ORIGINAL RESEARCH

Comparison of Characteristics Between ICS-Treated COPD Patients and ICS-Treated COPD Patients with Concomitant Asthma: A Study in Primary Care

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Background and Objective: Inhaled corticosteroids (ICS) for COPD has been much debated. Our aim was to identify characteristics associated with prescribing ICS for patients with COPD alone compared to those with concomitant asthma in general practice.

Patients and Methods: Participating general practitioners (GPs) (n=144) recruited patients with COPD (ICPC 2nd ed. code R95) currently prescribed ICS (ACT code R03AK and R03BA). Data, if available, on demographics, smoking habits, spirometry, COPD medication, dyspnea score, and exacerbation history were retrieved from the medical records. Logistic regression analysis was used to identify possible differences in characteristics between patients with COPD alone compared to those having a concomitant diagnosis of asthma.

Results: A total of 2.289 (45% males) COPD patients on ICS were recruited. Compared to patients with COPD alone (n=1.749), those with COPD and concomitant asthma (n=540) were younger (p<0.001), had higher BMI, higher FEV_1/FVC ratio, higher blood eosinophil count and less life-time tobacco exposure (36 and 26 pack-years, respectively). Compared to COPD alone, logistic regression analysis showed that COPD with concomitant asthma was significantly associated to age (OR 0.94; CI 0.92 to 0.97; p<0.001), pack-years of smoking (OR 0.98; CI 0.97 to 0.99; p<0.001), FEV_1%pred (OR 1.02; CI 1.00 to 1.03; p=0.005), and doctor-diagnosed depression (OR 2.59; CI 1.20 to 5.58; p=0.015).

Conclusion: In COPD patients currently prescribed ICS, the presence of concomitant asthma was associated with being younger, having less tobacco exposure, more preserved lung function and a higher likelihood of doctor-diagnosed depression compared to COPD alone.

Keywords: COPD, concomitant asthma, inhaled corticosteroids (ICS), general practice

Introduction

Long-acting bronchodilators are the cornerstone of pharmacological treatment of chronic obstructive pulmonary disease (COPD).[1] However, inhaled corticosteroids (ICS) have been shown to reduce exacerbations, hospitalizations and have also been linked to a reduction in mortality in COPD patients.[2–5] Global Initiative of Chronic Obstructive Lung Disease (GOLD) has recommended using ICS in patients with severe airflow limitation and/or patients at high risk of COPD exacerbations.[1] However, there is evidence of widespread use of ICS in patients with less severe COPD not fulfilling the GOLD criteria for ICS use.[6–8]

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A meta-analysis of available clinical trials suggested that ICS treatment in patients with COPD may reduce the annual decline in lung function.[2] Furthermore, improvements in health status has been demonstrated in COPD patients prescribed monotherapy with LABA or LAMA,[9,10] but add-on ICS to long-acting bronchodilator treatment has been demonstrated to improve health status even further.[11]

ICS-therapy may be associated with potentially severe side effects as studies have demonstrated an increased risk of fractures and pneumonia.[12–14] Furthermore, the distinction between side effects such as pneumonia and symptoms is difficult to define in a primary care setting.[15] The adverse effects of ICS treatment in COPD patients points to the importance of more research on the risk-benefit profile of ICS.[16,17] It is therefore crucial to understand what determines the use of ICS in COPD patients.

In recent years there has been an increasing interest in understanding the concomitant diagnosis of asthma in COPD patients and distinguishing clinical features associated with either COPD or asthma in patients presenting with obstructive lung diseases.[18,19] This has given rise to treatment recommendations for COPD patients with concomitant asthma.[20] However, there is no consensus on a definition of COPD patients with a concomitant asthma diagnosis, and it has proven challenging to properly characterize these patients. In a large cohort of patients with COPD managed in primary care and currently prescribed inhaled corticosteroids, our aim was to identify possible differences in characteristics associated with prescribing ICS for patients diagnosed with COPD alone and those with concomitant asthma.

Patients and Methods

All study participants had a confirmed diagnosis of COPD, were currently prescribed ICS (coded as International Classification of Primary Care, 2nd ed. code R95 in electronic patient journals and with the ACT code R03AK and R03BA, indicating ICS treatment), and were managed by general practitioners (GPs) in primary care, and for some patients, also specialists. The selection process of patients participating in the study is summarized in Figure 1, also illustrating the primary focus of the present study. Further details related to the selection procedure has been published previously.[21] Participating GPs provided information, if available, on demographics, clinical characteristics, blood eosinophils, consultations for respiratory disease, prescribed medication, hospital admissions for COPD, previous COPD exacerbations, smoking status, selected comorbidities, and

duration of COPD for all recruited patients. Each general practice included up to a maximum of 20 randomly selected patients. All patients were assigned a unique project ID number to assure anonymity with only the designated GP being unblinded to patient identity.

The study was approved by the Danish Data Protection Agency. The present study was a non-interventional, non-drug study, and, therefore, it was not mandatory to obtain approval from the ethical committee and the Danish Medicines Agency.

Assessment of Symptoms, Airflow Limitation and Acute Exacerbations

Severity of symptoms was assessed by the Medical Research Council (MRC) scale[22] and/or the COPD assessment test (CAT). Spirometric findings were used to estimate airflow obstruction and categorize the severity of the disease, based on a cut-off for FEV_1 according to the classification provided by GOLD.[23] Patients were also classified into four groups, i.e., A, B, C and D, according to the GOLD 2017 classification, based on COPD symptoms (MRC-scale score $\geq$ 2 and/or CAT score $\geq$ 10) and the exacerbation history.

Data Analysis

Data are reported as mean values $\pm$ one standard deviation (SD). Clinical variables and characteristics of COPD alone were compared to COPD with concomitant asthma using independent sample t-test for continuous variables. The comparison between COPD alone and COPD patients with a concomitant asthma diagnosis in terms of possible clinically-relevant variables and characteristics was conducted using a multinomial logistic regression model and reported as odds ratios and 95% confidence intervals. A p-value <0.05 was considered statistically significant. Data were analyzed using the statistical program IBM SPSS version 25 (IBM Corporation, Armonk, NY, USA).

Results
Characteristics of Enrolled Patients with COPD

Of the COPD patients currently on ICS therapy (n=2289) included in the present study, 540 (24%) were classified by the GP as having concomitant asthma.

Slightly more female than male patients were recruited (55% vs. 45%), whereas no difference was found in mean age between sexes (71 years; p=0.83). Further characteristics of the patients are given in Table 1.
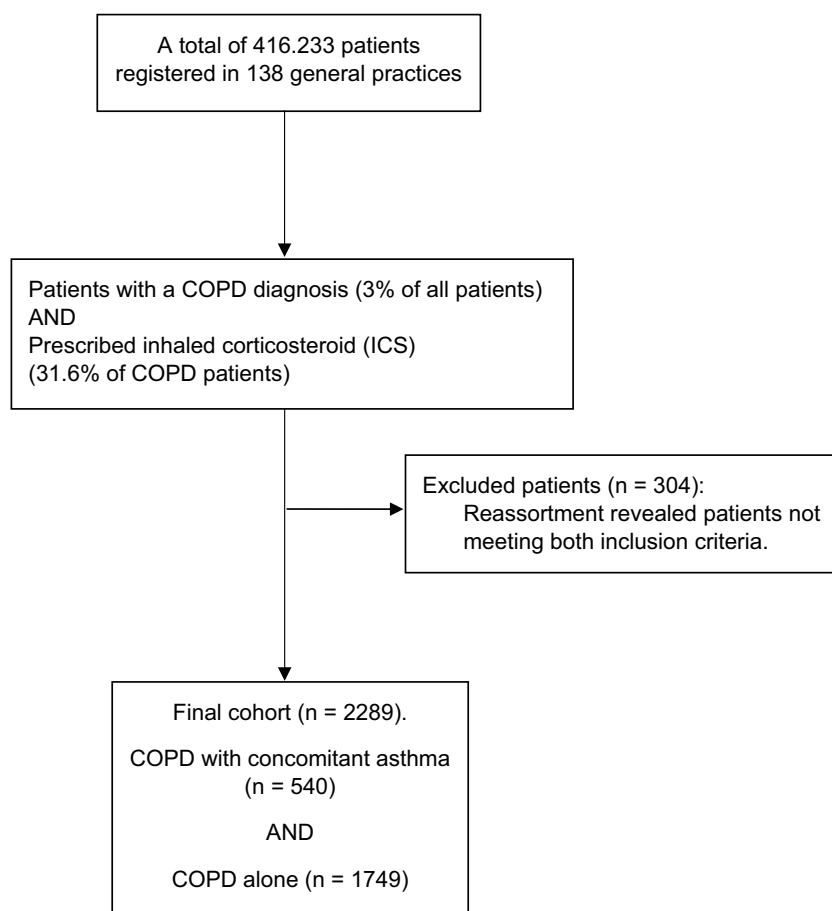
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┌─────────────────────────────────┐
│ A total of 416.233 patients     │
│ registered in 138 general       │
│ practices                       │
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│ Patients with a COPD diagnosis  │
│ (3% of all patients)            │
│ AND                             │
│ Prescribed inhaled corticosteroid│
│ (ICS)                           │
│ (31.6% of COPD patients)        │
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                 │          ┌──────────────────────────────┐
                 ├─────────▶│ Excluded patients (n = 304): │
                 │          │   Reassortment revealed      │
                 │          │   patients not meeting both  │
                 │          │   inclusion criteria.        │
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│ Final cohort (n = 2289).        │
│                                 │
│ COPD with concomitant asthma    │
│       (n = 540)                 │
│                                 │
│          AND                    │
│                                 │
│ COPD alone (n = 1749)           │
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Figure 1 Selection process of patients with chronic obstructive pulmonary disease (COPD) alone and COPD with concomitant asthma, recruited from general practice and currently prescribed inhaled corticosteroids (ICS).

COPD Alone and COPD Patients with a Concomitant Asthma Diagnosis

Baseline characteristics of the two groups, i.e., COPD alone and COPD with concomitant asthma, are outlined in Table 2. A statistically significant difference was found in mean MRC for COPD alone and for COPD patients with concomitant asthma (p<0.001). The mean number of pack years for COPD alone patients and for COPD patients with concomitant asthma, respectively, was 36 and 26 (p<0.001). COPD patients with concomitant asthma had higher blood-eosinophil count than patients with COPD alone (p=0.02). Further details are given in Table 2.

The distribution of severity of airflow limitation, based on the GOLD classification, among patients with COPD alone and COPD with concomitant asthma is presented in Figure 2, revealing a significant difference between the two groups (p<0.001). The distribution of the most common comorbidities and levels of blood eosinophils, respectively, in patients with COPD alone and COPD with concomitant asthma are presented in Figure 3 and Table 3.

Compared to COPD alone, logistic regression analysis showed that COPD with concomitant asthma was significantly associated to age (OR 0.94; CI 0.92 to 0.97; p<0.001), pack-years of smoking (OR 0.98; CI 0.97 to 0.99; p<0.001), FEV_1%pred (OR 1.02; CI 1.00 to 1.03; p=0.005), and doctor-diagnosed depression (OR 2.59; CI 1.20 to 5.58; p=0.015) (Table 4).

Discussion

This study shows that a concomitant asthma diagnosis in COPD patients treated with ICS in primary care is associated with younger age, less airflow limitation, but more likely to be associated with a doctor-diagnosis of depression compared to patients with COPD alone.

Reduced benefit from corticosteroids and increased inflammation in the airways has previously been suggested as a side effect of being a current smoker in patients with chronic airway diseases such as COPD and asthma.[24] On the other hand, a recent study analyzing data from three randomized controlled trials of budesonide-formoterol

Table 1 Characteristics of Enrolled Patients (n=2289) with Chronic Obstructive Pulmonary Disease (COPD) Managed in Primary Care and Currently Prescribed Inhaled Corticosteroids (ICS) According to Sex

	Males (n=1024)	Females (n=1265)
Age (years)	71.06 (SD 10.84)	70.96 (SD 10.79)
BMI (kg/m^2)	27.53 (SD 5.47)	26.57 (SD 6.86)
Pack-years (n)	36.62 (SD 22.71)	30.21 (SD 21.55)
FEV_1/FVC	0.56 (SD 0.15)	0.59 (SD 0.14)
FEV_1%predicted (%)	57.38 (SD 22.89)	62.50 (SD 23.63)
FEV_1(L)	1.74 (SD 0.73)	1.32 (SD 0.53)

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2 Baseline Characteristics of Enrolled Patients (n=2289) with Chronic Obstructive Pulmonary Disease (COPD) Managed in Primary Care and Currently Prescribed Inhaled Corticosteroids (ICS) Divided by Whether Patients Have a Concomitant Diagnosis of Asthma (n=540) or COPD Alone (n=1749)

	COPD with Concomitant Asthma (n=540)	COPD Alone (n=1749)
Age (years), mean	69.35 (SD 11.99)	72.83 (SD 10.28)*
BMI (kg/m^2), mean	28.10 (SD 6.47)	26.68 (SD 6.21)*
Pack-years (n), mean	25.75 (SD 20.97)	35.52 (SD 22.21)*
FEV_1/FVC, mean	0.62 (SD 0.14)	0.56 (SD 0.15)*
FEV_1%predicted (%), mean	68.89 (SD 22.33)	57.47 (SD 23.11)*
FEV_1(L), mean	1.75 (SD 0.68)	1.43 (SD 0.64)*
B-eosinophils (10^9/L), mean	0.27 (SD 0.23)	0.24 (SD 0.20)**
MRC-score (n=1163), mean	2.35 (SD 0.98)	2.79 (SD 1.13)*
CAT-score (n=54), mean	14.75 (SD 8.42)	17.56 (SD 7.54)
Annual exacerbation, mean	0.66 (SD 1.15)	0.95 (SD 1.64)*

Notes: CAT, COPD assessment test. For the comparison between COPD with concomitant asthma and COPD alone: *p<0.001; **p<0.05.
Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; B-eosinophils, blood eosinophils; MRC, medical research council.

studies in COPD patients concluded that currently smoking COPD patients on ICS/LABA therapy had reduced exacerbation rates compared to those on LABA alone treatment at greater blood-eosinophil counts.[25] In line with this, the present study found that COPD patients with concomitant asthma and on average higher mean blood eosinophil count had a lower exacerbation rate compared to patients with COPD alone and a lower blood eosinophil count indicating that ICS is more beneficial in the COPD with concomitant asthma group of patients. COPD patients with concomitant asthma also

had higher lung function, however, this might be due to the fewer pack-years smoked.

A quarter of a cohort of COPD patients have asthma characteristics and according to the strategy document by GOLD might be eligible for ICS treatment.[20] In keeping with these facts, the respective GPs in this study have rightfully continued ICS prescription because of concomitant asthma in a quarter of included patients. Continued ICS prescription might also depend on whether patients presented with airflow limitation and/or severe symptoms, although these predictors alone should not determine ICS prescription according to the strategy document by GOLD.[20]

In this study, classification of participants to have COPD with concomitant asthma was based on the participating GPs interpretation of the overall case history, objective findings and response to therapy. As this was a non-interventional study, no formal criteria for a concomitant diagnosis of asthma was applied, which may be the background for the observation that the proportion of COPD patients in the present study with a concomitant diagnosis of asthma was a little higher compared to what has been reported from other studies. However, on the other hand, all patients in the present study were currently prescribed ICS and by that, it may be expected to observe a slightly higher proportion of patients classified as having concomitant asthma.

Similar to the present study, other studies have previously found higher prevalence of depressive symptoms among patients with chronic airway disease such as asthma.[26,27] Another study also found prevalence of depression to be greater among patients with uncontrolled asthma compared to those with well-controlled asthma, suggesting that treatment is crucial in depression prevalence in chronic airway disease.[28] In addition, another recent study found that the risk of depression is higher in patients presenting with symptoms of both asthma and COPD.[29]

Our study has strengths worth mentioning. First, we included a large cohort based on a real-world population of COPD patients followed by their designated GPs. This reflects information gathered by day-to-day clinical visits of patients in general practices and follow-up by GPs, including information on hospital admissions and respiratory outpatient visits. Additionally, plenty of data was available from this large population-based cohort, which at first sight makes it exceptionally relevant in finding
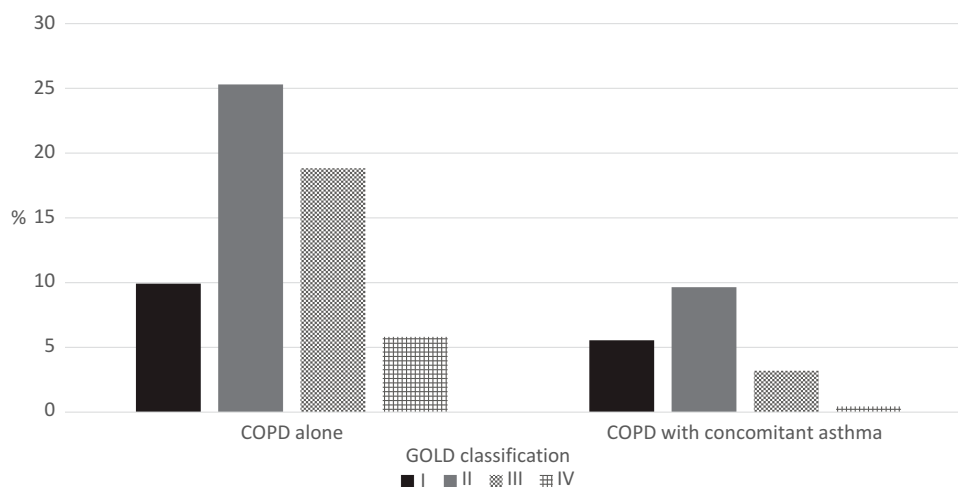
Figure 2 Distribution of severity of airflow limitation, defined according to Global Initiative of Obstructive Lung Disease (GOLD), among patients with chronic obstructive pulmonary disease (COPD) alone and COPD with concomitant asthma.
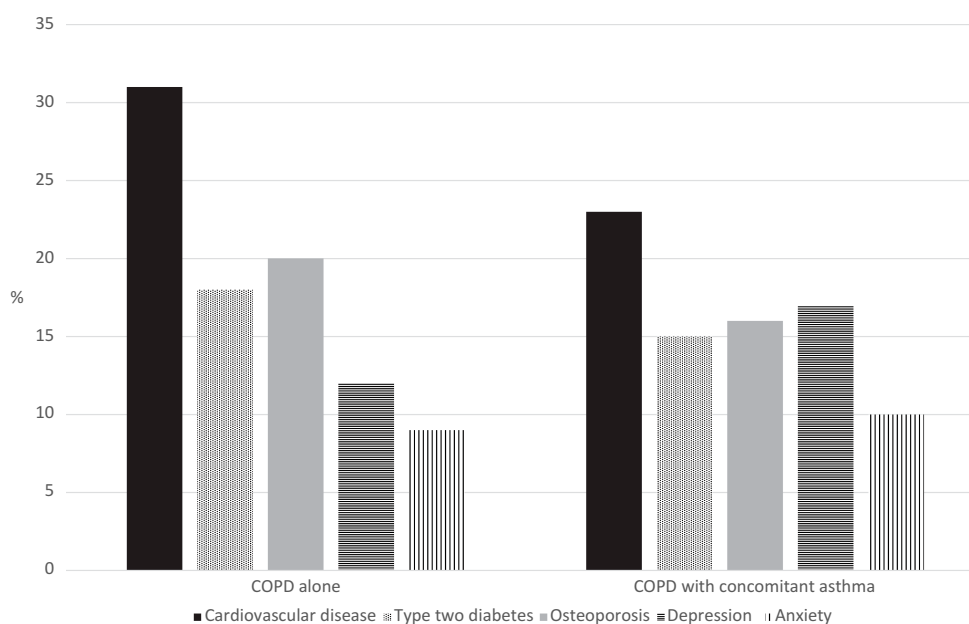

Figure 3 Comorbidities in patients with chronic obstructive pulmonary disease (COPD) alone compared to COPD patients with concomitant asthma.

different significances among different subsets of included COPD patients.

Certain limitations should be emphasized in the current study. The results presented here might resemble random significant associations between clinical variables and characteristics in subpopulations of COPD patients treated with ICS in primary care. We found a significant association between depression and concomitant asthma, which has also been reported in previous studies of the so-called asthma-COPD overlap. As shown in Table 4, the confidence interval for the association was wide, but based on previous findings, also in patient with more severe asthma,

the overserved association in the present study is likely to be valid.

On the other hand, some of the significant associations found in this study might have been influenced by a possible lack of a thorough examination and diagnosis of COPD patients in general practice leading to less clinical important differences and findings between patients with COPD alone and COPD with concomitant asthma. In line with this, patients with COPD alone may have a history with more exacerbations primarily due to having more severe disease (Figure 2). Lastly, very few patients had information on CAT-score (2.4%), which might have

Table 3 Blood Eosinophil Distribution in Patients with Information on Blood Eosinophils (n=1536). Chronic Obstructive Pulmonary Disease (COPD) Alone Compared to COPD with a Concomitant Diagnosis of Asthma Low Blood Eosinophils (<150 Cells/μL), Intermediate Blood Eosinophils (150–<300 Cells/μL) and High Blood Eosinophils (≥300 Cells/μL)

Blood Eosinophils	Low	Intermediate	High
COPD alone	18.4%	19.5%	14.9%
COPD with concomitant asthma	5%	5.8%	4.9%

Table 4 Characteristics Associated with Concomitant Asthma Among Patients (n=2289) with Chronic Obstructive Pulmonary Disease (COPD) Managed in Primary Care and Currently Prescribed Inhaled Corticosteroids (ICS)

Characteristic	95% CI for OR	P-value
Gender (n)		
Female	1.46 (0.87–2.45)	0.159
Male		
Age (years)	0.94 (0.92–0.97)	<0.001
BMI (kg/m^2)	1.02 (0.98–1.07)	0.340
FEV$_1$/FVC	1.63 (0.17–15.54)	0.670
B-eosinophils (10^9/L)	1.18 (0.32–4.35)	0.800
Pack-years (n)	0.98 (0.97–0.99)	<0.001
FEV$_1$%predicted (%)	1.02 (1.01–1.03)	0.005
Annual exacerbation (n)	0.90 (0.74–1.11)	0.338
Comorbidities (n)		
Cardiovascular disease	0.74 (0.40–1.36)	0.331
Diabetes	0.84 (0.43–1.65)	0.613
Osteoporosis	1.36 (0.71–2.61)	0.363
Depression	2.59 (1.20–5.58)	0.015
Anxiety	0.49 (0.19–1.28)	0.145

Notes: The 95% confidence intervals (CI) and p-values for odds ratios (OR) were obtained from multinomial logistic regression with "COPD alone" as the reference category. For every one unit added to a variable included in this analysis there is either an increase or decrease in odds.
Abbreviations: BMI, body mass index; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; B-eosinophils, blood eosinophils.

made it difficult to demonstrate genuinely significant difference in symptoms amongst patients with COPD alone and COPD patients with concomitant asthma. Meanwhile, almost all patients had information on exacerbation rate (99.3%) and all had information on whether they had a concomitant diagnosis of asthma. This reflects a necessity for further use of symptom scores as part of the assessment of COPD patients in primary care.

In the current study investigating COPD patients prescribed ICS in primary care, a diagnosis of concomitant asthma indicated higher risk of depression, less exposure to tobacco smoke, and greater lung function. These main differences between patients with COPD alone and COPD with concomitant asthma indicate the need for investigation of detailed treatment strategies in primary care COPD patients, not least for those with concomitant asthma, and hopefully, reduce risk of unbeneficial ICS treatment in the future.

Disclosure

Dr Christian Jensen reports personal fees from Boehringer Ingelheim, personal fees from Astra Zeneca, personal fees from Novo Nordisk, and personal fees from Novartis, during the conduct of the study. The authors report no other conflicts of interest in this work.

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