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Original Research

COPD maintenance medication is linked to left atrial size: Results from the COSYCONET cohort

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ABSTRACT

Background: Lung function impairment in COPD is known to be related to reductions of left heart size, while short-term interventional trials with bronchodilators showed positive effects on cardiac parameters. We investigated whether COPD maintenance therapy has analogous long-term effects.
Methods: Pooled data of GOLD grade 1–4 patients from visits 1 and 3 (1.5 y apart) of the COSYCONET cohort were used. Medication was categorized as use of ICS, LABA + ICS, LABA + LAMA and triple therapy (LABA + LAMA + ICS), contrasting "always" versus "never". Echocardiographic parameters comprised left ventricular end-diastolic and -systolic diameter (LVEDD, LVESD), ejection fraction (LVEF) and left atrial diameter (LA). Associations were identified by multiple regression analysis, as well as propensity score analysis.
Results: Overall, 846 patients (mean age 64.5 y; 41% female) were included, 53% using ICS at both visits, 51% LABA + ICS, 56% LABA + LAMA, 40% LABA + LAMA + ICS (triple) therapy. Conversely, 30%, 32%, 28% and 42% had no ICS, LABA + ICS, LABA + LAMA or triple therapy, respectively, at both visits. Among echocardiographic measures, only LA showed statistically significant associations (increases) with medication, whereby significant effects were linked to ICS, LABA + ICS and LABA + LAMA ($p < 0.05$ each, "always" versus "never") and propensity score analyses underlined the role of LABA + LAMA.
Conclusions: In this observational study, COPD maintenance therapy, especially LABA + LAMA, was linked to left atrial size, consistent with the results of short-term interventional trials. These findings suggest that maintenance medication for COPD does not only improve lung function and patient reported outcomes but may also have an impact on the cardiovascular system.
Trial registration: NCT01245933

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1. Introduction

Cardiovascular comorbidities are common in patients with chronic obstructive pulmonary disease (COPD) [1–3]. Beyond a variety of shared risk factors and potential systemic facets, e.g. increased inflammation, specific interactions between lung and heart have been discovered [4–6]. For instance, airway obstruction and hyperinflation have been linked to a reduction of left heart size, which contributes to dyspnea in COPD [2,7–9]. On the other hand, clinical studies using randomized designs and cardiac magnetic resonance (CMR) imaging, have demonstrated that a reduction of airway obstruction and lung hyperinflation through bronchodilator therapy, especially with LABA/ICS or LABA/LAMA, led to short-term improvements in cardiac function [10,11]. However, treatment duration in these trials did not exceed 2 weeks, and it is not clear whether the observed effects translate into long-term cardiac changes. Moreover, it is unknown, whether such effects are elicited by all compounds of maintenance medication in COPD, including long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS). Recent findings suggested beneficial effects of long-term triple therapy on mortality from cardiac causes [12], and such effects might also have been involved in the reported reduction of all-cause mortality by triple therapy [13], but the underlying mechanisms are largely unknown.

To our knowledge, prospective studies addressing long-term cardiac effects are not available. Thus, it is reasonable to use data from existing observational cohorts to get first clues on the presence, type and magnitude of long-term effects of respiratory medication on cardiac size and function. We investigated such effects in a population of patients receiving their usual COPD maintenance therapy, using clinical, lung function and echocardiographic data from the COPD cohort COSYCONET (COPD and Systemic Consequences - Comorbidities Network) [14]. We focused our study on left ventricular and atrial characteristics, since left heart dimensions have consistently been shown to be sensitive to changes of lung function [5–8,15,16].

2. Methods

2.1. Study population and assessments

COSYCONET is a multi-center observational study addressing the role of comorbidities in COPD through regular follow-up examinations [14]. After enrollment at visit 1, visits 2 and 3 were scheduled at 6 and 18 months, respectively. At all visits, patients were required to be in stable clinical condition [14]. In the present analysis, we included patients of GOLD grades 1–4 [17,18] participating in visits 1 and 3, since at these visits echocardiography was performed. Technical details on the assessments are given in the supplement.

2.2. Classes of respiratory medication and categories of usage

Patients were attributed to four classes of medication according to the fact whether their maintenance therapy contained ICS, or LABA + ICS, or LABA + LAMA, or triple therapy (LABA + LAMA + ICS). For each class, the presence of the respective compounds was required irrespective of the potential presence of further compounds or the formulation as free versus fixed-dose combination.

For each class we defined two categories of medication usage reflecting a constant use or non-use over at least the time period of 1.5 y covered by the clinical and functional assessments. The category “always” was assumed when the respective therapy was present at visit 1 and 3, the category “never” when the respective therapy was absent at visit 1 and 3. In order to have groups with maximal contrast, the present analysis focused on the comparison of “always” with “never”. In sensitivity analyses we also performed comparisons between “always” and its complement, i.e. patients having the therapy at only one or none of the visits, and of “never” with its complement, i.e. patients having the therapy at one or both of the visits. These comparisons had the advantage of using the full data set but the disadvantage of less sharp contrasts and served as additional checks of the results.

2.3. Data analysis

For data description, mean values and standard deviations (SD) were used. Group differences were evaluated using analysis of variance for continuous and the chi-square test for categorical variables. As analytical tools we employed multiple regression analysis and propensity score matching to compare echocardiographic measures between groups of patients with similar profiles of risk factors but different medication. First, associations between medication and the echocardiographic measures LVEDD, LVESD, LVEF and LA (for abbreviations see supplement) as outcomes were assessed via multiple linear regression analyses (for details see supplement). In addition to one of the four medication classes, the following parameters were used as predictors: FEV_1, FVC, FRC, RV and TLCO (each as % predicted), FEV_1/FVC and RV/TLC (each as ratio; for abbreviations see supplement), cardiac history, cardiac medication, symptoms and exacerbation history (both according to GOLD groups [17]), age, sex, height and BSA (body surface area). Echocardiographic measures and lung function predictors were taken as mean values across visits 1 and 3, while the values of the other variables were taken from visit 1 data. This approach was chosen to achieve better comparability with the analyses via propensity scores in which repeated measures designs are uncommon. Statistical significance and confidence intervals were checked via bootstrapping with 1000 repetitions. Echocardiographic measures, except LVEF, were normalized by division through the square root of BSA, which resulted in a better normalization than the commonly used division by BSA itself (see discussion). Second, the conventional regression analyses were supplemented by analyses using propensity score matching, in order to rely on different approaches in the detection of potential treatment effects in our observational data (for detailed information see the supplement).

3. Results

3.1. Baseline description

Among 2741 patients participating in visit 1, 2291 were of GOLD grades 1–4, and 1724 participated in visit 3 (Supplemental Fig. S1). At visit 1, 1675 measurements of LVEDD, LVESD, LVEF and LA were available, of which 1658 showed values satisfying the chosen quality criteria (see supplement). At visit 3, 1120 measurements of LVEDD, LVESD, LVEF and LA were available, of which 1111 were valid, while 976 patients had valid assessments of all four echocardiographic measures at both visits. In addition, we required valid and complete measurements of the predictor variables FEV_1, FVC, FRC, RV, TLC and TLCO, cardiac history, cardiac medication, smoking status, GOLD groups, age, sex, height and BSA at both visits. In total, 846 patients of GOLD grades 1–4 (n = 97/417/283/49) with complete assessments participated in the analysis (Table 1). Compared to the remaining 1445 (=2291 minus 846) of the GOLD 1–4 patients initially included in COSYCONET, there were a number of significant differences regarding visit 1 data, indicating slightly better lung function and slightly less symptoms, exacerbations, cardiac disease and cardiac medication in the patients included in the present study compared to the patients excluded or the overall population (Table 1). All lung function measures differed been visits 1 and 3 ($p < 0.001$ each), in contrast to echocardiographic measures ($p > 0.30$ each; Supplemental Table S1). In view of the fact, that the numerical differences in all measures were small and to ensure comparability between the different statistical approaches, we used mean values of visits 1 and 3 for analysis.

Table 1
Characteristics of the study population of GOLD grades 1 to 4 at visit 1. Data are given as mean ± standard deviation, numbers, or percentages. FEV_1 = forced expiratory volume in 1 s; FVC = functional vital capacity; FRC = functional residual capacity; RV = Residual volume; TLCO = diffusing capacity for carbon monoxide. COPD symptom groups (B or D) and exacerbation groups (C or D) according to GOLD recommendations. Cardiac history and medication were binary summary indicators; for their definition see Methods.

	Study population n = 846
Anthropometry	
Sex [m/f]	58.7%/41.3%
Age [y]	64.5 ± 8.4
Height [cm]	170.9 ± 9.1
BSA [m^2]	1.90 ± 0.22
Smoking status [active]	211 (24.9%)
Lung function	
FEV_1 [%predicted]	57.0 ± 17.6
FVC [%predicted]	82.5 ± 17.8
FEV_1/FVC	0.53 ± 0.11
FRC [%predicted]	144.4 ± 32.9
RV [%predicted]	164.0 ± 47.1
RV/TLC	51.9 ± 10.0
TLCO [%predicted]	58.9 ± 21.0
Cardiac history and medication	
History [present]	152 (18.0%)
Medication [present]	448 (53.0%)
COPD symptoms and exacerbations	
Symptoms, GOLD B or D [present]	328 (38.8%)
Exacerbations, GOLD C or D [present]	256 (30.3%)

3.2. Medication classes and usage

For each of the four medication classes, the relationship between their presence or absence at visits 1 and 3 was assessed in 2 × 2 tables (Table 2). The mean (±SD) time interval between both visits was 573 ± 48 days, the median 564 days (IQR 25%/75% 546–592 days). Medication did not markedly change between both visits, with kappa values ranging from 0.640 to 0.650 for all four medication classes. Specifically, the "always" vs "never" comparisons corresponded to 449 vs 254 patients for ICS, 429 vs 269 patients for LABA + ICS, 475 vs 235 patients for LABA + LAMA, and 337 vs 359 patients for LABA + LAMA + ICS therapy.

Supplemental Table S2 presents the basic, unadjusted description of the groups of patients using the respective medication "always" vs "never" in each of the four medication classes. It includes the variables included as covariates in the regression and propensity score analyses. Lung function, symptoms and exacerbations showed significant differences between "always" and "never" in each of the four comparisons. In view of the known relationship between cardiac measures and lung function, this illustrated the need for adjustment to reveal potential effects of medication that were masked by the dependence from the confounders.

3.3. Regression analysis of echocardiographic measures

To identify associations between echocardiographic measures and medication, linear regression analyses were performed, using FEV_1, FVC, FRC, RV and TLCO (each as %predicted), FEV_1/FVC and RV/TLC (each as ratio), cardiac history, cardiac medication (both as defined in the supplement), symptoms (GOLD BD vs AC), exacerbation history (GOLD CD vs AB), age, sex, height and BSA as predictors, in addition to the medication indicators "always" vs "never" for each of the four classes.

Regarding LVEDD, LVESD and LVEF, no significant ($p < 0.05$) associations with medication were observed. In contrast, LA showed significant associations with ICS ($p = 0.028$), LABA + ICS ($p = 0.024$), LABA + LAMA ($p = 0.012$) but not triple therapy ($p = 0.059$). Regarding "always" vs "never" that turned out to be robust in bootstrap analyses, as the pattern of significance was not altered. A summary of the associations is shown in Table 3, and the sizes of the effects on LA, which were in the order of increases by 0.5–0.8 mm, are illustrated in Fig. 1. The case numbers for these comparisons can be derived from Table 2. These findings were independent (multivariate approach) of influences of both cardiac history and medication on LA in all 4 medication classes. Additional sensitivity analyses using other types of comparisons revealed effects of about the same order of magnitude and are described in the supplement.

Table 2
Cross-tabulation of the numbers of patients with the respective respiratory medication among visits 1 and 3, including values of kappa to indicate the degree of constancy over time. The numbers on the diagonal constitute the groups of "never" and "always" that were the primary target of comparisons. For example, in the case of LABA + LAMA the comparison "never" (no-no) vs "always" (yes-yes) comprised 235 vs 475 patients, that of "never" vs complement ("not never") 235 vs all other patients, and that of "always" vs complement ("not always") 475 vs all other patients.

ICS

Visit 1 \ Visit 3	no	yes
no	254	82
yes	61	449

κ=0.643

LABA + ICS

Visit 1 \ Visit 3	no	yes
no	269	82
yes	66	429

κ=0.637

LABA + LAMA

Visit 1 \ Visit 3	no	yes
no	235	75
yes	61	475

κ=0.650

Triple

Visit 1 \ Visit 3	no	yes
no	359	83
yes	67	337

κ=0.645

Table 3
Results of multiple linear regression analyses of the comparison of "always" vs "never" for ICS, LABA + ICS, LABA + LAMA and triple therapy regarding their effects on the left atrial diameter, LA, given in mm. The table shows the respective regression coefficients (estimate, in mm), their standard errors and the corresponding p values. For abbreviations see Tables 1 and 3 Very similar results were obtained when repeatedly performing bootstrap analyses with 1000 samples, and estimates as well as p values were very similar. P values < 0.05 are highlighted. The 95% confidence intervals of the medication effects are shown in Fig. 1.

Medication	ICS			LABA + ICS			LABA + LAMA			Triple therapy		
	Estimate	Standard error	p value	Estimate	Standard error	p value	Estimate	Standard error	p value	Estimate	Standard error	p value
Effect of medication	0.644	0.292	**0.028**	0.657	0.291	**0.024**	0.798	0.318	**0.012**	0.557	0.294	0.059
Sex [female vs male]	−0.650	0.387	0.093	−0.617	0.388	0.112	−0.755	0.388	0.052	−0.653	0.388	0.092
Age [y]	0.116	0.030	**<0.001**	0.118	0.030	**<0.001**	0.105	0.030	**<0.001**	0.111	0.030	**<0.001**
Height [cm]	−0.069	0.029	**0.017**	−0.075	0.029	**0.009**	−0.081	0.028	**0.004**	−0.073	0.029	**0.011**
BSA [m^2]	1.770	1.079	0.101	2.036	1.074	0.058	2.441	1.067	**0.022**	2.217	1.069	**0.038**
Smoking status [active]	−0.016	0.058	0.776	−0.004	0.058	0.951	0.059	0.059	0.319	0.015	0.058	0.791
FEV_1 [%predicted]	−0.029	0.013	**0.023**	−0.028	0.013	**0.028**	−0.026	0.012	**0.036**	−0.024	0.012	0.051
FVC [%predicted]	0.018	0.013	0.158	0.018	0.013	0.151	0.014	0.012	0.269	0.014	0.012	0.251
FEV_1/FVC	4.175	6.389	0.514	2.835	6.441	0.660	−3.110	6.458	0.630	1.491	6.481	0.818
FRC [%predicted]	−0.020	0.055	0.721	−0.024	0.055	0.657	−0.006	0.055	0.917	−0.017	0.055	0.751
RV [%predicted]	0.021	0.043	0.626	0.014	0.043	0.746	−0.021	0.043	0.625	0.003	0.043	0.950
RV/TLC	0.340	0.320	0.288	0.333	0.318	0.295	0.227	0.312	0.466	0.340	0.315	0.280
TLCO [%predicted]	0.021	0.008	**0.010**	0.020	0.008	**0.015**	0.015	0.008	0.075	0.015	0.008	0.069
Cardiac history [yes vs no]	1.364	0.354	**<0.001**	1.506	0.357	**<0.001**	1.401	0.358	**<0.001**	1.286	0.355	**<0.001**
Cardiac medication [yes vs no]	0.868	0.280	**0.002**	0.816	0.282	**0.004**	0.783	0.277	**0.005**	0.847	0.282	**0.003**
Symptoms, GOLD BD [yes] vs AC	0.458	0.300	0.127	0.458	0.301	0.128	0.224	0.300	0.455	0.333	0.304	0.273
Exacerbations, GOLD CD [yes] vs AB	0.070	0.292	0.811	0.004	0.293	0.988	−0.119	0.288	0.681	−0.006	0.296	0.983

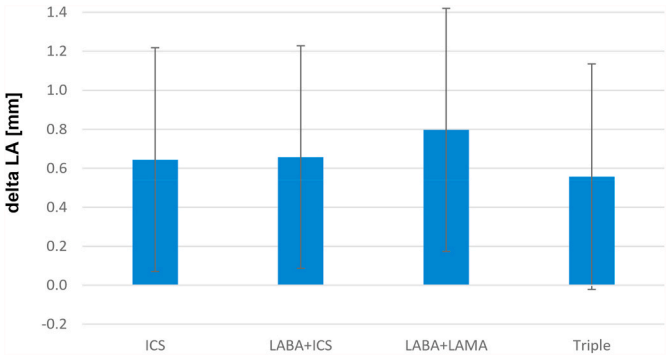

Fig. 1. The four bars show the estimated mean effects of medication ("always" vs "never") on LA (in mm) and their 95% confidence intervals for each of the medication classes ICS, LABA + ICS, LABA + LAMA and triple therapy according to the adjusted regression models (see Table 3). All effects on LA were positive and statistically significant except for triple therapy. If the 95% confidence intervals do not cross the zero line, changes were statistically significant ($p < 0.05$).

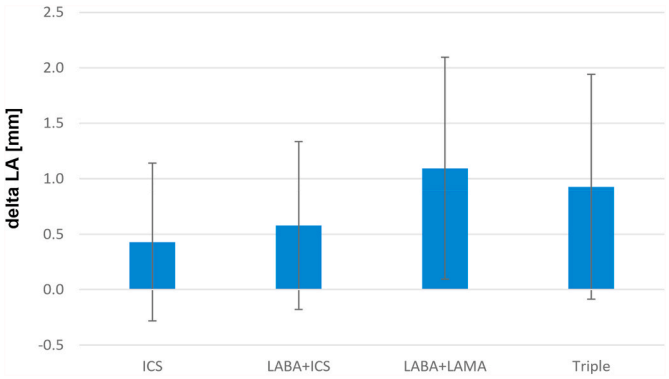

Fig. 2. In analogy to Fig. 1, the mean effects of medication ("always" vs "never") on LA (in mm) and their 95% confidence intervals as estimated by propensity score full matching (see text) are given for each of the four medication classes ICS, LABA + ICS, LABA + LAMA and triple therapy. Please note that the scale is different from that of Fig. 1. All effects on LA were positive and that of LABA + LAMA statistically significant. If the 95% confidence intervals do not cross the zero line, changes were statistically significant ($p < 0.05$).

3.4. Propensity score matching

This analysis was performed to check the results with a different statistical approach. Regarding the comparison "always" vs "never" in the four medication classes, the results obtained by regression analysis for LA were examined by propensity score analysis using full matching as the primary approach. LABA + LAMA showed significant treatment effects ($p = 0.0325$), whereas this was not the case for ICS and LABA + ICS and there was only a tendency for triple therapy ($p = 0.0731$). The mean effects and their 95% confidence intervals are shown in Fig. 2. Regarding other comparisons, only that referring to "always" vs complement for LABA + LAMA ($p = 0.0407$) and that referring to "never" vs complement for LABA + ICS ($p = 0.0418$) were statistically significant.

4. Discussion

In this observational study of GOLD 1–4 COPD patients evaluated by echocardiography, we detected positive cardiac effects from respiratory maintenance medication. Despite the presence of multiple functional and clinical factors that may have influenced the echocardiographic measures, we identified statistically significant effects of ICS, LABA + ICS and especially LABA + LAMA on the left atrial diameter, LA. This is important since a reduced left atrial size is a sensitive indicator of an impaired filling in COPD [5], followed by reductions of left ventricular size [7,8] and contributing to dyspnoea in COPD [2]. In contrast, three echocardiographic measures referring to the left ventricle were not affected. The explanation might be that due to its thin wall the atrium is particularly susceptible to mechanical influences and thus suited to detect effects elicited by changes in lung function via echocardiography.

Respiratory medication did not markedly change between both visits and it is likely that it was unchanged also beyond the examined study period, especially prior to recruitment. We therefore consider the observed associations as reflecting stable long-term conditions and effects.

From previous studies it is known that hyperinflation is associated with a decrease in cardiac chamber size [7] and that the extent of pulmonary emphysema and airflow obstruction is related to an impaired left ventricular filling and size, while in parallel LV mass is reduced as indicated by MRI [8]. This is supported by other findings linking airway obstruction and hyperinflation to impaired left heart filling, which includes reductions of LA [5] and out-of-proportion reductions of LV mass [19]. This might result in increased LV wall stress linked to airway obstruction and hyperinflation [6,15]. An increase of ventricular wall stress is usually rated as being unfavourable for clinical state [20,21], as well as symptoms and prognosis. For instance, increased ventricular wall stress is associated with adverse cardiac remodelling [22,23] and increased risk of arrhythmia [24–27]. Thus, a reduction of the cardiac filling impairment in COPD by respiratory maintenance medication may contribute to a reduction of symptoms and an improvement of physical capacity [11].

Observational findings have to be interpreted with great care due to the possibility of unobserved bias and confounding but the results obtained by conventional regression analysis were confirmed by two methods of propensity score matching, at least regarding LABA + LAMA. Thus, our results appear consistent and in favour of the hypothesis that established COPD maintenance medication has beneficial long-term effects on the heart. To identify potential effects of respiratory medication and to account for its great variety in the COSYCONET cohort, we used a structured approach. First, medication classes were defined that covered the major compounds used in COPD therapy and comprised ICS, LABA + ICS, LABA + LAMA and triple therapy. This was based solely on the presence or absence of these compounds at each visit, irrespective of the presence of other compounds. The second step was to require constancy of either the presence or the absence of these compounds over visits 1 to 3, i.e. over a period of 1.5 years. We then performed three types of comparisons. The major one was that between “always” and “never”, as this enabled the maximal separation between groups for all four medication classes, albeit at the price of the loss of samples that fell not into these two categories. To test for the robustness of results und to use the full data set, secondary comparisons were performed, specifically between “always” versus its complement, i.e. the respective medication at only one or none of the visits, and between “never” versus its complement, i.e. the respective medication at one or two of the visits. The results were consistent and robust at least for LABA + LAMA.

Propensity score matching is a statistical approach that aims to generate an analogue of an RCT from observational data via the generation of matched groups. It clearly confirmed the findings for LABA + LAMA. The fact that overall the results were weaker than those of the conventional regression analysis might be due to the fact that the distribution of propensity scores showed clear differences between treatment and control groups, which put limits to the degree of matching achievable with a not small, but still limited number of data. The results of Table 3 suggest that lung function apparently had a decisive effect on the type of treatment, as the treated patients showed impairments compared to their controls. In this sense, medication formally showed detrimental effects on the patients’ functional state. On the other hand, lung function has detrimental effects on characteristics of the left heart [5,6,16]. It was therefore a challenge to investigate whether an opposite, beneficial effect could be detected in patients treated with specific medication classes.

While lung-heart interactions in COPD are traditionally attributed to the right heart, the last decade brought growing interest in alterations of the left heart [3]. In line with observational findings of associations between airway obstruction or lung hyperinflation and echocardiographic indices [6,7] and of data obtained via MRI [8,9], beneficial effects of respiratory COPD medication on the heart have been hypothesized [28]. The associations are attributed to reductions of left heart size, reduced filling [5,29] and impaired function, as well as increased pulmonary flow resistance [30–32]. The major mechanistic factors appear to be alterations in intrathoracic pressure and chest cavity volume affecting the dimensions of the heart and vascular blood flow. Based on such data, short-term trials have been initiated, in which significant effects of LABA + ICS [10] and of LABA + LAMA [11] on indices of cardiac size and function were found after 1 or 2 weeks of treatment of patients with COPD. Similar to these studies, we kept patients with cardiac disease in the analysis, but accounted for its presence as well as cardiac medication in the regression analyses. Only patients with implausible echocardiographic data were excluded. Noteworthy enough, the major results did not depend on the inclusion or exclusion of patients with cardiac disease.

The effects of lung function on the heart not only comprised cardiac morphology and function [5,6] but also electrophysiological alterations in terms of the orientation of electrical axes, heart rate and further electrical disturbances [16,33]. Experimental findings regarding LABA + ICS therapy and relying on MRI assessments indicated that the effects on LA volume were more homogenous than those on the left ventricle [10]. This is in full accordance with our observation that LA was the only sensitive measure and that for ventricular measures there was no detectable signal of medication. Based on the present findings, it may be speculated whether COPD maintenance medication is suited, at least in part, to prevent a decrease of LV muscle mass as frequently observed in COPD or emphysema [8,16]. Further topics regarding the methodology of the present study and the interpretation of its findings can be found in the supplement.

4.1. Limitations and strengths

The present study has the obvious limitation of being a cross-sectional analysis, despite the fact that we adjusted for potential confounders as far as possible and included propensity score matching as an advanced method to approach the conditions of an RCT as closely as possible from a statistical perspective. We also did not perform a follow-up analysis as the number of patients having echocardiographic follow-up data from visits 3 and 4 was limited. In the trade-off between patient and visit numbers, we preferred to keep a high patient number. We also pooled data from visits 1 and 3 despite statistically significant differences between them. These differences were, however, small, and more complicated statistical designs yielded the same results but at the cost of loss of direct comparability with propensity score matching (see additional discussion in the supplement). Our data based on two-dimensional echocardiography are also probably less precise than those obtained via MRI in experimental studies, but our findings suggest that they were sufficiently accurate. Regarding medication we had data on its type but not necessarily its daily dose. On the other hand, a previous study of COSYCONET patients at least indicated that the adherence to treatment in COSYCONET is very high [34]; this study also showed that the difference in adherence between fixed-dose combinations and free combinations was small. As there is a tendency towards over-medication in COSYCONET [35] it was particularly difficult to define suitable control groups in which a certain medication was absent. We thus performed different types of comparisons and at least for LABA + LAMA found consistent results.

The strengths of the study were the large sample size, the comprehensive data on patients’ characteristics including respiratory medication and lung function, and the availability of data from two visits that allowed to increase statistical power, while at the same time close enough to each other in order to render clinically significant changes unlikely.

5. Conclusion

In a large COPD cohort, we found associations of respiratory maintenance medication containing ICS, LABA and LAMA on the left heart. Among four echocardiographic parameters of the left heart, the atrial diameter (LA) was significantly associated with medication; this was true for ICS, LABA + ICS and most consistently for LABA + LAMA. These findings suggest that prospective studies on long-term cardiac effects of respiratory maintenance medication in COPD could be promising.

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The study was based on 2741 patients recruited within the COSYCONET framework (ClinicalTrials.gov, Identifier: NCT01245933). For further information see Karch A, Vogelmeier C, Welte T, Bals R, Kauczor HU, Biederer J, Heinrich J, Schulz H, Glaser S, Holle R et al.: The German COPD cohort COSYCONET: Aims, methods and descriptive analysis of the study population at baseline. Respir Med 2016, 114:27–37.

Availability of data and materials

The basic data are part of the German COPD cohort COSYCONET (www.asconet.net) and available upon request. The website of the network provides a detailed procedure for respective applications. The data can be obtained after submission of a proposal that is evaluated by the steering committee. All results to which the manuscript refers, are documented appropriately in the text, figures or tables.

Consent for publication

Within the ethical approval of COSYCONET, the participants of the study gave their consent to publish the data collected without reference to their person.

CRediT authorship contribution statement

Christina Kellerer: was involved in the design of the study, Formal analysis, the interpretation of the data, drafting and finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Kathrin Kahnert:** was involved in the design of the study, the interpretation of the data, drafting and finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Franziska C. Trudzinski:** was involved in the interpretation of the data, finalization of the manuscript. **Johanna Lutter:** was involved in the interpretation of the data, finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Korbinian Berschneider:** was involved in the interpretation of the data, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Tim Speicher:** was involved in preparation and, Formal analysis, of the data, finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Henrik Watz:** was involved in the interpretation of the data, finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Robert Bals:** was involved in the interpretation of the data, finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Tobias Welte:** was involved in the interpretation of the data, finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Claus F. Vogelmeier:** was involved in the design of the study, interpretation of the data, finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Rudolf A. Jörres:** was involved in the design of the study, statistical, Formal analysis, interpretation of the data, drafting and finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. **Peter Alter:** was involved in the design of the study, statistical, Formal analysis, interpretation of the data, drafting and finalization of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors declare that they have no competing interests. Financial support provided to individuals is disclosed on the conflict of interest declaration provided from each single author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2021.106461.

Conflicts of interest

All authors have nothing to disclose with regard to this manuscript.

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