Online Data Supplement

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

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ADDITIONAL INFORMATION ON METHODS

Clinical assessments

Clinical history and prescribed medication were assessed as described previously [1, 2]. Comorbidities were determined from patients' reports of physician-diagnosed diseases, supplemented by the evaluation of disease-specific medication, wherever possible [2]. The diagnoses of remote myocardial infarction, coronary artery disease and heart failure (at least one of them) were combined into a variable termed "cardiovascular history" [3]. Among cardiovascular drugs, betablockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor (AR) blockers and diuretics (at least one of them) were combined into a binary variable termed "cardiovascular medication". To account for influences of cardiovascular medication in COPD (e.g. symptoms) [3], this combined variable was included as predictor in the analyses. The assessment of anthropometric data and the classification into GOLD groups [4] based on the modified Medical Research Council scale mMRC [5] followed standardized protocols [1]. For the present analysis, GOLD grouping BD vs AC were taken as binary indicator of symptoms, and grouping CD vs AB as binary indicator of exacerbation history, as done previously [6, 7]. Body Surface Area (BSA) was computed according to DuBois [8].

The study was conducted in accordance with the amended Declaration of Helsinki. All participants had given their written informed consent, and the study was approved by the Ethics Committee of the University of Marburg as coordinating center and the Ethics Committees of all study centers; it is registered on ClinicalTrials.gov (registration number NCT01245933).

Measurements of lung function and echocardiography

The assessment of post-bronchodilator lung function included spirometry, bodyplethysmography and the determination of carbon monoxide (CO) diffusing capacity via the single-breath method [1]. We determined forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), their ratio FEV_1/FVC, residual volume (RV), total lung capacity (TLC), their ratio RV/TLC, functional residual capacity (FRC), and the CO transfer factor (TLCO) [9]. All measures, except RV/TLC and FEV_1/FVC, were taken as percent of their respective GLI or ECSC predicted values [10-12]; RV/TLC and FEV_1/FVC were used as absolute ratio, as their determinants [10] sex, height and age were included as predictors.

Echocardiography was performed using standard techniques [13, 14] and detailed protocols supplied to the study centers [1]. The following measures were analyzed: left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF), and left atrial diameter (LA). For reasons of quality control, only examinations showing values within the following ranges were used: LVEDD ≥ 25 mm; LVESD ≥ 10 mm; LA ≥ 20 and ≤ 60 mm, and only patients fulfilling the criteria at both visits were included.

Propensity score analysis

Propensity scores were computed via logistic regression analysis using the predictors from the linear regression analyses and further used as logit scores. These scores were used to match patients between the medication and their respective comparison groups, using full matching [15, 16], a procedure allowing for multiple correspondences between groups and utilizing the whole data set. Echocardiographic outcomes were compared between groups in linear regression analyses comprising all predictors that had been included in the conventional regression analyses and using weights derived from the propensity scores. There are various methods of matching that might yield different results, thus for further analysis we also employed another advances approach, i.e. genetic matching [17] resulting in the definition of coordinated subgroups that again were evaluated via weighted regression analysis for outcome assessment. The quality of matching for each variable was quantified via the

standardized mean differences between the matched groups, assuming values below 0.25 as acceptable [18]. To indicate the overall quality of matching for each of the comparisons we show a mean value computed by averaging squares of these differences as well as their maximum.

Software used for statistical procedures

Basic statistical analyses were performed via the software package SPSS (26.0.0.0, Armonk, NY, US), while propensity scores were computed using the package "dplyr" from R (Version 4.0.2), matching was performed via the packages "MatchIt" and "optmatch", using the different options in this package, and outcome evaluation by weighted regression using the package "survey". The level of statistical significance was assumed at p=0.05.

ADDITIONAL RESULTS

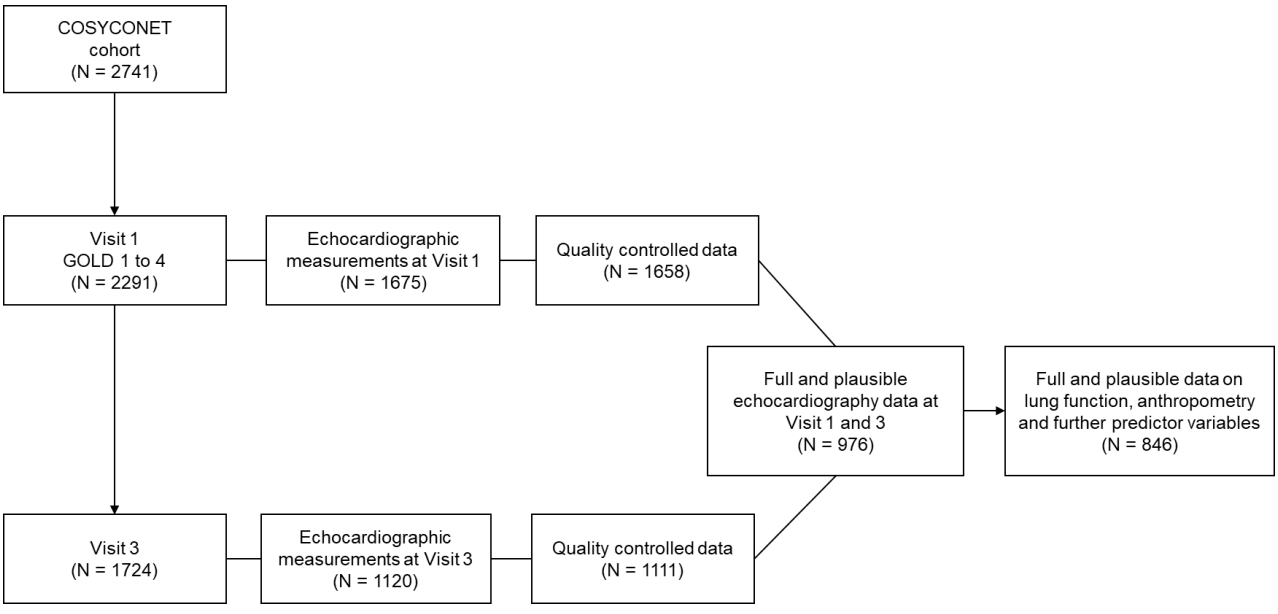
Sensitivity analyses

We first examined to which extent the results depended on the choice of the categories of usage, realizing that "always" vs "never" offered the clearest contrast but was associated with a reduction in case numbers. The numbers for "always" vs complement ("not always") and "never" vs complement ("not never") can also be taken from Table 2. When comparing "never" with its complement, there were still some significant differences, regarding ICS (p=0.006), LABA+ICS (p=0.007), LABA+LAMA (p=0.080) and triple therapy (p=0.042). Their number was lower when comparing "always" with its complement, regarding ICS (p=0.198), LABA+ICS (p=0.206), LABA+LAMA (p=0.014) and triple therapy (p=0.283). This pattern of significances was robust in bootstrap repetitions. Moreover, we repeated the analysis when excluding all patients having ICS in any combination in GOLD groups A and B at visits 1 and 3. In this case (n=467), "always" vs "never" yielded a significant difference only for LABA+LAMA (p=0.011), as well as for the comparison "always" vs complement (p=0.013) and "never" vs complement (p=0.046). For the other three medication classes comprising ICS, LABA+ICS and triple therapy, there were no significant associations in any of the comparisons of medication usage, and p

values were far from 0.05. An additional sensitivity analysis performed by excluding all patients with cardiac disease showed that for LABA+LAMA the “always” vs “never” comparison was still statistically significant (p=0.019), as well as that for “always” vs complement (p=0.041) and for ICS and LABA+ICS the comparison “never” vs complement (p<0.015 each). Again, these results were confirmed in bootstrap analyses. Moreover, the inclusion of the separate visits in a repeated measures design did not yield different outcomes but resulted in a design that was not directly comparable to that used in the propensity score matching.

Regarding propensity score analysis, the alternative approach of genetic matching confirmed the difference “always” vs “never” for LABA+LAMA (p=0.0169) found by full matching, and also showed a tendency regarding “always” vs complement (p=0.0626). Similarly, there was a tendency (p=0.0574) for “always” vs complement regarding LABA+ICS. All other comparisons were not statistically significant (p>0.10 always).

Supplemental Figure S1. Flow diagram showing the selection of participants included in the analysis



Supplemental Table S1. Lung function and echocardiographic characteristics of the study population at visits 1 and 3

	Visit 1 n = 846	**Visit 3 n = 846**	**p value**
Lung function			
FEV_1 [%predicted]	57.0 ± 17.6	55.0 ± 18.4	<0.001
FVC [%predicted]	82.5 ± 17.8	80.6 ± 18.7	<0.001
FEV_1/FVC	0.5 ± 0.1	0.5 ± 0.1	<0.001
FRC [%predicted]	144.4 ± 32.9	146.9 ± 32.7	0.003
RV [%predicted]	164.0 ± 47.1	168.3 ± 46.7	<0.001
RV/TLC	51.9 ± 10.0	53.6± 10.2	<0.001
TLCO [%predicted]	58.9 ± 21.0	57.4 ± 21.4	0.003
Left heart size and function			
LVEDD [mm]	48.1 ± 7.1	48.1 ± 6.7	0.805
LVESD [mm]	32.4 ± 7.2	32.2 ± 7.2	0.459
LVEF [%]	61.9 ± 8.9	61.6 ± 8.1	0.301
LA [mm]	36.0 ± 6.3	36.2 ± 6.4	0.409

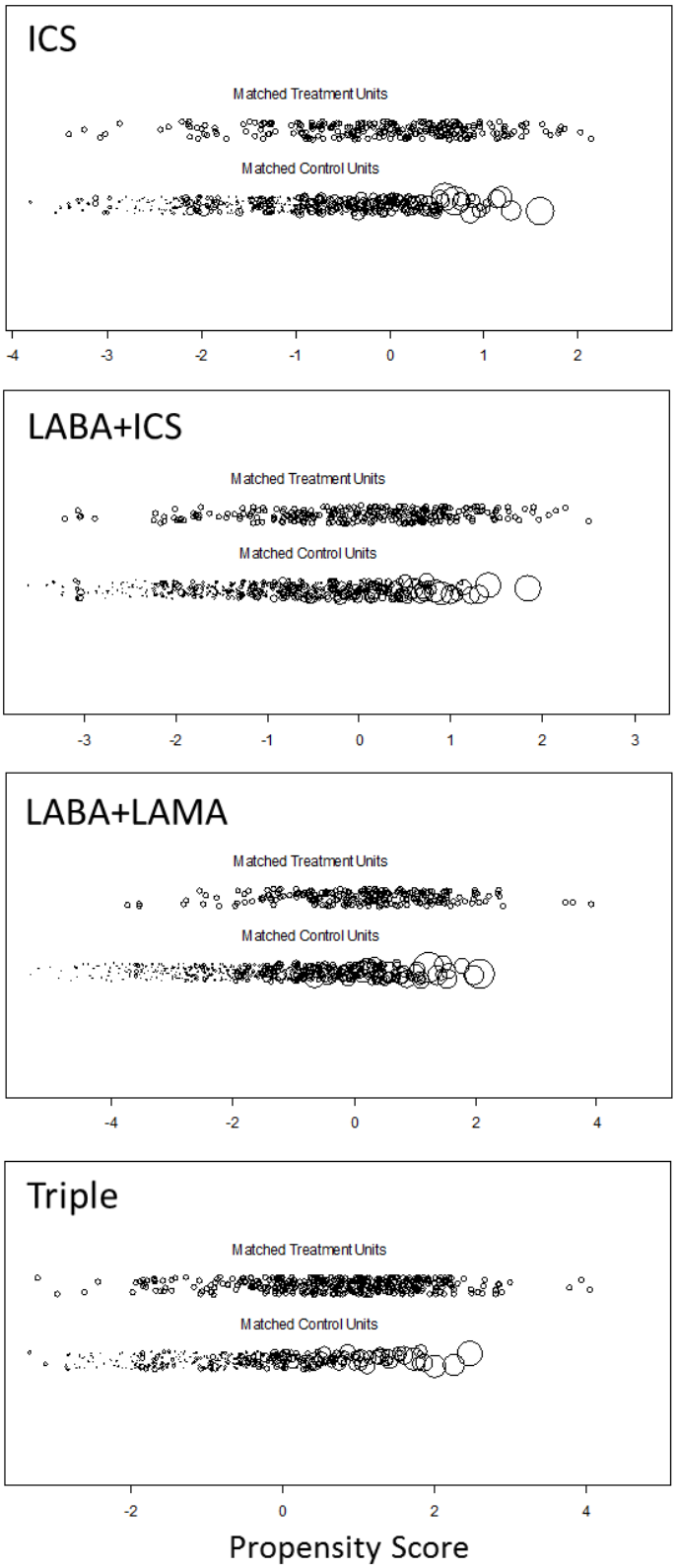
Data given as mean ± standard deviation, numbers, or percentages. FEV_1 = forced expiratory volume in 1 second; FVC = functional vital capacity; FRC = functional residual capacity; RV = Residual volume; TLCO = total diffusing capacity for carbon monoxide; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; LA = left atrial diameter. Statistical comparisons and p values were derived from t-tests.

Supplemental Table S2. Subject characteristics among the four medications classes regarding the categories “always” versus “never”.

	ICS		LABA + ICS		LABA + LAMA		Triple therapy	
	always	**never**	**always**	**never**	**always**	**never**	**always**	**never**
Numbers	449	254	429	269	475	235	337	359
Anthropometry								
Sex [males/females]	58.8%/41.2%	58.3%/41.7%	58.7%/41.3%	57.2%/42.8%	58.1%/41.9%	60.4%/39.6%	59.3%/40.7%	57.9%/42.1%
Age [y]	65.0 ± 8.4	64.1 ± 8.6	65.0 ± 8.4	64.0 ± 8.6	64.3 ± 8.5	64.9 ± 8.6	64.5 ± 8.4	64.7 ± 8.7
Height [cm]	170.6 ± 8.9	171.6 ± 9.4	170.7 ± 8.9	171.5 ± 9.3	170.8 ± 9.1	171.3 ± 9.1	170.9 ± 9.0	171.3 ± 9.3
BSA [m²]	1.89 ± 0.21	1.90 ± 0.23	1.90 ± 0.21	1.90 ± 0.23	1.89 ± 0.21	1.91 ± 0.22	1.90 ± 0.22	1.90 ± 0.23
Smoking status [active]	76 (16.9%)	96 (37.8%)***	74 (17.2%)	100 (37.2%)***	102 (21.5%)	77 (32.8%)***	58 (17.2%)	119 (33.1%)***
Lung function								
FEV_1 [%predicted]	53.2 ± 17.2	63.9 ± 16.9***	52.9 ± 17.0	64.1 ± 16.8***	51.2 ± 15.5	68.8 ± 15.8***	49.8 ± 15.4	64.9 ± 16.7***
FVC [%predicted]	79.1 ± 17.4	88.0 ± 17.6***	79.0 ± 17.4	88.2 ± 17.4***	78.7 ± 17.4	90.1 ± 16.3***	76.7 ± 17.0	88.2 ± 17.3***
FEV_1/FVC	0.52 ± 0.10	0.56 ± 0.10***	0.51 ± 0.10	0.56 ± 0.10***	0.50 ± 0.10	0.59 ± 0.08***	0.50 ± 0.10	0.57 ± 0.09***
FRC [%predicted]	146.3 ± 32.8	141.1 ± 32.2*	146.9 ± 32.8	141.2 ± 32.1*	150.6 ± 33.2	132.8 ± 30.3***	150.4 ± 33.5	138.7 ± 31.8***
RV [%predicted]	168.8 ± 47.8	154.7 ± 45.1***	169.5 ± 48.3	154.7 ± 44.3***	174.2 ± 48.1	144.9 ± 40.4***	174.8 ± 49.4	152.6 ± 42.8***
RV/TLC	53.7 ± 9.8	49.0 ± 9.8***	53.8 ± 9.9	49.0 ± 9.6***	54.2 ± 9.9	47.4 ± 8.7***	54.8 ± 9.9	49.0 ± 9.4***
TLCO [%predicted]	58.1 ± 20.9	61.3 ± 21.8	57.5 ± 20.9	61.7 ± 21.4*	54.4 ± 19.1	68.0 ± 22.7***	54.3 ± 18.8	64.4 ± 22.1***
Cardiovascul. history & medication								
History	79 (17.6%)	48 (18.9%)	73 (17.0%)	53 (19.7%)	84 (17.7%)	37 (15.7%)	62 (18.4%)	64 (17.8%)
Medication	246 (54.8%)	126 (49.6%)	235 (54.8%)	134 (49.8%)	264 (55.6%)	103 (43.8%)**	194 (57.6%)	176 (49.0%)*
COPD symptoms & exacerbations								
Symptoms, GOLD BD	212 (47.2%)	61 (24.0%)***	206 (48.0%)	65 (24.2%)***	227 (47.8%)	48 (20.4%)***	174 (51.6%)	90 (25.1%)***
Exacerbations, GOLD CD	170 (37.9%)	42 (16.5%)***	164 (38.2%)	45 (16.7%)***	182 (38.3%)	35 (14.9%)***	140 (41.5%)	63 (17.5%)***
Left heart size and function								
LVEDD [mm]	48.3 ± 6.3	47.9 ± 5.5	48.2 ± 6.2	47.9 ± 5.5	47.9 ± 6.1	48.4 ± 5.7	48.0 ± 6.3	48.3 ± 5.6
LVESD [mm]	32.2 ± 6.5	32.6 ± 5.6	32.3 ± 6.5	32.4 ± 5.6	32.4 ± 6.3	32.3 ± 6.0	32.2 ± 6.5	32.5 ± 5.8
LVEF [%]	61.8 ± 7.1	61.7 ± 6.7	61.8 ± 7.1	61.6 ± 6.7	61.4 ± 7.1	62.6 ± 6.9*	61.6 ± 6.9	62.1 ± 7.2
LA [mm]	36.3 ± 5.7	35.5 ± 5.9	36.2 ± 5.8	35.6 ± 5.8	36.1 ± 5.9	36.3 ± 5.6	36.1 ± 5.8	36.1 ± 5.8

Data is given as mean ± standard deviation, numbers or percentages. FEV_1 = forced expiratory volume in 1 second; FVC = functional vital capacity; FRC = functional residual capacity; RV = Residual volume; TLC = total lung capacity; TLCO = diffusing capacity for carbon monoxide. COPD symptom groups (B or D) and exacerbation groups (C or D) according to GOLD recommendations. LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; LA = left atrial diameter. Significant differences are denoted as follows: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Supplemental Figure S2. Results of full matching in propensity score analysis



The four panels show the logit-transformed propensity score after matching for the four medication classes when comparing "never" with "always", as resulting from the full matching procedure. This direction of comparison was chosen for technical reasons in order to better utilize the adaptive matching capability of the full matching algorithm, and afterwards coefficients were inverted to "always" vs "never". The size of the circles represents patients' weight in the subsequent regression analysis of the effect on LA (see Figure 2)

ADDITIONAL TOPICS FOR DISCUSSION

Rationale for averaging visit 1 and 3 data

For analysis, we used average data from visits 1 and 3, although there were small differences in lung function measures that were in the range to be expected over a period of about 1.5 years in COPD patients. This approach was chosen to avoid additional variability from changes of covariates over time that did not correspond to change in outcome variables of a similar size. The data shown in table S1 underline that echocardiographic measures showed less change over time than lung function. Moreover, their correlations with lung function were weak compared to the correlation between lung function measures. In view of this it is unreasonable to expect statistically significant correlations between the changes of echocardiographic and lung function variables. It is therefore justified to choose mean values of the data from two visits. Using a repeated-measures design resulted in similar findings for each of the two visits, but with larger confidence intervals for each of them despite a relatively high level of significance for the total effect. This rendered it more difficult to compute confidence intervals for the total effect, especially when using the bootstrap approach for estimation of confidence intervals. The consistency of our findings indicates that the use of average data from visits 1 and 3 did not induce statistical artefacts, in particular, as the omission of a potential fine-structure in the predictors would not favour significant results. Moreover, the pooled regression approach allowed a direct comparison with that of propensity score matching for which repeated-measures designs are difficult to implement.

Assessment of medication and comorbidities

Our analysis required detailed information on respiratory medication. This was assessed at each visit by a structured approach[1] and evaluated via ATC codes,[2] thereby allowing for comprehensive lists of individual respiratory and non-respiratory medication. Information on medication has been used previously in COSYCONET studies,[2, 3, 19, 20] as well as data on cardiac and other comorbidities that were derived from patients' reports of physician-based diagnoses, supplemented by the evaluation of

disease-specific medication if possible.[2] The combined cardiac indicator variable has been used in a previous study on the prevalence of cardiac disorders in COPD,[3] and the combined cardiac medication variable was defined in a similar way. Therefore, the present analysis relied upon data that had been proven as meaningful in previous studies and could be considered as reliable. The fact that the presence of cardiac disease showed a strong positive correlation to LA was consistent with the alterations expected with cardiac failure and similar disorders, while the observation that cardiac medication also showed positive effects might seem counterintuitive. It probably reflected the fact that we only included the presence of cardiac disease not its severity, and that the presence of medication indicated increased severity. It also should be kept in mind that the exclusion of patients with cardiac disease did not alter the main results (sensitivity analyses).

The groups defined by “always” vs complement and by “never” vs complement were less separated and pure than “always” vs “never” but included the whole set of patients. For example, the complementary group of “always triple” comprised patients with triple only once, and additionally always LABA+ICS without LAMA, or always LABA+LAMA without ICS, i.e. patients with respiratory medication that could be considered as much more effective than placebo. Even in the “always” vs “never” comparison, which was our primary goal, the “never” group would contain patients with effective medication. The differences in the purity of groups, especially complementary groups, were probably the major source of the differences in results between different medication conditions.

We normalized the echocardiographic measures, except LVEF, by the square root of body surface area (BSA), and not the commonly used BSA. The reason was twofold. First, the residual dependence on BSA was much smaller when using the square root. Second, a parameter of length such as the LA diameter should be normalized by a parameter of length, such as the square root of BSA. When using BSA for normalization, the results were similar, although significance levels were lower and the dependence on BSA stronger which led to difficulties in propensity score matching. We thus believe that our standardization of echocardiographic measures was justified. Lung function was incorporated into the analyses via FEV_1, FVC and FEV_1/FVC as indicators of airway obstruction, FRC, RV and RV/TLC

as indicators of lung hyperinflation, and TLCO as indicator of gas exchange impairment. All of them were expressed as percent predicted or as ratio as indicated. We kept these measures in all analyses irrespective of the fact whether they were statistically significantly associated with either medication or echocardiographic measures. The same applied to all other predictors, and we thereby ensured comparability between analyses. It is generally recommended to keep in propensity score matching all meaningful predictors irrespective of their statistical significance.[21]

In COSYCONET, lung function was measured after supervised bronchodilation including 400 µg Salbutamol and 80 µg Ipratropium bromide[1] to achieve a maximum standardization of bronchodilator status at the start of each study visit. In this regard, patients were comparable. On the other hand, in the patients' daily life their medication may be different and less intense. Although in COSYCONET there is a tendency towards over-therapy[22] compared to GOLD 2017 recommendations[4] and treatment adherence is very high;[19] nothing is known about inhalation techniques and effectiveness compared to the prescribed doses per day. It might be therefore hypothesized that the relationship between LA diameter and medication comprised two components. The first component reflected the long-term relationship between echocardiographic and lung function parameters, which is a function of clinical status. This component was manifest in the association between LA and lung function measures that were established over time irrespective of medication. According to the regression analyses, the additive effects of medication that we found would represent an upward shift in LA while maintaining the correlation between lung function and LA. With a high level of therapy, especially over-therapy, one might expect lower effects of a level of bronchodilator therapy that is in line with recommendations. Indeed, a sensitivity analysis performed by omission of patients of GOLD groups A and B who had ICS and thus over-therapy according to GOLD recommendations, showed that the effects of LABA+LAMA on LA were even exaggerated compared to the total group while those of ICS which could still be present in group C and D patients, completely disappeared.

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