiratory death	Jutland)	determined by physicians (who may prescribe certain medications based on risk factors for endpoints under study) and not by investigators using random assignment
Suissa [5]	Acute MI	Subjects who had been dispensed at least three bronchodilator prescriptions within a 1-year period between January 1, 1980 and December 31, 1997; follow-up until the date of death, emigration from the province, end of health insurance plan coverage or December 31, 1999	Precise indications whether drugs were prescribed are unavailable (study cohort was formed from administrative databases)
Verhamme [13]	CV and cerebrovascular endpoints, mortality	One-year pre-enrollment period for patient characterization followed by a study period started in January 2000 and ended in May 2007	Confounders: COPD severity, misclassification of the outcome, investigation of tiotropium HandiHaler (dry powder inhaler) only due to national restricted launch policies of other manufacturers (tiotropium Respimat (softmist inhaler))
Jara [12]	CV AE (aneurysm, atrial fibrillation, cardiac arrest, coronary artery disease, angina, MI, heart failure, hypertension, stroke, syncope, (ventricular) tachycardia), respiratory AE (COPD exacerbation, asthma exacerbation and pneumonia) and other AE (constipation, dry mouth, dysphagia, paralytic ileus/ bowel obstruction, renal failure, tremor, urinary retention), all-cause mortality	November 2002 (the earliest use of tiotropium) until January 2007 (exposure to study medication for duration of prescribed therapy plus 30 days; patients were followed from the date of their first eligible prescription until the earliest date of treatment end, date of study end point, date of transfer to a new practice, death or January 2007)	Missing routine lung function measures, composite endpoints (all-cause mortality and all strokes) potentially reduce associations for cardiovascular mortality and ischaemic stroke differences in baseline risks between treatment groups (e.g., lung function results; more LABA patients than tiotropium patients exhibited an asthma diagnosis additionally to COPD diagnosis) potential underreporting of non-serious anticholinergic end points (e.g., constipation, urinary retention) resulting in diluted RR estimates, missing evaluation of dose response (tiotropium HandiHaler)

AE: adverse event; CV: cardiovascular; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MI: myocardial infarction; n/r: not reported; QoL: quality of life; PE: primary endpoint; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; SE: secondary endpoint; SGRQ: St George's Respiratory Questionnaire; SVC: slow vital capacity; TDI: Transitional Dyspnea Index.

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Table 3 Risk estimators and quality assessment.

First author	Type of risk estimate	Comparator	Estimator	Quality (score/ max. score)	Comments
Barr [7]	Odds ratio (95% CI)	Tiotropium vs. placebo Tiotropium vs. ipratropium	Adjusted 1.0 (0.2—3.9) Adjusted 1.5 (0.2—15)	Very good (7/8)	Only AE severity is not described
Celli [8]	Incidence rate ratios stratified by study (Cochrane-Mantel-Haenszel test)	Tiotropium vs. placebo	Adjusted 0.78 (0.59—1.02)	Good (6/8)	—
Tashkin [9]	Incidence rate ratio per 100 person years	Tiotropium vs. placebo	Adjusted 0.71 (0.52—0.99)	Good (12/17)	Shortcomings in AE definition, causality assessment, and lack of AE severity
Vogelmeier [10]	Incidence rate ratio	Tiotropium vs. salmeterol	Adjusted 1.50 (0.74—3.02)	Good (12/17)	Shortcomings in AE definition, causality assessment, and lack of AE severity
de Luise [11]	Incidence rate ratio	Periods of tiotropium use vs. periods of non tiotropium use	Crude 0.97 (0.64—1.46) adjusted 1.05 (0.69—1.60)	Very good (11/12)	—
Suissa [5]	Rate ratio	SABA no use vs. any use SABA no use — SABA any current use* SABA no use — SABA new use** SABA no use — SABA first time use	Adjusted 1.06 (0.92—1.23) Adjusted 1.12 (0.95—1.33) Adjusted 1.12 (0.69—1.80) Adjusted 1.02 (0.52—2.00)	Very good (10/10)	—
Verhamme [13]	Odds ratio	Tiotropium vs. LABA	Crude 0.76 (0.26—2.25) adjusted 0.67 (0.22—2.00)	Very good (10/10)	—
Jara [12]	Hazard ratio	Tiotropium vs. LABA	Crude 1.26 adjusted 1.26 (0.72—2.21)	Good (10/12)	Presentation of results could have been improved

AE: adverse event; SABA: short-acting beta-2-agonists; LABA: long-acting beta-2-agonists; *Any current use: use of inhaled beta-2-agonists in the 2 months before the index date, **New use: current use of beta-2agonists with no other beta-2 agonist use of any form during the year before the index date.

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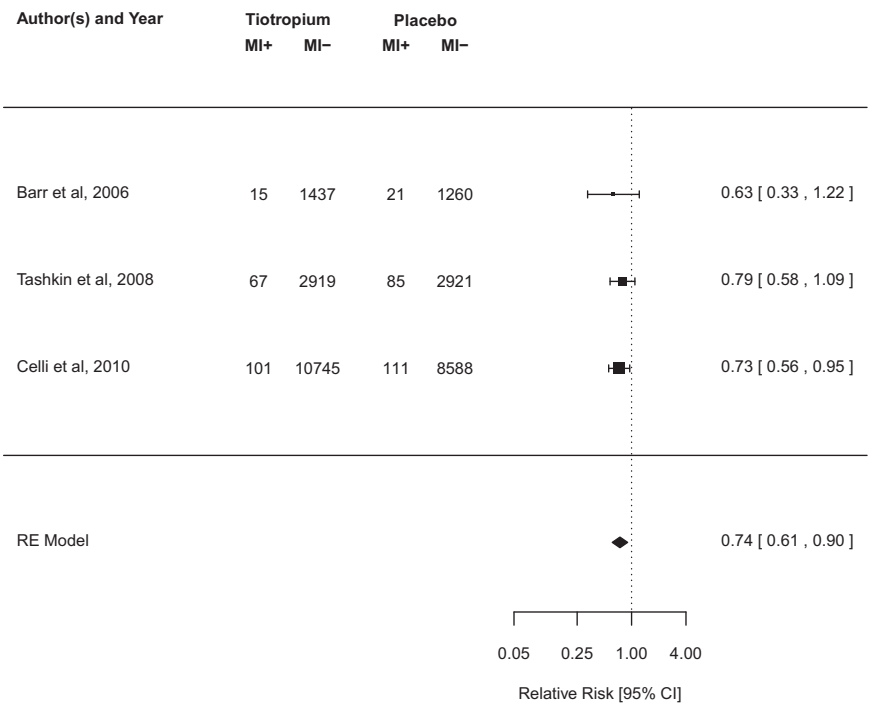

Figure 2 Forest plot of single studies. (MI+: patients having at least one acute MI during the study, MI-: patients having no acute MI during the study). RE Model: Random effects model.

model and no evidence of statistical heterogeneity among the included trials ($I^2 = 0\%$; $p = 0.8090$). From a pharmacological perspective, this finding is to some extent unexpected. By using MA leading to a decreased cholinergic activity, an overweight in sympathetic activation leading to an increased risk for MI seems reasonable. Nevertheless, an increased risk of tiotropium might have been masked by an efficacious COPD treatment leading to a decreased number of COPD-related cardiovascular events. For quantifying the exact cardiovascular substance-related CV risk, active comparisons assuring a sufficient COPD treatment (e.g. LABA) might be of outstanding importance. Nevertheless, results will be also influenced by a LABA-containing control arm due to LABA-related CV risks.

Endpoint "myocardial infarction"

Influence of all drugs in both classes (B2A and MA) on the cardiovascular system is well-known [2,3]. Onset of these symptoms is certainly followed by a dose reduction or discontinuation of drug therapy, which may prevent from more severe cardiac AEs (e.g., myocardial infarction) resulting in a low number of these AEs. Currently, only a few clinical studies dealing with MI (at least as secondary endpoint) are available on this account as most investigators refer to it within the common term "side effects". In contrast, pharmacoepidemiological database studies more often contain specific analyses on MI as these studies were conducted based on large datasets [4,5,18]. However, a combined endpoint is used in most studies only. The study by *Calverley* et al. [19] summarized a mixture of different specific symptoms within the general term "cardiovascular event" ("coronary artery disorders", "cardiac arrhythmias", "heart failures", "cardiac disorder signs and symptoms", "myocardial disorders", "cardiac valve disorders", "pericardial disorders", "central nervous system vascular disorders", "arteriosclerosis", "stenosis", "vascular insufficiency and necrosis", "aneurysms and artery dissections", and "embolism and thrombosis"). In this context, *Dong* et al. [20] utilized a clinical endpoint called "cardiovascular death".

Comparison of endpoints in systematic reviews is impeded by semantic heterogeneity and, hence, inter-study comparability is limited (Table 2). Similar results compared to ours concerning the MI endpoint were found in studies containing combined endpoints. In a comprehensive meta-analysis of 42 studies, *Rodrigo* et al. [21] found a slightly lower risk for the combined endpoint "cardiovascular event" for the treatment with tiotropium vs. placebo ($n = 13$ studies; risk ratio Mantel–Haenszel: 0.91; 95% CI [0.77–1.07]), but a significant higher risk for tiotropium vs. the combination of salmeterol and fluticasone ($n = 2$ studies; risk ratio Mantel–Haenszel: 1.94, 95% CI [1.06–3.55]). A study by *Wedzicha* et al. [22] verified these results by reporting a higher rate of "cardiac events" in the tiotropium treatment arm (5%) compared to patients treated with salmeterol and fluticasone (3%).

A further problem concerning study comparability is the uniform definition of the diagnosis "myocardial infarction", as a standardized definition is available since the year 2000 for the first time [23]. However, the problem remains that most studies use different coding systems possibly influencing the results. Particularly, coding systems in observational studies and secondary database studies differ between single countries as International Statistical Classification of Diseases and Related Health Problems (ICD) and International Classification of Primary Care (ICPC) codes are used more often than Medical Dictionary for

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Regulatory Activities (MedDRA) classification terms normally used in clinical trials [5,8,13].

Background prevalence of myocardial infarction

COPD and MI are diseases occurring more often in elder people as prevalence is sharply increasing for both diseases starting from an age of 40 years [24,25]. In addition to age, the existence of common risk factors (e.g., smoking and air pollution) increases the risk for both COPD and MI [26–28]. Therefore, the assessment of causality between drug therapy and onset of adverse event is very difficult, as COPD patients without B2A or MA may also suffer from MI. In this context, randomization enables a uniform distribution of both known and unknown risk factors in clinical trials; hence, detected effects can be assigned more precisely to a particular drug therapy. However, strict inclusion and exclusion criteria lower the number of patients eligible for these studies. For example, a frequent inclusion criterion in almost all studies dealing with B2A and MA in COPD patients was being a current smoker or ex-smoker with at least $\geq$ 10 pack-years smoking history, which is limiting the generalization of results significantly. Controlling for confounders is difficult in non-randomized studies, as these confounders cannot adequately be considered due to a high number of concomitant diseases and co-medication influencing the risk for cardiac adverse events in COPD patients [29,30]. That is the reason why comparability of observational studies is strongly limited, as every study presents a different selection of confounders [12,13].

Heterogeneity of control arms

Another problem emerging in all study types is the large number of drug therapy combinations available for COPD treatment [31]. GOLD guidelines recommend LABA or LAMA in treatment step 2 [1], but even drugs of one class differ in important pharmacological aspects (e.g., onset time of bronchodilator effects is much shorter when using formoterol instead of salmeterol (both LABA)) [32]. However, these differences may influence MI risk and a combination of active ingredients for a pooled evaluation or meta-analysis is inappropriate. Therefore, a large number of subgroup analyses is shown in systematic reviews [20].

Comparison of results for long-acting (LAMA, LABA) versus short-acting substances (SAMA, SABA) is difficult for several reasons. Whereas LAMA and LABA are used on a regular basis as controller medication, SAMA and SABA are used as reliever medication on an "as needed basis" resulting in different exposures [1]. For treatment step 1 (mild COPD), only short-acting agents are recommended, whereas for patients with a more severe COPD (steps 2–4) a combined usage of long-acting and short-acting compounds is recommended [1] resulting in patient groups with different baseline characteristics. In general, a similar distribution of co-medication is essential for assessing the risk of an adverse event for a specific drug. Nevertheless, particularly in observational studies, but also in randomised controlled trials, there might be differences in co-medication utilization. For example, in patients receiving placebo, a more frequent usage of reliever drugs cannot be excluded and should be considered as a confounder in all studies.

Many patients are treated with a combination of B2A or MA and inhaled ICS. Drug combinations are frequently available as one inhaler (e.g., fixed combination of formoterol and budesonide). ICS influence the inflammatory processes of both the lung and coronary artery diseases and, therefore, a protective cardiac effect of ICS in terms of reducing inflammatory processes influencing coronary artery disease cannot be excluded [33,34]. In most studies ICS is one of the permitted co-medications and, therefore, a possible protective cardiac effect of ICS could bias the results. In contrast, use of OCS is associated with an increased risk for AMI in COPD patients [35,36]. Since OCS are used for treating acute exacerbations, increased AMI risk might primarily reflect a higher probability of cardiac events in these vulnerable patients instead of a causal relationship for OCS usage. Hence, adjusting for ICS and OCS co-medication is highly important. However, observational studies often consider ICS as fixed combination therapies only [13], as it cannot be verified whether both substances are ingested simultaneously or consecutively.

In general, when analyzing secondary data it is difficult to assess whether the reliever drug was taken before the onset of the MI resulting in a difficult causality assessment for a particular respiratory drug. Periods of LABA/LAMA usage vs. periods without treatment are compared in the majority of observational studies based on secondary data. For this reason, users are categorized in "current users", "new users", and "past users", even though a uniform definition of these terms does not exist. For example, *Jara* et al. [12] defined "new users" as "patients [who] had to have at least two years of baseline data with no use of a long-acting inhaler prior to their first prescription for tiotropium or LABA", whereas *Suissa* et al. [5] considered patients who "had not received beta-2-agonists of any form during the 3–12 months before the index date".

Different risks for dosage and application forms

The majority of drugs for the treatment of COPD or asthma are used via inhalation. These drugs have been launched in a variety of devices (e.g., metered-dose inhaler with or without a spacer, dry powder inhaler or soft mist inhaler) differing in which way (passively or actively generated) the medication is dispensed [37]. For example for tiotropium, a soft mist inhaler device (Respimat) was developed due to irritant effects and insufficient drug application in patients with breathing difficulties using the dry powder application (HandiHaler). Since the Respimat aerosol contains a higher fraction of fine particles which is applied more slowly compared to the HandiHaler, a higher drug deposition in the lungs is reached. Accordingly, there is a lower recommended daily dose for Respimat compared to HandiHaler (5 μg versus 18 μg). Taking into account the somewhat conflicting pharmacokinetic data not excluding a higher systemic exposure of tiotropium Respimat 5 μg compared to tiotropium HandiHaler 18 μg [38–40] and a potential superiority of Respimat compared to HandiHaler regarding COPD exacerbations as suggested by cross-study comparisons [9,41], safety concerns regarding well-known dose-

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dependent antimuscarinic effects (e.g. cardiac arrhythmias) could be of clinical relevance.

Supporting these considerations, intake of tiotropium Respimat was found to be associated with an increased risk for safety issues in several studies. Singh et al. [42] found a dose-dependent all-cause mortality risk in patients receiving tiotropium Respimat compared to placebo (5 μg: RR = 1.46 [95%CI: 1.01–2.10] 10 μg: RR = 2.15 [95%CI: 1.05–4.51]). Supporting the dose-dependency of cardiac side effects, Verhamme et al. showed that patients suffering from a chronic kidney disease stage 3–5 were at increased mortality risk (aHR = 1.52 [95%CI: 1.02–2.28]) if they have received tiotropium, a compound partially excreted by the kidneys [43]. In a recently published meta-analysis, Dong et al. [20] found that the tiotropium Respimat was associated with an universally increased risk of overall death compared with tiotropium HandiHaler (OR 1.65; 95% CI 1.13–2.43). The risk was more evident for cardiovascular death, in patients with severe COPD and at higher daily dosages.

For evaluating the risk of death and major cardiovascular events of tiotropium Respimat versus HandiHaler in a direct comparison, a randomized, double-blind, parallel group trial (TIOSPIR) was conducted [44] in 17,135 COPD patients treated either with a once-daily dose of tiotropium Respimat (2.5 or 5 μg) or tiotropium HandiHaler (18 μg). To sum up, cardiovascular mortality was similar across the three treatment groups (2.1%, 2.0%, and 1.8% for Respimat 2.5 μg, Respimat 5 μg, and HandiHaler, respectively). Concerning major adverse CV events, no statistical significant differences (3.9%, 3.9%, and 3.6%) were found even though slightly fewer MI were reported in HandiHaler than Respimat group [44]. Nevertheless, subsequent analyses showed an increased risk for fatal and non-fatal MI when combining both Respimat groups compared to HandiHaler (RR 1.37; 95% CI 1.00–1.85; $p = 0.05$) [45] leading to a critical discussion of the cardiac safety of the Respimat device in particular in patients suffering from cardiac comorbidities [3].

A concomitant intake of beta-2-agonists and tiotropium is a further issue worth mentioning. For example in the TIOSPIR trial, 62% were taking long-acting beta-2-agonists in addition to tiotropium. From a pharmacological point of view, these patients might have an increased risk for cardiac adverse events due to a concomitant sympathetic activation (by beta-2-agonists) and antimuscarinic effects (by tiotropium). Nevertheless, there are only a few safety data focusing on a combined therapy including tiotropium and long-acting beta-2-agonists showing no clear evidence for an increased risk of adverse events [46–48]. In particular data for patients suffering from cardiac or renal comorbidities are lacking. For these patients whom might be at increased risk for cardiac events, further research is needed to allow a more reliable "real-life" benefit-risk-assessment of tiotropium.

Conclusion

To sum up, the evidence obtained from published meta-analyses, clinical trials, and observational studies provides no clear evidence for an increased MI risk in patients receiving short-acting B2A or tiotropium versus active control arm. By pooling all available studies for the comparison between tiotropium versus placebo, a previously reported protective effect of tiotropium regarding myocardial infarctions was supported in our meta-analysis. However, since a profound validation of MI events is lacking and device-related MI risk differences might not be excluded, additional device-specific studies with myocardial infarction as primary endpoint are required before a final conclusion can be drawn particularly for tiotropium.

Conflict of interest statement

Authors' disclosure information

MR, DR, RF, LI, EB, MS, PF, and JH have no conflicts of interest, SS and PT report personal lecture fees from Rottapharm Madaus (Cologne, Germany), JF 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 contribution under the IMI JU scheme.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.05.014.

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