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Cardiopulmonary risk in the COPD patient: the EPOCONSUL audit

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Having cardiovascular disease associated with COPD is important, as it increases the risk of adverse cardiopulmonary events. to evaluate the characteristics of COPD patients with cardiovascular disease (CVD) and the therapeutic measures adopted for COPD at the follow-up visit according to COPD clinical control. A is a cross-sectional study with prospective recruitment. This analysis used data from the EPOCONSUL audit, which evaluated outpatient care provided to COPD patients in respiratory clinics in Spain. 4225 patients from 45 hospitals in Spain were audited. Cardiovascular disease was defined as having a diagnosis of active cardiovascular disease. The clinical control of COPD was defined by the criteria established in the Spanish COPD Guidelines (GesEPOC), measured by the RADAR Score, which assesses the clinical impact and stability of COPD. The COPD risk was defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification and GesEPOC criteria based on the degree of dyspnea, history of exacerbations, and degree of airflow obstruction. 1562 (37%) patients had CVD, with the frequency increasing in high-risk COPD according to GesEPOC (42.3%) and in type E GOLD (43.4%). Factors associated with having CVD were age ≥ 55 years as a predictor [2.46 (1.60–3.78), p<0.001], being male [1.88 (1.47–2.39), p<0.001], history of at least one hospitalization for COPD in the previous year [1.82 (1.44–2.30), p<0.001], having sleep apnoea [1.62 (1.20–2.20), p = 0.002], dyspnea (MRC-m) ≥ 2 [1.54 (1.26–1.90), p<0.001] and Charlson index without cardiovascular disease ≥ 3 [1.16 (1.09–1.24), p<0.001]. In patients with CVD, poor control of COPD was more frequent (with CVD: 44.2%; without CVD: 29.1%, p < 0.001). Closer follow-up was more frequent in patients with CVD (follow-up visits < 6 months in CVD: 44.5% vs. without CVD: 38.6%, p < 0.001). Changes in COPD treatment during the visit were more frequent in patients with poor control (in 37.8%) vs. good control (in 20.3%), p < 0.001. Cardiovascular disease was common, present in almost half of high-risk COPD patients. Poor clinical control of COPD was more common in patients with CVD, with triple therapy being the most commonly used pharmacological strategy. No differences were observed in the measures taken during the visit, nor in the request for tests or changes made to COPD treatment based on having active CVD associated with COPD. It is urgent and necessary to promote an integrated approach to improve identification and management of cardiopulmonary risk in COPD patients.

Keywords Chronic obstructive pulmonary disease, Cardiovascular disease, Clinical control, Cardiovascular risk factors, Clinical guidelines

Clinical practice guidelines in chronic obstructive pulmonary disease (COPD) establish the importance of systematic cardiovascular risk assessment in COPD due to the high prevalence of cardiovascular disease (CVD) and its impact on morbidity and mortality[1,2]. Previous studies have shown that in these patients there is a significantly higher risk of developing CVD compared to the general population[3]. The relationship between

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COPD and CVD can be attributed to several shared factors, such as smoking, chronic systemic inflammation, oxidative stress and vascular dysfunction that through their systemic effects may contribute to the development of CVD[4], in addition to the deleterious effect of pulmonary hyperinflation on left ventricular diastolic function that may aggravate CVD[5].

COPD is also a cardiovascular risk factor. Studies have shown that acute exacerbations of COPD are associated with a significant increase in cardiovascular events[6–8] which underlines the importance of surveillance and management of cardiovascular disease, along with the need for a proactive and comprehensive approach to cardiopulmonary risk in the COPD patient especially in those patients experiencing exacerbations[6,9].

Reducing exacerbations and minimising cardiovascular risk are therapeutic goals identified as priorities in clinical guidelines for the management of COPD and CVD[1,2]. However, studies indicate that there are several gaps in the health management of cardiopulmonary risk in patients with COPD. CVD is often underdiagnosed and undertreated[10]. There is evidence that cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes are inadequately monitored and controlled in COPD patients[11]. Cardiovascular therapies such as angiotensin-converting enzyme inhibitors, statins and smoking cessation therapies are underused in COPD patients, together with poor control of cardiovascular risk factors in COPD patients[12–14] despite their high prevalence and important impact on morbidity and mortality. Scientific evidence has also shown that the use of long-acting bronchodilators and inhaled corticosteroids can offer significant benefits in the reduction of cardiovascular risk in COPD patients, mainly through the reduction of exacerbations and the improvement of lung function and quality of life. Recent studies have shown offers potential benefits in reducing specific cardiovascular events such as heart failure and coronary heart disease, with reduced all-cause mortality and cardiovascular mortality[15,16].

This study is an analysis of the EPOCONSUL 2021 clinical audit that evaluated the outpatient care provided to patients with COPD in respiratory clinics in Spain. Our analysis aimed to evaluate the clinical characteristics of COPD patients with CVD and their potentially associated factors, and to analyse the therapeutic measures adopted for COPD at the follow-up visit according to COPD clinical control and CVD in daily clinical practice.

Methodology

The methodology of the EPOCONSUL audit has been previously reported[17,18]. Briefly, the EPOCONSUL audit promoted by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) was designed to evaluate outpatient care provided to patients with COPD in respiratory clinics in Spain as an observational non-interventional cross-sectional study. The study inclusion was performed between April 15, 2021, and January 31, 2022. Recruitment was intermittent; every month, each investigator recruited the clinical records of the first 10 patients identified as being diagnosed with COPD who were seen in the outpatient respiratory clinic. Subsequently, the patients identified were reevaluated to determine if they met the inclusion/exclusion criteria described in Appendix (1) Risk level was defined according to the GesEPOC criteria (post-bronchodilator FEV1%, degree of dyspnoea and history of exacerbations) described in Appendix (2) The level of clinical control of COPD was assessed according to the GesEPOC criteria based on two components: impact and stability, through the 'RADAR' Score, recently developed by Calle et al.[19] which points the validated criteria proposed by GesEPOC[2], and establishes a score range from 0 to 8 points, where good clinical control is defined by RADAR score of 0 or 1, insufficient control by a score of 2 or 3 and poor control with a score ≥ 4 as described in Appendix (3) In our analysis, having CVD was defined as having a history of CVD, such as coronary artery disease, congestive heart failure, peripheral artery disease, stroke, myocardial infarction, metabolic syndrome, or diabetes mellitus with target organ disease. The investigators who participated in EPOCONSUL 2021 are listed in Appendix 4.

The protocol was approved by the Ethics Committee of the Hospital Clínico San Carlos (Madrid, Spain; internal code 20/722-E). Additionally, according to current research laws in Spain, the ethics committee at each participating hospital evaluated and agreed to the study protocol. The need for informed consent was waived because ours is a clinical audit, in addition to the non-interventional nature of the study, the anonymization of data and the blind evaluation of clinical performance. The medical staff responsible for the outpatient respiratory clinic weren't informed about the audit in order to avoid modifications to the usual clinical practice and to preserve the blinding of the clinical performance evaluation.

Statistical analysis

Qualitative variables were summarized as frequency distribution and continuous variables as mean values and standard deviations. Continuous, non-normally distributed variables were expressed as medians and interquartile ranges (IQR). The association between qualitative variables was performed using the chi-square test. For quantitative variables comparisons between two independent groups was performed using the Student's t-test or Mann-Whitney U test in case of non-normally distributed variables.

A multiple logistic regression model, using cluster-robust standard errors to take into account patients tested within the same hospital, was fitted in order to identify factors associated to CVD. Adjusted odds ratios (OR) and their 95% confidence intervals are shown. The model included those factors that were significantly ($p < 0.05$) associated with CVR in the univariate analysis and/or were clinically relevant and presented a proportion of missing values of less than 25%. A two-sided $p < 0.05$ was considered statistically significant. All analyses were performed using Stata software version 16 (StataCorp LLC, College Station, TX, USA).

Results

Population of the study

A total of 4225 patients diagnosed with COPD were audited in 45 centres. Of these, 1562 (37%) patients had CVD, with congestive heart failure being the most frequent, present in 595 (38%) as shown in Fig. 1.

Distribution of CVD according to COPD risk level

Figures 2 show how the population with and without CVD is distributed according to risk level GesEPOC (Fig. 2A), clinical phenotype based on GesEPOC criteria (Fig. 2B) and GOLD classification (Fig. 2C). There were significant differences, with an increased frequency of patients with CVD in the high-risk level (42.3%), in frequent exacerbator (non-eosinophilic: 47.4%; eosinophilic exacerbator: 44.5%) and in type E GOLD (43.4%).

Factors associated with having CVD

The characteristics of the patients according to having CVD are summarised in Suplemmentary Tables 1 and 2. Table 1 shows the bivariate association between CVD and clinical variables. In the multivariate analysis of CVD in COPD patients (Table 2), the adjusted model identified age ≥ 55 years as a predictor [2.46 (1.60–3.78), $p<0.001$], followed, being male [1.88 (1.47–2.39), $p<0.001$], history of at least one hospitalisation in the previous year [1.82 (1.44–2.30), $p<0.001$], having sleep apnoea [1.62 (1.20–2.20), $p=0.002$], dyspnea (MRC-m) ≥ 2 [1.54 (1.26–1.90), $p<0.001$] and Charlson index without cardiovascular disease ≥ 3 [1.16 (1.09–1.24), $p<0.001$]. Active smoking was more frequent in patients without CVD [0.76 (0.61–0.95), p00.008].

The distribution of the most frequent comorbidities according to having CVD is shown in Fig. 3.

Therapeutic interventions in COPD according to having CVD

Table 3 shows the interventions and therapeutic actions performed at the visit and their distribution according to CVD history. Triple inhaled therapy (long-acting anticholinergic, long-acting beta-adrenergic and corticosteroid) is the most commonly used pharmacological strategy for COPD, with a higher frequency in patients with CVD (with CVD: 52.3%; without CVD: 49.5%, $p=0.065$). Home oxygen therapy (with CVD: 29.6%; without CVD: 22.4%, $p<0.001$) and home ventilatory support (with CVD: 11.6%; without CVD: 6.8%, $p<0.001$) were more frequent in patients with CVD. In addition, closer follow-up was more frequent in the scheduling of check-ups, with follow-up visits < 6 months (with CVD: 44.5%; without CVD: 38.6%, $p<0.001$). There were no differences in the actions taken at the visit, neither in the ordering of tests nor in the change made in COPD treatment during the visit according to having CVD.

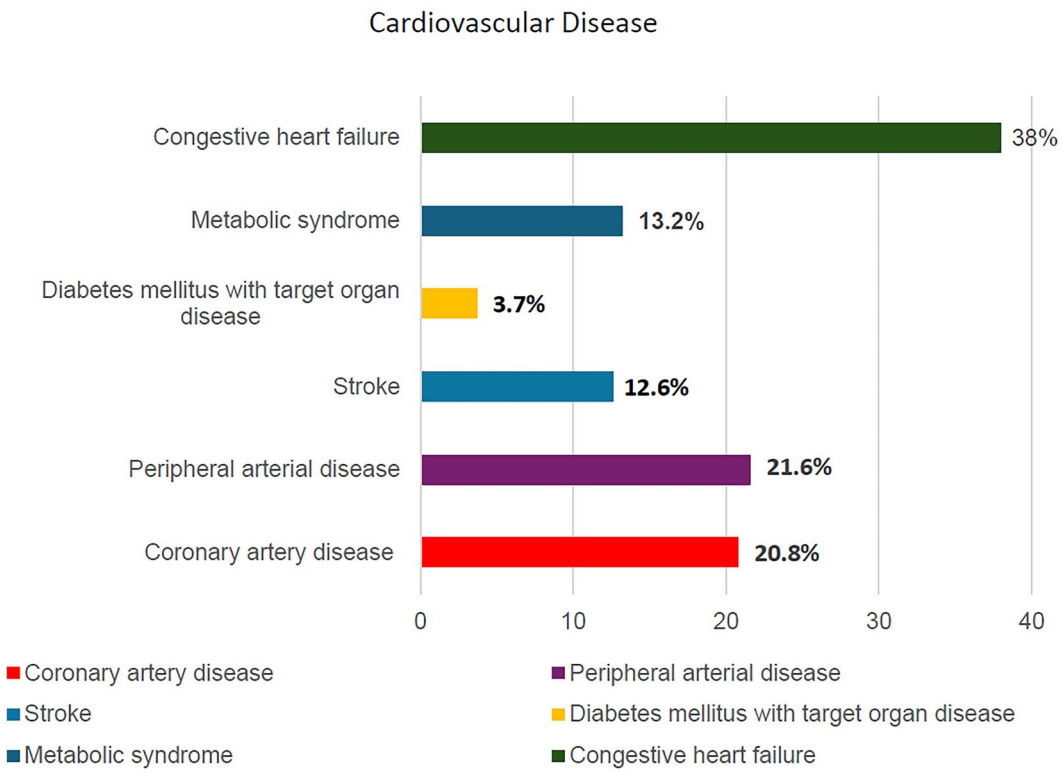

Fig. 1. Frequency of CVD diagnoses in our population. Note: Metabolic syndrome was defined by the presence of at least three clinical conditions: central obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting plasma glucose.

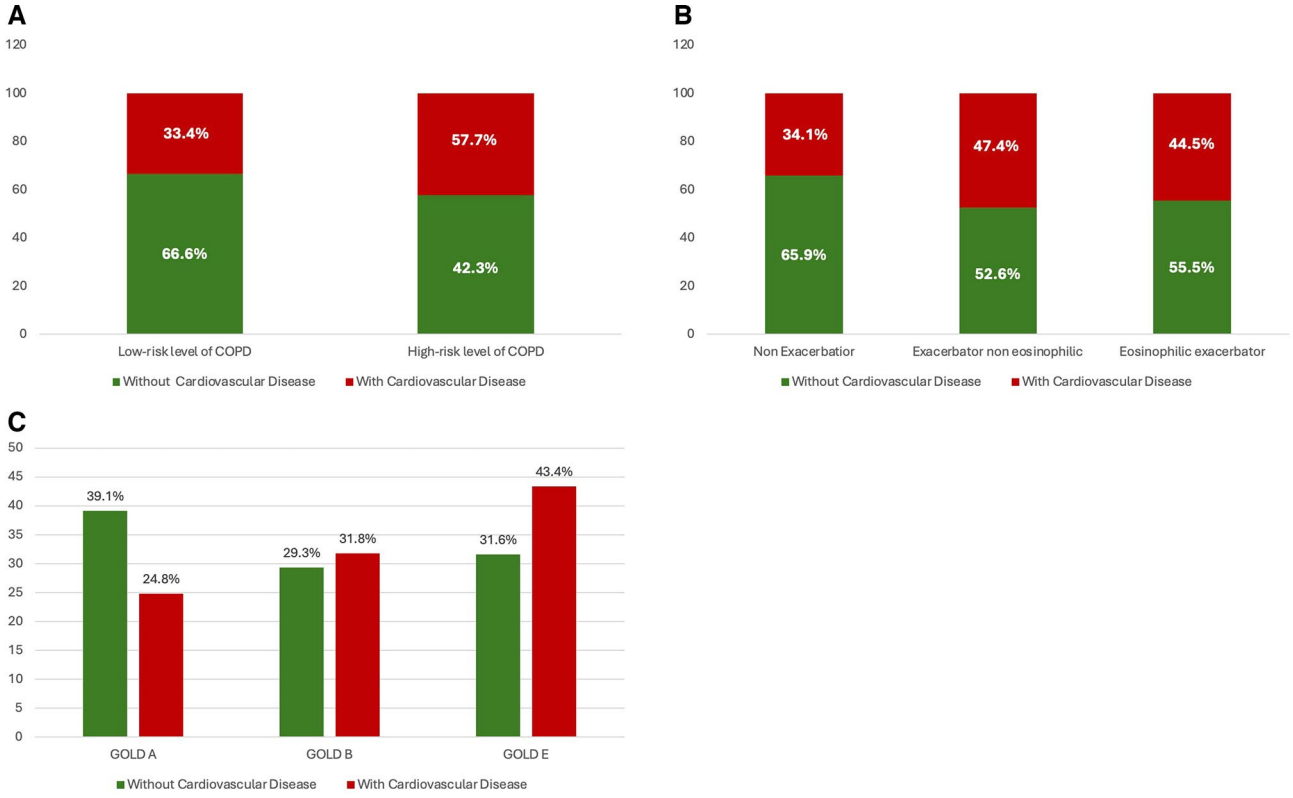

Fig. 2 . **A**) Distribution of CVD by risk level of COPD according to GesEPOC. The difference is significant ($p < 0{,}001$) between high-risk vs. low-risk level. **B**) Distribution of CVD according to clinical phenotypes GesEPOC. Significant difference ($p < 0.001$) between non-exacerbating phenotype vs. frequent exacerbating phenotypes. **C**) Distribution of CVD according to Type GOLD. Significant difference ($p < 0.001$) between GOLD types.

Control status according to having CVD and actions taken

Of the 4225 patients evaluated, 1318 met the criteria to define the degree of clinical control at the visit. Figure 4 shows the distribution of the level of COPD control assessed by RADAR Quantitative Score, and the differences in its distribution according to have a CVD. Poor control of COPD was present in 461 (35%) of the patients evaluated. In patients with cardiovascular disease, both poor control as defined by Score ≥ 4 (with CVD: 44.2%; without CVD:29.1%, $p < 0.001$) and insufficient control as defined by Score 2–3 (with CVD: 27.7%; without CVD: 24.4%, $p < 0.001$) were more frequent.

Table 3 shows the therapeutic actions carried out during the visit according to the degree of clinical control. Treatment changes during the visit were made more frequently in patients with poor control, in 37.8% of uncontrolled patients with RADAR score ≥ 4 versus 20.3% of patients with good control with RADAR Score score of 0–1 ($p < 0.001$). In patients with cardiovascular disease in whom a change in treatment was made at the visit, escalation (increased or added) was more frequent when there was poor clinical control (44.9%) versus good control (34.3%).

Discussion

This study provides novel information on CVD in COPD patients undergoing follow-up in outpatient respiratory clinics as well as factors associated to have a history of CVD using real data generated in a clinical audit performed in Spain. This analysis describes the frequency of CVD according to the level of COPD risk and explores the level of clinical control of COPD, therapeutic interventions and the actions taken and changes made in COPD treatment during the visit according to having CVD.

Our key take aways are that CVD is common in COPD patients, most commonly coronary artery disease, peripheral arterial disease and metabolic syndrome, even in low-risk COPD patients, although cardiovascular disease is much more prevalent in patients with frequent exacerbations. Factors associated with having CVD in our analysis were clinical characteristics such as older age, being male, having a BMI ≥ 30 kg/m2, having a higher comorbidity burden, having sleep apnoea, and in relation to COPD, having a dyspnoea ≥ 2 MRCm and previous history of hospitalisation for COPD.

In our study, in COPD with CVD, closer follow-up, the use of oxygen therapy and home ventilatory support were more frequent. Also, poor or insufficient clinical control of COPD was more frequent in COPD with CVD. In patients with CVD in whom a change in COPD treatment was made at the visit, escalation (increased or added) in inhaled therapy was more frequent when there was poor clinical control.

	With CVD $N=1562$ (37%)	Without CVD $N=2663$ (63%)	OR (95%CI)	*P*
Sex Female, (*n*, %) (reference) Male, (*n*, %)	1285 (82.4)	1788 (67.1)	1 1.91 (1.50–2.43)	< 0.001
Age (years), m (SD) < 55, (*n*, %) (reference) ≥ 55, (*n*, %)	1516 (97)	2438 (91.5)	1 2.30 (1.53–3.46)	< 0.001
IPA (Pack-years), m (SD)	52.6 (24.7)	47.8 (23.5)	1.00 (0.99–1.00)	0.672
Active smokers No (n, %) (reference) Yes (n, %)	308 (19.7)	745 (28)	1 0.76 (0.61–0.96)	0.021
BMI kg/m2, m (SD) < 30 (n, %) (reference) ≥ 30 (n, %)	508 (34.3)	702 (27.9)	1 1.31 (1.03–1.66)	0.023
Charlson index < 3 (n, %) (reference) ≥ 3 (n, %)	722 (46.3)	463 (17.4)	1 3.41 (2.74–4.24)	< 0.001
Arterial hypertension Not (n, %) (reference) Yes (n, %)	1084 (69.9)	1114 (42.6)	1 3.14 (2.69–3.65)	< 0.001
Dyslipidaemia Not (n, %) (reference) Yes (n, %)	798 (51.3)	844 (32.2)	1 2.22 (1.85–2.67)	< 0.001
Depression Not (n, %) (reference) Yes (n, %)	174 (11.2)	307 (11.6)	1 0.95 (0.70–1.28)	0.767
Anxiety Not (n, %) (reference) Yes (n, %)	127 (8.1)	319 (12.1)	1 0.64 (0.48–0.86)	0.003
Sleep apnoea Not (n, %) (reference) Yes (n, %)	476 (30.5)	513 (19.4)	1 1.82 (1.45–2.27)	< 0.001
Dyspnea (MRC-m) < 2 (n, %) (reference) ≥ 2 (n, %)	778 (65.8)	1009 (50.3)	1 1.54 (1.24–1.90)	< 0.001
Chronic bronchitis Not (n, %) (reference) Yes (n, %)	521 (33.4)	777 (29.2)	1 1.14 (0.90–1.45)	0.251
Number of hospital admissions in the last year < 1 (n, %) (reference) ≥ 1 (n, %)	358 (22.9)	334 (12.5)	1 1.77 (1.37–2.29)	< 0.001
Post-FEV_1, % predicted ≥ 50%, (n, %) (reference) < 50%, n (%)	712 (45.6)	1210 (45.5)	1 1.00 (0.85–1.18)	0.968

Table 1. Characteristics sociodemographic and clinical of the COPD and association with to having cardiovascular disease (logistic regression bivariate analysis). Abbreviations: CVD: cardiovascular disease; BMI: body mass index; mMRC: modified Medical Research Council; FEV1%: post-bronchodilator FEV1% predicted.

COPD is an inflammatory disease that is associated with an increased prevalence of CVD and worsening of CVD outcomes[3]. Approximately 35% of deaths among patients with COPD are attributed to cardiovascular events[20]. Compared with the general public, patients with COPD are 2.5 times more likely to have cardiovascular disease[21]. In our population, 37% of COPD patients were diagnosed with CVD, the most frequent being ischaemic heart disease, present in 77% of COPD patients with CVD. COPD and cardiovascular diseases are intertwined in many complex ways. Systemic inflammation contributes to endothelial dysfunction, promoting atherosclerosis and increasing the risk of cardiovascular events[5]. In addition, oxidative stress[22] and hypoxia-promoted neutrophil degranulation increases the potential for vascular injury, thereby elevating cardiovascular risk[23]. The two organs are anatomically and physiologically interconnected. It is well established that hypoxemia induces vasoconstriction, leading to chronic pulmonary hypertension and right heart failure, and that pulmonary hyperinflation has a detrimental effect on left ventricular diastolic function by increasing intrathoracic pressure[5]. In addition, both share risk factors such as smoking, physical inactivity and ageing that contribute to the development of both[23]. There is evidence that cardiovascular risk factors such as hypertension, dyslipidaemia and diabetes are more common in COPD patients but are often not monitored and inadequately controlled in COPD patients[12]. In our study, comorbidities such as hypertension, dyslipidaemia, diabetes and sleep apnoea were more frequent in patients with CVD. There is growing recognition of the importance of multimorbidity and the importance of a comprehensive approach to patients with COPD. Strategies are needed to improve control of cardiovascular risk factors in order to reduce morbidity and mortality in this high-risk patient group.

Smoking is a highly relevant risk factor for both COPD and CVD, through endothelial dysfunction, oxidative stress, systemic inflammation, contributing to arterial stiffness and the development of atherosclerosis[24,25].

Variable	OR (95%CI)	*p*
Sex, Female (reference) Male	1 1.88 (1.47–2.39)	< 0.001
Age < 55 **years**, (reference) ≥ 55	1 2.46 (1.60–3.78)	< 0.001
IPA (x1 Pack-years)	1.00 (0.99–1.00)	0.252
Active smokers, Not (reference) Yes	1 0.76 (0.61–0.95)	0.018
BMI < 30**kg/m2** (reference) ≥ 30	1 1.13 (0.88–1.46)	0.324
Charlson index without cardiovascular disease	1.16 (1.09–1.24)	< 0.001
Anxiety, Not (reference) Yes	1 0.77 (0.55–1.08)	0.134
Sleep apnoea, Not (reference) Yes (n, %)	1 1.62 (1.20–2.20)	0.002
Dyspnea (MRC-m) < 2 (reference) ≥ 2	1 1.54 (1.26–1.90)	< 0.001
Chronic bronchitis, Not (reference) Yes	1 1.14 (0.91–1.44)	0.235
Number of hospital admissions in the last year, < 1 (reference) ≥ 1	1 1.82 (1.44–2.30)	< 0.001

Table 2. Factors related to having CVD in COPD patients. "Multivariable logistic model". Abbreviations: BMI: body mass index; mMRC: modified Medical Research Council.

These interrelated mechanisms underscore the critical importance of smoking cessation in mitigating the risks associated with these diseases. In our analysis, a quarter of the patients analyzed were active smokers being more frequent in patients without CVD (without CVD: 28% vs. with CVD: 19.7%, $p < 0.001$), which could be explained more as a consequence of a lower motivation or decision to quit smoking in a patient without a diagnosis of CVD.

In our study, CVD was more frequent in patients with high-risk COPD (42.3%) or GOLD E (43.4%) and in patients with a frequent exacerbator phenotype. Having had at least one COPD hospitalisation in the previous year was identified as a factor associated with an increased likelihood of having CVD. The risk of cardiovascular events dramatically increases in the 30 days after a COPD exacerbation and persists up to one year[6,21,26–29]. The risk of cardiovascular events increases with the frequency and severity of exacerbations and is associated with changes occurring during and after an acute exacerbation of COPD in vascular function, arterial stiffness and systemic inflammation[30]. These results point to the importance of COPD exacerbation as a promoter of cardiovascular events and highlight the importance of prevention and proper management of exacerbations to reduce cardiovascular risk in COPD patients who experience frequent exacerbations.

Clinical practice guidelines in COPD establish risk minimisation as the main therapeutic goal[1,2]. Achieving clinical control of the disease is the overall goal in the therapeutic approach. The concept of COPD control is a measure proposed in GesEPOC, based on two components: clinical impact (degree of dyspnoea, use of rescue medication, limitations in daily physical activity) and stability (absence of exacerbations in the last 3 months) that aims to help clinicians assess the clinical status of COPD patients during visits[2]. This is similar to the GOLD guidelines, which recommend that two key treatable characteristics, dyspnoea and the occurrence of exacerbations, should be assessed at each visit during treatment monitoring[1]. Evidence has shown that the COPD control status proposed by GesEPOC is a good predictor of short- and medium-term negative outcomes[31–33]. Recently, a scoring system for the criteria defining clinical control proposed by GesEPOC has been developed that provides a quantitative assessment, the RADAR score, which allows greater discrimination between levels of control and more direct comparisons[19,34]. In our study, 44.2% of patients with CVD had poor clinical control as defined by RADAR score greater than or equal to 4 points compared to 29.1% of patients without CVD who had poor control. In the analysis of therapeutic interventions in COPD according to having CVD, closer follow-up, the use of oxygen therapy and home ventilatory support were more frequent in patients with CVD, which could be a consequence of more frequent high-risk COPD. In the analysis of the actions taken at the follow-up visit, there was no difference based on the presence or absence of CVD. However, when analysing the actions taken at the visit according to COPD control, significant differences were observed, with a higher frequency of treatment changes in patients with poor control. In patients with CVD in whom a treatment change was made at the visit, escalation (increase or addition) of inhaled therapy was more frequent when there was poor clinical control.

During these years, summative strategies, such as triple therapy have been recommended to achieve greater benefit in the prevention of COPD exacerbations[35–39]. Regarding the reduction of cardiovascular events, the evidence is still inconclusive, as although some studies show benefits in cardiovascular risk associated with the use of inhaled corticosteroids (CSI) demonstrate that triple therapy reduces exacerbations, all-cause mortality, and cardiovascular events in high-risk populations, with the magnitude of benefit greatest in those with elevated BEC and frequent exacerbations[40–42]. Recent publications suggest adding a third dimension (E + and B+) to the GOLD risk classification, according to which patients with COPD and known cardiovascular disease should be prioritized and start triple therapy first. This is based on some results, although not entirely consistent, that patients with COPD and cardiovascular disease obtain better results with therapy containing inhaled

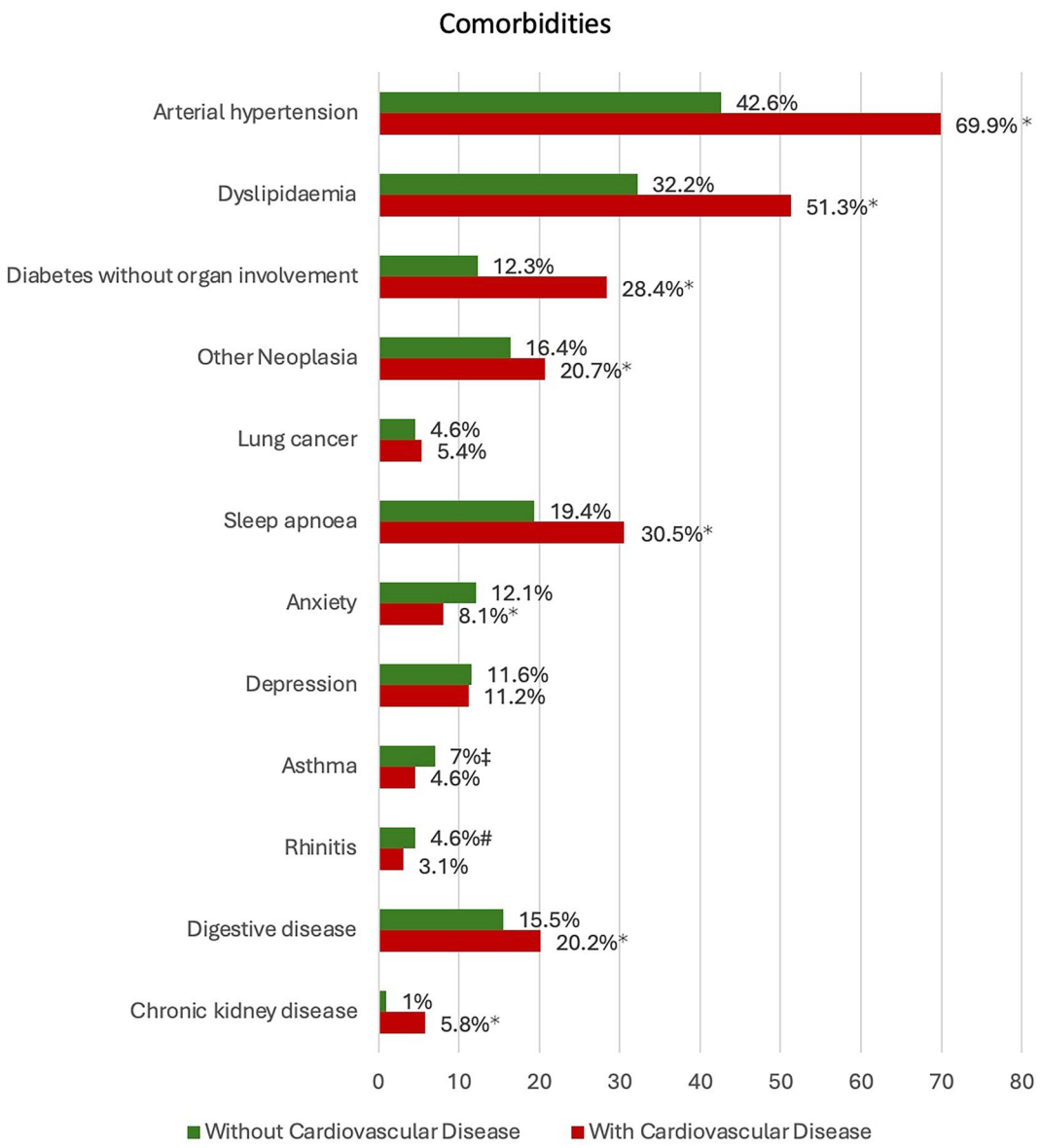

Fig. 3. Distribution of comorbidities according to having CVD. *$p < 0.001$; ‡$p = 0.002$; #$p = 0.013$.

corticosteroids (6, 38, 42). Further studies are needed to evaluate the possible benefit of CSI in the prevention of cardiovascular events in COPD beyond its benefit in preventing COPD exacerbations as a cardiovascular risk factor. Our results show that in the care offered in pulmonology consultations there are no differences in the adjustment of COPD pharmacological treatment according to the presence or absence of CVD, and there are differences according to the level of COPD control. This could be interpreted as a missed opportunity to get a head start on risk control in patients with CVD. We must not forget that cardiovascular risk factors are common in patients with COPD and are often underdiagnosed and undertreated. A multidisciplinary approach is needed to address cardiopulmonary risk in COPD, with comprehensive treatment strategies that address COPD and cardiovascular disease as intertwined and interrelated diseases[43,44]. The numerous evidences that show us that COPD exacerbations are associated with a drastic increase in the risk of morbidity and mortality, are pointing out the need to carry out a more proactive clinical practice, identifying cardiovascular risk in patients with COPD using adapted risk tools such as Framingham or Qrisk[11], although these scores can underestimate the risk in COPD and be more proactive in patients with higher risk, considering the need for close follow-up with cardiac marker monitoring. Studies that have assessed the severity of cardiovascular disease using cardiac biomarkers (such as elevated troponin and ischemic changes on ECG) are associated with an up to fourfold increased risk of mortality in patients with COPD, regardless of pulmonary severity. Therefore, the identification and active management of cardiovascular disease in COPD is essential to improve overall prognosis and reduce mortality[45].

Recent insights emphasize the need for integrated care pathways that recognize and manage cardiopulmonary risk in COPD. The recommendations include early identification of patients at high risk for cardiopulmonary events, comprehensive risk factor modification (including aggressive management of hypertension, dyslipidemia,

	With CVD $N=1562$	Without CVD $N=2663$	p
Therapeutic interventions			
- Monotherapy (LAMA), n (%) - Monotherapy (LABA), n (%) - LAMA + LABA combination, n (%) - LABA + CSI combination, n (%) - Triple therapy (LAMA + LABA + CSI), n (%)	78 (5.2) 5 (0.3) 518 (34.5) 109 (7.3) 786 (52.3)	179 (7.1) 20 (0.8) 844 (33.5) 229 (9.1) 1248 (49.5)	0.018 0.074 0.463 0.047 0.065
- Long-term oxygen therapy, n (%)	463 (29.6)	596 (22.4)	< 0.001
- Home ventilation, n (%)	181 (11.6)	181 (6.8)	< 0.001
- Respiratory rehabilitation, n (%)	187 (12)	278 (10.4)	0.124
- Treated in specialized COPD outpatient clinic, n (%)	573 (36.7)	1047 (39.5)	0.077
Scheduled follow-up visits (< 6 months), n (%)	625 (44.5)	900 (38.4)	< 0.001
Respiratory care follow-up (years) median, (IQR)	6 (3.7–9.4)	5.7 (3.5–8.8)	0.002
Actions taken in visit			
No action, n (%) Only Testing was requested, n (%) Only change in COPD treatment was made, n (%) Change of treatment and request test, n (%)	201 (13) 999 (64.4) 44 (2.8) 307 (19.8)	380 (14.3) 1636 (61.7) 87 (3.3) 549 (20.7)	0.321
No change, n (%) Change performed, n (%) – Scaling (increased or added) – De-escalate (decrease or remove) – Changes to similar regimen	1210 (77.5) 147 (9.4) 23 (1.5) 182 (11.7)	2027 (76.1) 270 (10.1) 66 (2.5) 300 (11.3)	0.132 0.156

Table 3. Therapeutic interventions in COPD according to having CVD. Abbreviations: LABA: long-acting beta-2 agonists; LAMA: long-acting antimuscarinic agents; CSI: Inhaled corticosteroids.

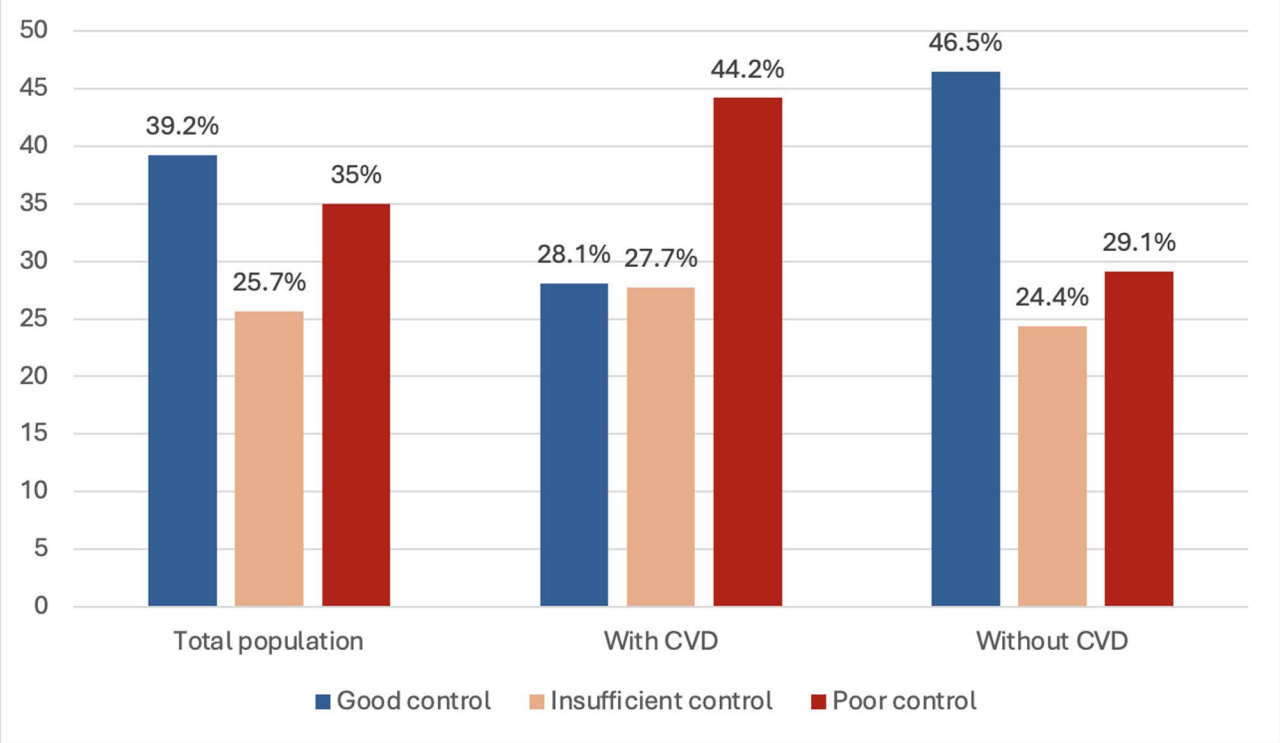

Fig. 4. COPD Clinical Control Level (RADAR Score) according to having CVD. Good control: Score RADAR 0–1; Insufficient control: Score RADAR 2–3; Poor control: Score RADAR ≥ 4. $p < 0.001$: with cardiovascular vs. without cardiovascular risk (CVD) in the different levels of clinical control.

diabetes, and smoking cessation), and improved coordination between respiratory and cardiovascular care teams. The clinical implications of this intersection include diagnostic challenges such as the need for rigorous cardiovascular risk assessment in patients with COPD, with an active search for cardiovascular diseases, as these represent important risk factors for patient prognosis and have therapeutic implications. Furthermore, it

is urgent and necessary to characterize the events that occur in patients with COPD, which will help distinguish between exacerbations and cardiac events. It is necessary to promote an integrated and multidisciplinary approach to COPD management in our clinical practice, involving primary care, pulmonology, and cardiology, to address the double burden and optimize outcomes[46,47].

Limitations to consider are that this is a post hoc analysis of the EPOCONSUL audit, whose objective was to evaluate the characteristics of patients treated for COPD in pulmonology clinics and analyse clinical practice focused on COPD management. Therefore, our analysis evaluates the frequency of cardiovascular disease in COPD treated in pulmonology clinics, identifying associated factors and analysing the treatment of COPD with or without cardiovascular disease, based on evidence that has shown a possible benefit of inhaled corticosteroids combined with bronchodilators on cardiovascular morbidity and mortality. Furthermore, the severity of cardiovascular disease and the treatment prescribed for CVD and risk factors were not evaluated, except for therapeutic interventions performed for COPD. The data were obtained retrospectively, with all the limitations of this approach for establishing risks and causal relationships. Furthermore, any clinical audit has the intrinsic limitation of lost values (data not available), regardless of the inclusion methodology and periodic supervision of the database. Another limitation to consider is that, due to the nature of the cross-sectional design, it is difficult to determine the temporal sequence when assessing factors associated with CVD, as they could be either a cause or consequence. In addition, participating centers were not selected randomly and hospitals' participation was voluntary, depending on their previous experience with clinical studies on COPD and their interest in participating. Therefore, the results cannot be considered representative of the national population with COPD. Despite these limitations, we believe that this dataset represents the most extensive sample from respiratory clinics in Spain, offering real-world data on patients with COPD.

Conclusion

The results show that CVD is present in almost half of the patients with high-risk COPD, with poor COPD control being more frequent. There are no differences in the pharmacological treatment of COPD according to the presence or absence of CVD, although escalation strategies were more frequent in patients with poor control with CVD. In COPD, it is necessary to recognize the importance of multimorbidity in order to treat the patient holistically and address cardiopulmonary risk. It is urgent and necessary to promote an integrated and multidisciplinary approach to improve identification and management of cardiopulmonary risk in COPD patients.

Data availability

The data presented in this study are available on request from the corresponding author.

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References

1. Chronic obstructive pulmonary disease (COPD). [Internet]. [citado 18 de mayo de 2025]. Disponible en: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).
2. Miravitlles, M., Calle, M. & Soler-Cataluña, J. J. GesEPOC 2021: one more step towards personalized treatment of COPD. *Arch. Bronconeumol.* **57**, 9–10. https://doi.org/10.1016/j.arbres.2020.08.002 (2021).
3. Meng, K. et al. Prevalence and impact of chronic obstructive pulmonary disease in ischemic heart disease: A systematic review and Meta-Analysis of 18 million patients. *Int. J. Chron. Obstruct Pulmon Dis.* **19**, 2333–2345 (2024). PMID: 39465033; PMCID: PMC11512537.
4. Simons, S. O. Temporal dynamics of cardiovascular risk in patients with chronic obstructive pulmonary disease during stable disease and exacerbations: review of the mechanisms and implications. *Int. J. Chron. Obstruct Pulmon Dis.* **19**, 2259–2271 (2024). PMID: 39411574; PMCID: PMC11474009.
5. Pirera, E. et al. Risk trajectory of cardiovascular events after an exacerbation of chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Eur. J. Intern. Med.* **135**, 74–82. https://doi.org/10.1016/j.ejim.2025.01.016 (2025). Epub 2025 Jan 30. PMID:39884921.
6. Kunisaki, K. M. et al. SUMMIT Investigators. Exacerbations of chronic obstructive pulmonary disease and cardiac Events. A post hoc cohort analysis from the SUMMIT randomized clinical trial. *Am. J. Respir Crit. Care Med.* **198** (1), 51–57. https://doi.org/10.1164/rccm.201711-2239OC (2018).
7. Yang, H. M. et al. COPDGene Investigators. Chronic obstructive pulmonary disease exacerbations increase the risk of subsequent cardiovascular events: A longitudinal analysis of the COPDGene study. *J. Am. Heart Assoc.* **13** (11), e033882. https://doi.org/10.1161/JAHA.123.033882 (2024).
8. Swart, K. M. A. et al. Risk of cardiovascular events after an exacerbation of chronic obstructive pulmonary disease: results from the EXACOS-CV cohort study using the PHARMO data network in the Netherlands. *Respir Res.* **24** (1), 293. https://doi.org/10.1186/s12931-023-02601-4 (2023).
9. Anghel, L., Ciubară, A., Patraș, D. & Ciubară, A. B. Chronic obstructive pulmonary disease and type 2 diabetes mellitus: complex interactions and clinical implications. *J. Clin. Med.* **14** (6), 1809. https://doi.org/10.3390/jcm14061809 (2025).
10. Leong, P., Macdonald, M. I., Ko, B. S. & Bardin, P. G. Coexisting chronic obstructive pulmonary disease and cardiovascular disease in clinical practice: a diagnostic and therapeutic challenge. *Med. J. Aust.* **210** (9), 417–423. https://doi.org/10.5694/mja2.50120 (2019).
11. Hawkins, N. M. et al. Control of cardiovascular risk factors in patients with chronic obstructive pulmonary disease. *Ann. Am. Thorac. Soc.* **19** (7), 1102–1111. https://doi.org/10.1513/AnnalsATS.202104-463OC (2022).
12. Balbirsingh, V., Mohammed, A. S., Turner, A. M. & Newnham, M. Cardiovascular disease in chronic obstructive pulmonary disease: a narrative review. *Thorax 2022 Jun* **30**:thoraxjnl-2021-218333. https://doi.org/10.1136/thoraxjnl-2021-218333
13. Cazzola, M. et al. Management of chronic obstructive pulmonary disease in patients with cardiovascular diseases. *Drugs* **77** (7), 721–732. https://doi.org/10.1007/s40265-017-0731-3 (2017).
14. Puente-Maestu, L. et al. Multicentric study on the beta-blocker use and relation with exacerbations in COPD. *Respir Med.* **108** (5), 737–744. https://doi.org/10.1016/j.rmed.2014.02.009 (2014).

15. Papi, A. et al. Long-term inhaled corticosteroid treatment in patients with chronic obstructive pulmonary disease, cardiovascular disease, and a recent hospitalised exacerbation: the ICSLIFE pragmatic, randomised controlled study. *Eur. J. Intern. Med.* **128**, 104–111. https://doi.org/10.1016/j.ejim.2024.07.001 (2024).
16. Hammadi, A. et al. All-Cause and cardiovascular mortality with single inhaler triple therapy versus double therapies for COPD: A systematic review and Metanalysis. *Arch Bronconeumol. Published Online Febr.* **21** https://doi.org/10.1016/j.arbres.2025.02.004 (2025).
17. Calle, M. et al. Clinical audit of COPD in outpatient respiratory clinics in Spain: the EPOCONSUL study. Int J Chron Obstruct Pulm Dis 2017: 12:417 – 26. https://doi.org/10.2147/COPD.S124482
18. Calle Rubio, M. et al. Variations in chronic obstructive pulmonary disease outpatient care in respiratory clinics: results from the 2021 EPOCONSUL audit. *Arch. Bronconeumol.* **59**, 295–304. https://doi.org/10.1016/j.arbres.2023.02.004 (2023).
19. Calle Rubio, M. et al. Development and validation of a quantitative score for the criteria clinical control in stable COPD proposed in the Spanish COPD guidelines (GesEPOC): results of the EPOCONSUL audit. *J. Clin. Med.* **14** (3), 707. https://doi.org/10.3390/jcm14030707 (2025).
20. Vaduganathan, M., Mensah George, A., Turco Justine, V., Fuster, V. & Roth Gregory, A. The global burden of cardiovascular diseases and risk. *J. Am. Coll. Cardiol.* **80**, 2361–2371 (2022).
21. Rhee, C. K. et al. Management of COPD with cardiovascular risk in asia: A review by the Asian Pacific society of respirology COPD assembly. *Respirology* **30** (9), 817–830. https://doi.org/10.1111/resp.70103 (2025).
22. Brassington, K., Selemidis, S., Bozinovski, S. & Vlahos, R. Chronic obstructive pulmonary disease and atherosclerosis: common mechanisms and novel therapeutics. *Clin. Sci. (Lond).* **136** (6), 405–423. https://doi.org/10.1042/CS20210835 (2022).
23. Lodge, K. M. et al. Hypoxia increases the potential for Neutrophil-mediated endothelial damage in chronic obstructive pulmonary disease. *Am. J. Respir Crit. Care Med.* **205** (8), 903–916. https://doi.org/10.1164/rccm.202006-2467OC (2022).
24. Roversi, S., Fabbri, L. M., Sin, D. D., Hawkins, N. M. & Agustí, A. Chronic obstructive pulmonary disease and cardiac diseases. An urgent need for integrated care. *Am. J. Respir Crit. Care Med.* **194** (11), 1319–1336. https://doi.org/10.1164/rccm.201604-0690SO (2016).
25. Ishida, M., Sakai, C., Kobayashi, Y. & Ishida, T. Cigarette smoking and atherosclerotic cardiovascular disease. *J. Atheroscler Thromb.* **31** (3), 189–200. https://doi.org/10.5551/jat.RV22015 (2024).
26. Dransfield, M. T. et al. Time-dependent risk of cardiovascular events following an exacerbation in patients with chronic obstructive pulmonary disease: post hoc analysis from the IMPACT trial. *J. Am. Heart Assoc.* **11**, e024350 (2022).
27. Hawkins, N. M. et al. Heightened long-term cardiovascular risks after exacerbation of chronic obstructive pulmonary disease. *Heart* **110**, 702–709 (2024).
28. Wallström, O., Stridsman, C., Lindberg, A., Nyberg, F. & Vanfleteren, L. E. G. W. Exacerbation history and risk of myocardial infarction and pulmonary embolism in COPD. *Chest* **166** (6), 1347–1359. https://doi.org/10.1016/j.chest.2024.07.150 (2024).
29. Graul, E. L. et al. Temporal risk of non-fatal cardiovascular events post COPD exacerbation: a population-based study. *Am. J. Respir Crit. Care Med.* **209**, 960–972 (2024).
30. Fuhr, D. P. et al. Examining changes in vascular function, arterial stiffness and systemic inflammation during hospitalization and recovery from an acute exacerbation of chronic obstructive pulmonary disease. *Sci. Rep.* **13** (1), 12245. https://doi.org/10.1038/s41598-023-39001-z (2023).
31. Soler-Cataluña, J. J. et al. Validation of clinical control in COPD as a new tool for optimizing treatment. *Int. J. Chron. Obstruct Pulmon Dis.* **13**, 3719–3731. https://doi.org/10.2147/COPD.S178149 (2018).
32. Miravitlles, M. et al. Predictive value of control of COPD for risk of exacerbations: an international, prospective study. *Respirology* **25** (11), 1136–1143. https://doi.org/10.1111/resp.13811 (2020).
33. Calle Rubio, M. et al. COPD clinical control: predictors and long-term follow-up of the CHAIN cohort. *Respir Res.* **22**, 36. https://doi.org/10.1186/s12931-021-01633-y (2021).
34. Soler-Cataluña, J. J. et al. Risk validation of a new quantitative score for clinical control of chronic obstructive pulmonary disease: The RADAR score. Arch Bronconeumol. Jun 16:S0300-2896(25)00216-9. English, Spanish. (2025). https://doi.org/10.1016/j.arbres.2025.06.003. Epub ahead of print. PMID: 40592678.
35. López-Campos, J. L. et al. Determinants of medical prescriptions for COPD care: an analysis of the EPOCONSUL clinical audit. *Int. J. Chron. Obstruct Pulmon Dis.* **13**, 2279–2288 (2018).
36. Calle Rubio, M. et al. Inhaled maintenance therapy in the Follow-Up of COPD in outpatient respiratory Clinics. Factors related to inhaled corticosteroid Use. EPOCONSUL 2021 audit. *Arch. Bronconeumol.* **59**, 725–735. https://doi.org/10.1016/j.arbres.2023.07.015 (2023).
37. Lipson, D. A. et al. IMPACT Investigators. Once-Daily Single-Inhaler triple versus dual therapy in patients with COPD. *N Engl. J. Med.* **378** (18), 1671–1680. https://doi.org/10.1056/NEJMoa1713901 (2018).
38. Papi, A. et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* **391** (10125), 1076–1084. https://doi.org/10.1016/S0140-6736(18)30206-X (2018).
39. Rabe, K. F. et al. ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in Moderate-to-Very-Severe COPD. *N Engl. J. Med.* **383** (1), 35–48. https://doi.org/10.1056/NEJMoa1916046 (2020).
40. Shin, J., Yoon, H. Y., Lee, Y. M., Ha, E. & Lee, J. H. Inhaled corticosteroids in COPD and the risk for coronary heart disease: a nationwide cohort study. *Sci. Rep.* **10** (1), 18973. https://doi.org/10.1038/s41598-020-74854-8 (2020).
41. Ioannides, A. E., Kallis, C., Whittaker, H. R. & Quint, J. K. Inhaled corticosteroids and major cardiovascular events in people with chronic obstructive pulmonary disease. Thorax. ;80(2):67–75. Thorax. 2025;80(2):67–75. (2025).
42. Li, Y., Li, J., Yang, H. & Zhang, Y. Effect of triple therapy on mortality and cardiovascular risk in patients with moderate to severe COPD: a meta-analysis of randomized controlled trials. *BMC Pulm Med.* **25** (1), 345. https://doi.org/10.1186/s12890-025-03823-6 (2025).
43. Gale, C. P. et al. Identification and management of cardiopulmonary risk in patients with COPD: a multidisciplinary consensus and modified Delphi study. *Eur. J. Prev. Cardiol.* https://doi.org/10.1093/eurjpc/zwaf119 (2025). zwaf119.
44. Shrikrishna, D. et al. Chronic obstructive pulmonary disease and the management of cardiopulmonary risk in the UK: A systematic literature review and modified Delphi study. *Int. J. Chron. Obstruct Pulmon Dis.* **20**, 2073–2090 (2025). PMID: 40585423; PMCID: PMC12206411.
45. Nilsson, U. et al. Cardiac biomarkers of prognostic importance in chronic obstructive pulmonary disease. *Respir Res.* **21** (1), 162. https://doi.org/10.1186/s12931-020-01430-z (2020).
46. Myers, L. C. et al. A research agenda to improve outcomes in patients with chronic obstructive pulmonary disease and cardiovascular disease: an official American thoracic society research statement. *Am. J. Respir Crit. Care Med.* **210** (6), 715–729. https://doi.org/10.1164/rccm.202407-1320ST (2024). PMID: 39133888; PMCID: PMC11418885.
47. Heffernan, M. & Rutherford, S. The intersection of chronic obstructive pulmonary disease and cardiovascular disease: recent insights in a challenging area. *CJC Open.* **7** (4), 493–507. https://doi.org/10.1016/j.cjco.2025.01.001 (2025). PMID: 40433143; PMCID: PMC12105754.

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Author contributions

Conceptualization, methodology, investigation, writing—review and editing JLRH, MM, JJLC, BAN, JJSC and MCR; validation, formal analysis, data curation and writing—original draft preparation MCR and JLRH; resources, supervision, project administration and funding acquisition MCR. MEFF did the statistical analysis. All authors contributed to data analysis, results interpretation, drafting and revising the paper, and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Ethics Committee at the Hospital Clínico San Carlos (Madrid, Spain; internal code 20/722-E).

Declarations

Competing interests

T he authors declare no competing interests.

Conflict of interest

JLRH has received speaker fees from Bial, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, Zambon and Grifols, and consulting fees from Bial. MM has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Menarini, Kamada, Takeda, Zambon, CSL Behring, Specialty Therapeutics, Janssen, Grifols and Novartis, consulting fees from AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, Inhibrx, Ferrer, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, ONO Pharma, Palobiofarma SL, Takeda, Novartis, Novo Nordisk, Sanofi, Zambon and Grifols and research grants from Grifols. JLLC has received honoraria for lecturing, scientific advice, participation in clinical studies or writing for publications for: AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, CSL Behring, Ferrer, Gebro, GlaxoSmithKline, Grifols, Menarini, Megalabs, Novartis and Rovi. JJSC has received speaker fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, FAES, GlaxoSmithKline, Menarini and Novartis, and consulting fees from Bi-al, Chiesi and GSK, and grants from GSK. BAN reports grants and personal fees from GSK, per-sonal fees and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Chiesi, non-financial support from Laboratorios Menarini, grants, personal fees and non-financial support from AstraZeneca, personal fees from Gilead, personal fees and non-financial support from MSD, personal fees from Laboratorios BIAL, personal fees from Zambon, outside the submitted work; in addition, Dr. Alcázar-Navarrete has a patent P201730724 issued. MCR has received speaker fees from AstraZeneca, Bial, Chiesi, CSL Behring, GlaxoSmithKline, Menarini, and Grifols, and consulting fees from GlaxoSmithKline and Bial. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Ethics Committee at the Hospital Clínico San Carlos (Madrid, Spain; internal code 20/722-E).

Informed consent statement

The need for informed consent was waived because this was a clinical audit, in addition to the non-interventional nature of the study, the anonymization of data and the blind evaluation of the clinical performance. This circumstance was clearly explained in the protocol, and the ethics committees approved this procedure.

Additional information

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