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Bronchodilation and Smoking Interaction in COPD: A Cohort Pilot Study to Assess Cardiovascular Risk

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Key Words
Bronchodilator · Ischemic cardiovascular disease · COPD · Interaction · Smoking

Abstract
Background: Smoking and bronchodilator treatment are both extensively studied as key elements in patients with chronic obstructive pulmonary disease. However, little is known about whether or not these elements interact in terms of developing cardiovascular diseases in patients with COPD. ***Objectives:*** To explore to what extent the risk of developing ischemic cardiovascular disease in COPD patients is mediated by smoking status, use of bronchodilators and – specifically – their interaction. ***Methods:*** We performed an observational pilot study on a relatively healthy Dutch COPD cohort from a primary care diagnostic center database with full information on spirometry tests, smoking status, bronchodilator use and other prescribed medication. We defined first ischemic cardiovascular events as primary outcome, measured by first prescription of antiplatelet drugs and/or nitrates. Unadjusted analyses by Kaplan-Meier were followed by adjusted Cox' proportional hazards. ***Results:*** 845 COPD patients, totaling 2,169 observation years, were included in the analyses. We observed an increased risk for nonfatal ischemic cardiovascular events by smoking (adjusted HR = 3.58, p = 0.001) and a protective effect of bronchodilators (adjusted HR = 0.43, p = 0.01). Although the protective effect of bronchodilators appears to be substantially minimized in patients that persist in smoking, we could not statistically confirm a hazardous interaction between bronchodilators and smoking (HR 2.50, p = 0.21). ***Conclusion:*** Our study reveals bronchodilators may protect from ischemic cardiovascular events in a relatively 'healthy' COPD population. We did not confirm a hazardous interaction between bronchodilators and smoking, although we observed current smokers benefit substantially less from the protective effect of bronchodilators. Copyright © 2011 S. Karger AG, Basel

Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic condition that is characterized by poorly reversible, obstructive airflow limitation [1]. This disease is caused by cigarette smoking in over 80% of patients [1]. COPD is associated with increased morbidity

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and mortality, an essential part of which is due to cardiovascular disease, mainly ischemic (heart) disease and heart failure, and, to a lesser degree, arrhythmias [1–4].

The cornerstone of pharmacological treatment of COPD symptoms is bronchodilation. About 50% of patients with COPD use long-acting bronchodilators, to achieve maximum airway dilatation [5]. Although these agents improve symptoms, recently doubt re-emerged concerning their safety, especially in terms of cardiovascular conditions. Whereas large trials on the long-term effects of long-acting bronchodilators indicate a decrease in cardiovascular disease and mortality, meta-analyses suggest an increase [6–9].

As (the amount of) smoke exposure is positively related to cardiovascular mortality [10–13], smoking cessation is essential in preventing development or worsening of cardiovascular disease in COPD patients [11, 12, 14]. Despite smoking cessation programs, approximately 50% of COPD patients continue to smoke [5, 15]. Although the effects of smoking and bronchodilators on mortality in COPD patients have been extensively studied, their interaction surprisingly has not.

We recently hypothesized that a hazardous interaction between (chronic use of) bronchodilators and continued smoking could be the missing link in the discussion about bronchodilator safety [16]. Bronchodilators diminish the hyperinflated state of the lungs, thus increasing air volume displacement and lung ventilation [5, 17]. This may well result in enhancement of tobacco smoke inhalation and, as a result, pulmonary deposition of harmful cigarette smoke constituents and hence an increased cardiovascular risk. A report which demonstrated that the protective effect of tiotropium bromide on mortality appeared to be significant only in nonsmokers indirectly supports this hypothesis [18]. If an interaction between smoking and bronchodilator treatment does indeed exist, it could have a substantial impact on the pharmacotherapeutic management of patients with COPD who persevere in cigarette smoking.

Our aim was to study to what extent the risk of developing cardiovascular disease in patients with COPD is mediated by smoking status, use of bronchodilators and – specifically – their interaction. In this paper, we investigated our hypothesis by conducting an explorative observational cohort study using a primary care pulmonary function database. The current study precedes an (ongoing) randomized controlled experiment, where we expose COPD patients who are current smokers to cigarette smoke during undilated and maximal bronchodilated conditions (www. clinicaltrials.gov, ID: NCT00981851).

Table 1. Available data from primary care database, measured on each visit

General characteristics	
Age	– date of birth (dd/mm/yyyy)
Sex	– male/female
Visit	– sequential number – date (dd/mm/yyyy)
Total follow-up	– visit of inclusion until last visit (months)
Questionnaires	
Symptoms	– MRC dyspnea scale (score 1–5) – exacerbations/rescue medication (yes/no)
Medication	– pulmonary (name, dosage, form) – comedication (name, dosage)
Smoking	– status (yes/never/quit) – history (pack-years) – current cigarette amount per day
Measurements	
BMI	– height (cm) – weight (kg)
Pulmonary function (by spirometry)	– FEV_1 before and after bronchodilation (ml) – FVC before and after bronchodilation (ml)

Methods

Study Design

We conducted an observational cohort study on patients with COPD, who were retrospectively selected and followed from a prospectively designed de-identified database from a Dutch primary care diagnostic center that supports general practitioners' diagnosis and monitoring of patients with COPD. The database encloses information as single records per yearly visit from 2001 to 2009, and includes spirometric tests, demographic information and questionnaires that concern smoking, respiratory symptoms, pulmonary medication, and all prescribed comedication (table 1) [19]. We defined new prescriptions for specific cardiovascular medication (see below) as a surrogate outcome marker for nonfatal ischemic cardiovascular events. Based on dichotomous current cigarette smoking and current bronchodilator status, four key study groups were defined. Current nonsmokers included both never-smokers and former smokers whereas a positive bronchodilator treatment was defined as short-acting (salbutamol, fenoterol, ipratropium, terbutaline) and/or long-acting treatment (salmeterol, formoterol, tiotropium).

Ethical Approval

The medical ethics review board of the Radboud University Nijmegen Medical Center (CMO Region Arnhem-Nijmegen) granted exemption from regular medical ethics review for this

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Table 2. Criteria to select patients with COPD from our database

Inclusion criteria
– Chronic respiratory symptoms
– Postbronchodilation FEV_1/FVC <0.70
– Postbronchodilation FEV_1 <100% of predicted value
– Age ≥40 years
– Follow-up ≥2 visits
– Documented pulmonary and comedication
– Documented smoking status
Exclusion criteria
– <10 min between pre- and postbronchodilation measurement
– ≥10% reversibility of predicted value after inhalation of 400 μg aerosolized salbutamol
– Cardiovascular medication at baseline
– Other comedication at baseline

Table 3. Predefined medication list as surrogate markers for ischemic cardiovascular disease

Generic drug name	Brand name (as from Dutch pharmacies)
Antiplatelet therapy	
Carbasalate calcium	Ascal
Acetylsalicylic acid	Aspirin
Clopidogrel	Plavix/Iscover
Dipyridamol	Persantin
Acetyls./dipyridamol	Asasantin
Nitrates	
Nitroglycerine	Nitrolingual
Isosorbidedinitrate	Cedocard/Isordil
Isosorbidemononitrate	Monocard/Promocard

database analysis. The Dutch Data Protection Authority (http://www.dutchdpa.nl/Pages/en_ind_cbp.aspx) judged that the use of these de-identified data for scientific research is in compliance with acts that regulate the use of personal data in the Netherlands. Hence, we did not need informed consent.

Subjects

We selected all COPD patients according to current Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [1], without an asthmatic component – i.e. ≥10% postbronchodilator reversibility of predicted value of forced expiratory volume in 1 s (FEV_1) – and aged over 40 years (table 2). At least one subsequent visit to the diagnostic center was required for follow-up. Meeting selection criteria was regarded as inclusion visit. Individual follow-up time was considered as the period between study entrance and the last available visit. Patients with any comedication at baseline were excluded to eliminate bias by registration errors due to extensive medication lists. We excluded patients with missing data on bronchodilators, comedication or smoking status. Baseline characteristics included smoking status, bronchodilator use, age, sex and COPD severity markers [FEV_1 percentage of predicted, Medical Research Council (MRC) scores [20] and body mass index (BMI)].

Outcomes

We studied first nonfatal ischemic cardiovascular events (including stroke) as our primary outcome. We assessed these events by first-ever prescriptions of either antiplatelet therapy and/or nitrates (table 3) as surrogates for the actual events as these are lifelong obligatory drugs in the Netherlands in the secondary prevention of ischemic cardiovascular conditions – according to Dutch guidelines for treatment of cardiovascular diseases [21–23].

Statistical Methods

We first analyzed the potential effect of bronchodilators and smoking on cardiovascular disease by unadjusted Kaplan-Meier analysis. Next, we performed adjusted survival analysis to assess their possible interaction by Cox' proportional-hazard modeling by SPSS 16.0. We built our model by backward stepwise likelihood ratio of all available baseline confounders as suggested in the literature (age, smoking, sex, GOLD stage, FEV_1%, inhaled corticosteroids, MRC score and BMI). The basic model was complemented by smoking status, bronchodilator status, and their interaction term. A hazards ratio (HR) >1 of this interaction term implies bronchodilators and smoking interact hazardously. Never-smokers and former smokers were also analyzed separately, to test if these subgroups could be grouped together as current nonsmokers. In addition, we tested the adjusted effect of bronchodilators in both the current smokers and the current nonsmokers. Statistical significance of HRs was set at a p value of <0.05. Our null hypothesis is: there is no (interactive) effect by smoking and bronchodilators on cardiovascular disease. To validate the surrogate definitions, we compared the incidence of ischemic cardiovascular events with those published in other studies.

Results

Population Characteristics

The database contained 44,921 records, representing about 30,000 patients. Patient selection (fig. 1) resulted in recruitment of 1,740 patients. Our surrogate marker revealed an ischemic cardiovascular disease prevalence of 15.0% (261 patients) with a subsequent incidence of 4.6% ischemic cardiovascular events (200 events together) in this general COPD population. After exclusion of patients with baseline comedication, the study sample consisted of 845 patients (table 4): 95 never-smokers, 331 former smokers and 419 smokers with an average follow-up of 31 months and 3.2 follow-ups, comprising 2,169 patient-years and 2,692 follow-ups. Together, they showed a yearly incidence of 1.8% first ischemic events (38 events together). Apart from differences in the rate of ischemic events, group differences particularly are based on sex,

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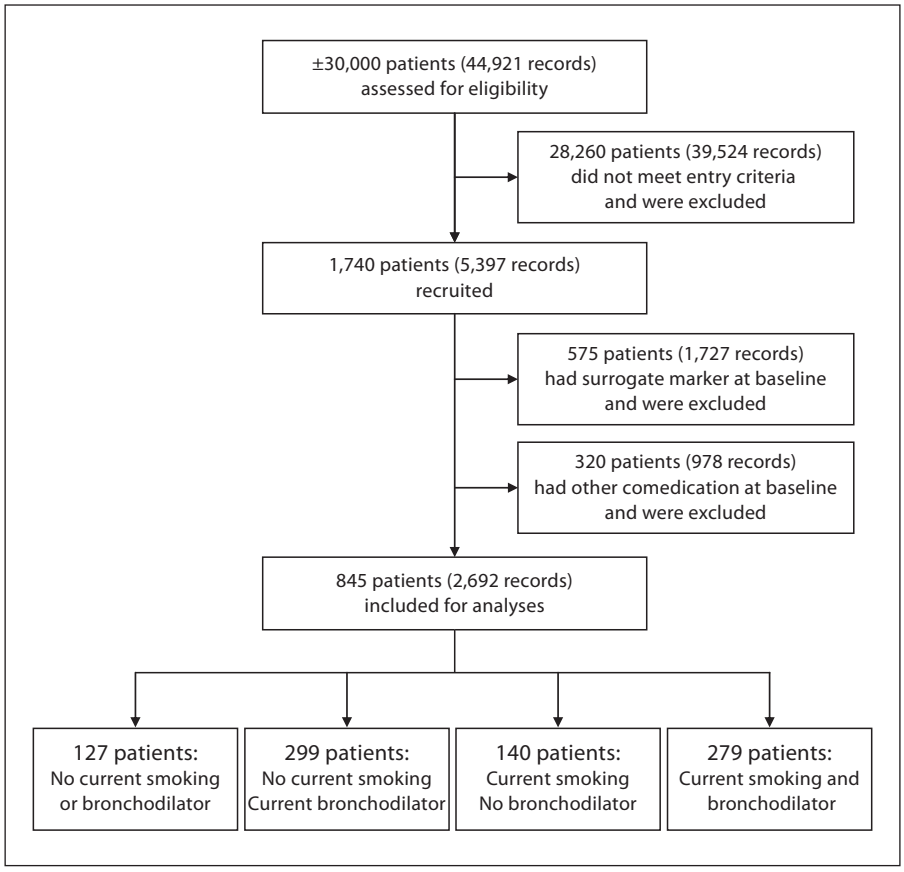

Fig. 1. Selection of records and patients for analysis to establish risk of (ischemic) cardiovascular disease. Selection criteria were based on age ≥40 years, FER <0.70, FEV_1 <100% of predicted, reversibility test >10 min after primary test, reversibility <10% of predicted, availability of smoking status, bronchodilators and comedication, and ≥2 visits.

Table 4. Characteristics of baseline study sample (845 patients), based on four key study groups

	Baseline nonsmokers		Baseline smokers	
Bronchodilator use	no (n = 127)	yes (n = 299)	no (n = 140)	yes (n = 279)
Demographics				
Age, years*	62 ± 10.0	61 ± 10.9	58 ± 8.3	57 ± 9.8
Sex, male*	88 (69)	183 (61)	93 (66)	142 (51)
Severity markers				
FEV_1% predicted post BD	72 ± 13.5	71 ± 15.1	71 ± 15.1	70 ± 14.8
MRC score (0–5)	1.6 ± 0.9	1.7 ± 0.9	1.7 ± 0.9	1.8 ± 0.9
Pulmonary medication				
Long-acting BD use*	–	202 (68)	–	161 (58)
Short-acting BD use*	–	150 (50)	–	168 (60)
Inhaled corticosteroids*	20 (16)	217 (73)	15 (11)	164 (59)
Outcome characteristics				
Mean follow-up, months	30.3 ± 19.8	31.8 ± 19.0	29.4 ± 18.7	30.7 ± 19.6
Ischemic events*	7 (5.5)	4 (1.3)	12 (8.6)	15 (5.4)
Time to event, months[1]	26.9 ± 15.9	39.5 ± 28.5	29.8 ± 18.8	33.1 ± 17.4

Data are number and percentages (in parentheses) or mean ± SD. BD = Bronchodilator.
* $p < 0.05$, significant difference between groups.
[1] Based on patients with an event.

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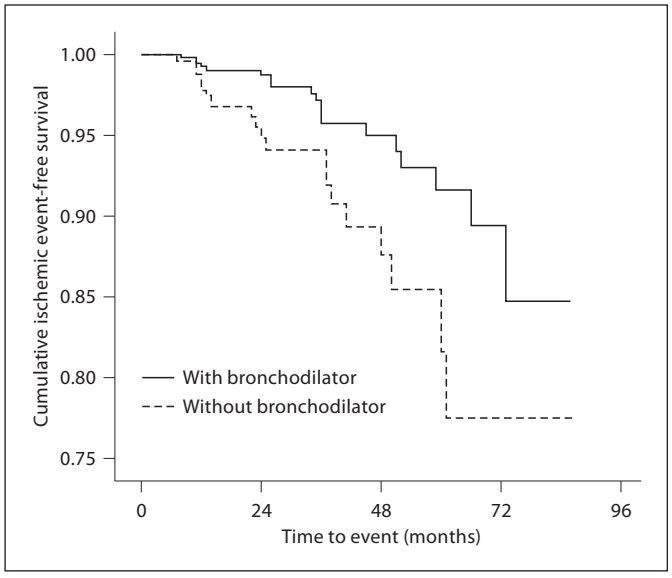

Fig. 2. Kaplan-Meier chart that shows the effect of bronchodilators on nonfatal ischemic cardiovascular events (log rank test $p < 0.01$).

Table 5. HRs for first nonfatal ischemic cardiovascular events

	HR	95% CI	p value
Age (per year)	1.08	1.04–1.11	<0.001
Smoking	2.32	0.89–6.07	0.09
Bronchodilator use	0.23	0.07–0.77	0.02
Smoking × BD interaction	2.50	0.59–10.63	0.21

HR <1 indicates protective effect; CI = confidence interval; BD = bronchodilator.

age and use of inhaled corticosteroids. The unadjusted figures of table 4 show that ischemic event rates were higher in smokers (regardless of bronchodilator use) and in patients that did not use bronchodilators (regardless of smoking status).

Statistical Analyses of Smoking and Bronchodilator Interaction

Unadjusted analyses of smoking and bronchodilators (fig. 2) as single factors for ischemic cardiovascular events by Kaplan-Meier revealed a hazardous and protective effect, respectively (both log rank tests $p < 0.01$). Backward stepwise analysis to select confounders for adjusted interaction analyses showed that age [HR = 1.08 (confidence interval, CI 1.04–1.12), $p < 0.001$), smoking (HR = 3.58 (CI 1.73–7.42), p = 0.001) and bronchodilators (HR = 0.43 (CI 0.23–0.82), p = 0.01] are significant predictors of ischemic cardiovascular events. As there was no signifi-cant difference between never and former smokers, these groups could be pooled together as current nonsmokers. The null hypothesis on interaction was not rejected: survival analysis (table 5) did not reveal a clear trend on hazardous interaction: bronchodilators HR = 0.23 (CI 0.07–0.77, p = 0.02) and interaction HR = 2.50 (CI 0.59–10.63, p = 0.21). However, a statistically significant age-adjusted protective effect of bronchodilators was observed in nonsmokers, whereas the effect was much smaller and nonsignificant in smokers: nonsmokers HR = 0.22 (CI 0.06–0.76, p = 0.02), smokers HR = 0.58 (CI 0.27–1.24, p = 0.16).

Discussion

Our aim was to explore to what extent the risk of developing cardiovascular disease in patients with COPD is mediated by smoking status, use of bronchodilators and – specifically – their interaction. This pilot study shows that smoking increases the risk to develop cardiovascular disease in relatively 'healthy' COPD patients (HR 3.58, p = 0.001) whereas bronchodilators may be protective (HR 0.43, p = 0.01). Although the protective effect of bronchodilators appears substantially minimized in patients that persist in smoking, we could not statistically confirm a hazardous interaction between bronchodilators and smoking (HR 2.50, p = 0.21).

Strengths and Limitations

Although our design restricted us to relatively 'healthy' COPD patients without an asthmatic component according to spirometry, we were able to include a substantial number of primary-care COPD patients in our analyses (n = 845). Nonetheless, the percentage of eligible patients selected for analyses was relatively small. Most patients failed inclusion in our study sample because they did not have any follow-up visits, i.e. they did not enter the diagnostic center's monitoring service (due to no confirmation of any pulmonary disease or due to noncompliance), and/or they did not meet the GOLD criteria for COPD [1]. A nonfatal ischemic cardiovascular event is not necessarily a reason to exclude a patient from further pulmonary follow-up and therefore would not present a large source of bias due to selective dropout from the study population. The power of our study is limited by the relative

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short follow-up of 2.5 years per patient and a relative long interval of usually 1 year between monitoring visits, which limits our ability to pinpoint the actual cardiovascular event to the specific date on which it occurred. Moreover, as patients accumulate substantial cardiovascular risk during their lifetime, an additive risk during follow-up based on interaction between bronchodilators and smoking would be relatively small.

Bias results in part from patient dynamics before and during the observation period, mainly due to a change in smoking and/or bronchodilator status. The cardiovascular risk of former smokers rapidly approximates the level of never-smokers [11, 12, 14] and hence these groups could be combined to form a composite 'current nonsmoker' group. Although former smokers specifically are prone to change in smoking habit, separate analyses did not reveal a significant difference in cardiovascular risk between former smokers and never-smokers, and both showed a significantly lower risk compared to current smokers.

Other potential sources of bias may result from our surrogate marker, registration errors and confounders other than the ones available in our dataset – i.e. hypertension, diabetes and heredity. The inability to adjust for hypertension and diabetes is somewhat counteracted due to its high correlation with age, smoking and BMI, confounders we did adjust for. Furthermore, our relatively healthy population did not use any other medication, and hence, hypertension and diabetes, if present, would be only mild. Next, registration errors were reduced by excluding patients with missing data on comedication and by excluding patients with comedication at baseline. Finally, our choice to use prescribed medication as surrogate markers for cardiovascular events warrants reflection. We based our primary outcome on antiplatelet therapy and nitrates. Dutch guidelines do not recommend these drugs for primary prevention, whereas they are clearly indicated for lifelong secondary prevention and symptomatic treatment, respectively [21, 22]. Indeed, a recent Dutch study reported antiplatelet prescriptions in approximately 90% of patients, 3 years after myocardial infarction [24]. In addition, other indications for these drugs by Dutch prescription regulations are rare [23]. Hence, the possible bias from not prescribing our listed medication after an event, only prescribing temporarily or prescribing for other diseases than our outcome – like hypertension – seems negligible. We therefore assume a high sensitivity and specificity for this surrogate outcome definition to actually reflect our primary outcome, i.e. ischemic cardiovascular events.

Validation

Our design resulted in a selection of relatively 'healthy' COPD patients without important comorbidity that are compliant with a primary care monitoring service. Hence, these patients would have less cardiovascular events, and translation of our results to the general COPD population with more risk of cardiovascular disease and (overruling) comorbidity tends to be difficult. To validate our method (i.e. prescriptions for secondary prevention of ischemic cardiovascular disease), we compared our results with the cardiovascular incidence of other studies. Incidence of (mainly nonfatal) ischemic cardiovascular events in COPD populations is reported as 1.7% [24]. Our recruited population therefore reveals a large overestimation at first, probably due to registration errors. The 1.8% incidence of our final study sample improves validity, but may still somewhat overestimate incidence since we did not any register fatal events and since our study sample is relatively healthy. Furthermore, our effect sizes of known risk factors – age and smoking – are comparable to other studies [10–13]. Altogether, we appreciate our markers as surrogate for outcome of ischemic cardiovascular disease as valid.

Interpretation

Several studies so far reported different findings on the cardiovascular effect of bronchodilators in COPD patients [6–9]. Our hypothesis could explain these differences and would enable guidelines to tailor treatment for individual patients more accurately [16]. Although this pilot study does not statistically confirm our hypothesis on a hazardous interaction, possibly due to a lack of power in these 'healthy' COPD patients, current nonsmokers seem to benefit more from the protective effect of bronchodilators than current smokers with regard to ischemic cardiovascular disease. The large UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) trial similarly demonstrates that the protective effect of bronchodilators depends on smoking status [18]. We believe this substantial minimization of the protective effect of bronchodilators in current smokers implies the existence of an interaction the extent of which still remains to be established. Although our study was restricted to nonfatal events, we assume a similar effect for mortality. Apart from the interaction, we assume bronchodilators themselves might protect from ischemic cardiovascular disease by both a suppressive effect on systemic inflammation and improvement of blood oxygenation that stimulates exercise and reduces cardiac stress. An alternative explanation is embedded in the

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causal relation between bronchodilators and cardiovascular outcome: patients taking medication could suggest merely good adherence, a healthier attitude and therefore fewer events [26]. However, as our study did not reveal true adherence, patients receiving treatment would be generally sicker.

Recommendations

We suggest that future prescription of bronchodilators to COPD patients that persevere in their smoking habit needs more consideration. Since our pilot study is only explorative, it does not settle the discussion on bronchodilators. In order to further explore this issue, we propose to first study the basic interaction between bronchodilators and smoking. A randomized controlled trial to document the possible pathologic mechanism on pulmonary smoke retention is currently in progress [27]. In addition, we recommend distinguishing between bronchodilator types and COPD phenotypes as these facilitate various pathways for interaction. Different bronchodilators act differently in different pulmonary regions. Accurate classification of phenotypes is subject to current discussion [28]. Finally, we suggest to study a more general COPD population and to study cardiovascular diseases other than ischemic.

In conclusion, this explorative study of relatively 'healthy' COPD patients supports a strongly increased risk of sustaining nonfatal ischemic cardiovascular events due to smoking, whereas bronchodilators may be moderately protective. We did not confirm a hazardous interaction between bronchodilators and smoking, although we observed that current smokers benefit substantially less from the protective effect of bronchodilators. We recommend to further study the safety of bronchodilators in COPD patients that persist in smoking.

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