



Management of cardiovascular comorbidities in chronic obstructive pulmonary disease patients

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Abstract: Chronic obstructive pulmonary disease (COPD) is highly prevalent, complex and heterogeneous clinical condition which is associated with significant concomitant diseases. COPD and cardiovascular diseases (CVDs) often coexist due to the high prevalence of each of these pathological conditions separately as well as the common risk factors (particularly smoking), mechanisms of interaction and influence of systemic inflammation. In addition, decreased pulmonary function in COPD is closely associated with an increased risk of congestive CVDs. One of the most important pathophysiological markers of COPD—lung hyperinflation—plays a significant role in the appearance of functional limitations of the pumping function of the heart, creating unfavorable conditions by exerting a compression effect on the heart muscle. The latter was confirmed by significant correlation between the COPD severity according to GOLD classification and the basic dimensions of the heart chambers. Several decades ago, the term “microcardia” was commonly used and indicated a radiological sign of emphysema. Some studies demonstrated a close relationship between the chance of occurrence of CVD and the severity of pulmonary dysfunction. Such an association has been demonstrated for the whole spectrum of CVD—including cerebrovascular disease, congestive heart failure (CHF) and rhythm disturbances—and was detected in the early stages of the disease. A large proportion of patients with mild and moderate COPD die due to CVD, which is much more likely than deaths in the same group due to respiratory insufficiency. COPD patients have a higher rate of hospitalization and death, the cause of which are coronary heart disease (CHD), stroke and CHF. Treatment of COPD today is mainly determined by national and international clinical guidelines, which should pay more attention to the problems of the treatment of COPD patients with comorbid conditions.

Keywords: Chronic obstructive pulmonary disease (COPD); cardio-vascular comorbidity; coronary heart disease (CHD); chronic heart failure; rhythm disturbances; atrial fibrillation (AF)

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Chronic respiratory diseases (CRDs) cause enormous burden to the society. In 2016, these diseases were responsible for 3.8 million deaths or 7% of all global deaths. Seventy-five percent of these deaths occurred in those aged 30–69 years, demonstrating that CRDs are not solely a problem for the elderly (1).

Chronic obstructive pulmonary disease (COPD) is a major CRD characterized by high prevalence and mortality, and by a persistent and usually progressive airflow limitation associated with different risk factors, the main of which being tobacco smoking and air pollution. Based on multiple large-scale epidemiological studies, the global prevalence of

COPD was estimated at 11.7% in 2010, with 384 million cases (2). There are around three million COPD deaths every year (3) making this disease the third leading cause of death worldwide. Numbers are increasing (4). With the growing prevalence of smoking in developing countries and population ageing in high-income countries, the prevalence of COPD is expected to rise over the next 30 years and, by 2030, there might be more than 4.5 million deaths per year from COPD and related conditions (5,6). In most patients, COPD is associated with significant concomitant disease/conditions, which increase morbidity and mortality (7). COPD is therefore a major public health problem globally in subjects over 40 years of age (8). Pharmacological therapy is used to reduce symptoms as well as the frequency and severity of exacerbations, and to improve health status and exercise tolerance (9).

In recent years, we have a greater understanding of the heterogeneity and complexity of this disease in terms of integrated clinical assessment of the severity, pathophysiology, and the relationship with other pathological conditions. New approaches to disease classification and assessment of severity and activity have appeared in recent international and national guidelines, based on the fact that the level of airflow limitation is not sufficiently interconnected with important characteristics of the disease such as exacerbations, quality of life, and risk of mortality (10-12).

COPD is a disease that occurs in the second half of life. A typical COPD patient suffers from an average of 4 or more comorbidities, and, every day, about one third of the patients take 5 to 10 different drugs (13). In this regard, it is important to determine the significance of a particular comorbidity for the treatment of COPD.

Concomitant disease can be considered significant for the course of the underlying pathological condition (COPD) if: (I) the disease affects the course and prognosis of the COPD and vice versa (14), (II) the frequency and impact on mortality from the concomitant disease exceeds the expected rate in the general population of COPD patients (15), or (III) the presence of the concomitant disease is part of a specific COPD phenotype (16).

The extent of the problem of COPD and the coexistence of cardiovascular diseases (CVDs) is determined by the prevalence of each of these pathological conditions separately and the fact that there are many similarities between these diseases. For COPD and CVD, there are common risk factors, the most important of which being smoking.

Mechanisms of interaction between COPD and CVD. Influence of systemic inflammation

Although the lungs are considered to be the main target organ for smoking, it is well known that other systems are also affected by this risk factor, particularly the cardiovascular system (17-19). In addition, decreased pulmonary function is closely associated with an increased risk of congestive heart failure (CHF) (20-22), myocardial infarction (MI) (23), and atrial fibrillation (AF) (24). Other common risk factors for COPD and CVD are age and healthy lifestyle violation (physical activity, nutrition, etc.).

Increased levels of inflammatory markers, such as C-reactive protein (CRP) and various chemokines, play a significant role in the development of atherosclerosis, coronary heart disease (CHD), CHF and AF (25). The content of the same inflammatory markers is increased in many patients with COPD (26). Moreover, the frequency of exacerbations in COPD is associated with a more pronounced inflammation and increased risk of MI (27). However, the development of any chronic disease is a complex process—dependent on many factors—and is difficult to explain by one unique mechanism. In addition, there is insufficient evidence today that suppressing inflammation can prevent COPD in combination or without association with other diseases (*Box 1*).

Individuals susceptible to damage caused by pollutants and smoking can suffer from both heart and lung disease. Just as pulmonary disease can contribute to heart disease, cardiac illness can itself contribute to pulmonary disease.

Box 1 Clinical notes I: note of COPD and comorbidities interrelationship

Patients with COPD and comorbidities require an integrated clinical assessment of the severity, pathophysiology, and relationship with other pathological conditions

The comorbid condition affects the course and prognosis of COPD and vice versa

Pulmonary disease can contribute to heart disease, and, on the other hand, a cardiac pathologic condition can itself contribute to pulmonary disease

COPD, chronic obstructive pulmonary disease.

Effect of lung hyperinflation

Increased air volume in the lungs is one of the most important pathophysiological markers of COPD, manifested by a decrease in exercise tolerance and an increased risk of

death (28,29).

Hyperinflation and air trapping lead to flattening of the diaphragm domes, its dysfunction, and impairment of the breathing mechanics. It is documented by an increase in the level of static volume indicators during the bodyplethysmographic study (functional residual capacity, residual volume, total lung capacity) and a decrease of their surrogate marker—inspiratory capacity (30,31).

The increase in the size of the lungs due to hyperinflation has a compression effect on the heart muscle, creating unfavorable conditions for its activity and hindering the implementation of its pumping function. A number of studies have shown that an increase in the severity of COPD and the appearance of emphysema are associated with a decrease in the size of the heart during X-ray examination (32–34). Almost 40 years ago, the term “microcardia” was widely used, and was considered a radiological sign of emphysema (33).

COPD patients with a ratio of inspiratory capacity/total lung capacity <0.25 were characterized by an impaired left ventricle (LV) function which was closely correlated with a decrease in exercise tolerance during the cardio-respiratory exercise test and a decrease in oxygen pulse indices, confirming the cardiac mechanism of exercise limitation (35). Later, it was shown that the main reason for the decrease in exercise tolerance was an impairment of the LV diastolic filling (36). The close correlation of COPD severity according to the GOLD classification and the basic dimension of the heart chambers has also been demonstrated: areas of the right and left atria, right ventricle diameter, left ventricular end-diastolic diameter (36).

Role of bronchial obstruction

Bronchial obstruction or narrowing of the bronchial tree lumen, functionally manifested by a limitation of airflow, is a mandatory criterion for documenting the diagnosis of COPD.

In a longitudinal population-based study and a meta-analysis of literature, it has been shown that a low lung function marker—decreased FEV₁—is associated with an increased risk of cardiovascular mortality (37). In the NHANES (National Health and Nutrition Examination Survey) epidemiological study, patients with CHD and low FEV₁ levels had a 5-fold higher risk of death. Moreover, a systematic review of large cohort studies (>500 participants) that reported on the relationship between FEV₁ and cardiovascular mortality (12 studies; $n=83,880$ participants)

showed that for every 10% reduction in FEV₁, CVD mortality increased by 28%, indicating a close link between cardiovascular mortality and low pulmonary function. Data from two other cohort studies involving more than 5,000 participants showed that the odds ratio (OR) of CVD presence reached 1.7 in individuals diagnosed with COPD (GOLD1). The OR index increased by up to 2.2 and 2.4 in GOLD2 and GOLD3–4 COPD patients respectively. These data demonstrate a close relationship between the possibility of occurrence of CVD and the severity of pulmonary dysfunction. It is important to note that such an association has been demonstrated for the whole spectrum of CVD, including cerebrovascular disease, CHF and rhythm disturbances, and can already be seen in the early stages of the disease (38,39).

For example, heart failure (HF) was observed in 12.1% of participants with COPD in the NHANES study [1998–2008], compared to 3.9% without a COPD diagnosis, and in 7% of participants in other large cohort studies (40).

As part of a large multicenter observational study conducted in 17 cardiac clinics in Japan, it was shown that the prevalence of spirometry markers of airflow limitation suitable for the definition of COPD was detected in 995 cardiac patients with a history of smoking (41). The overall prevalence of fixed bronchial obstruction (confirmed by the ratio of postbronchodilator spirometric ratio FEV₁/FVC <0.7) was 27.0%. Eighty-seven point seven percent of these patients had not previously been diagnosed with COPD (Box 2).

Box 2 Clinical notes II: note of the influence of lung function on cardiovascular comorbidity

Decreased pulmonary function is closely associated with an increased risk of CVD

Hyperinflation can render a compression effect on the heart, creating unfavorable conditions for myocardial function

Association between lung function and possibility of disease occurrence has been demonstrated for the whole spectrum of CVD, including cerebrovascular disease

CVD, cardiovascular disease.

The prevalence of CVD among COPD patients

In COPD patients, the risk of CVD is on average 2–3 times higher than in persons of comparable age in the general population, even when taking into account the risk of smoking (42).

Previously, it was shown that about 40% of patients

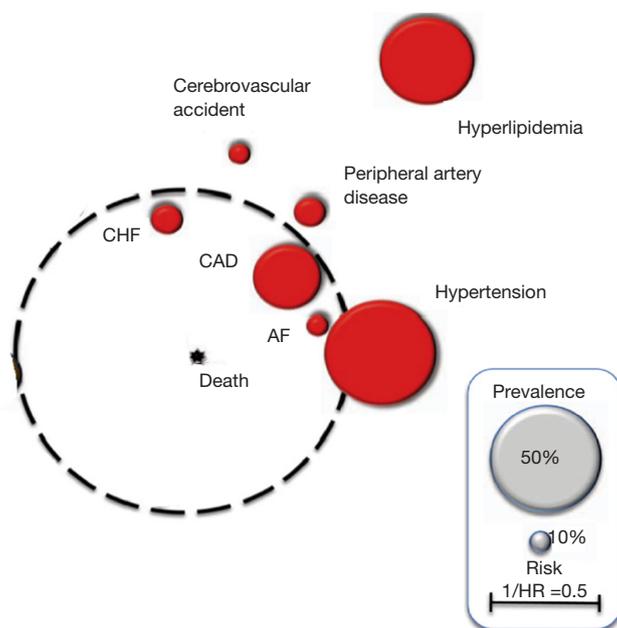


Figure 1 The “comorbidome” is a graphic expression of comorbidities with a prevalence of more than 10% in the entire cohort, and with the strongest relationship with mortality (HR: 0.1; 95% CI: 0.1; $P < 0.05$). Adapted with permission from *Am J Respir Crit Care Med*. HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure.

with mild and moderate COPD died due to CVD, which is 8–10 times more likely than deaths in the same group due to respiratory insufficiency (40,42). During the 5 years of follow-up, COPD patients had a higher rate of hospitalization and death, the cause of which was CHD, stroke and CHF.

One of the clear visual forms systematizing and reflecting the prevalence of various comorbid conditions in COPD—as well as their impact on the prognosis—is the so-called “comorbidome”, presented by Divo *et al.* (Figure 1) (15).

In this adapted diagram, the associated CVDs have a spherical image of varying magnitude.

The size of the circles reflects the prevalence of each disease in the population of COPD patients. The distance from the center of the diagram reflects the influence of this disease on the probability of death, expressed in the form of $1/\text{hazard ratio}$ (HR).

As a guideline for prevalence, grey circles are presented, the size of which reflects the prevalence of 50% (large) and 10% (small), respectively.

The above scheme clearly demonstrates that the most common comorbid conditions in COPD, conditionally related to the cardiovascular group, are hyperlipidemia and hypertension. At the same time, they play a smaller

role in increasing the likelihood of death when compared to the less common CHD, CHF and AF. These last 3 comorbidities are the most significant from the point of view of the prognosis of COPD and deserve a separate more detailed discussion, as they have accumulated the greatest amount of evidence (Box 3).

Box 3 Clinical notes III: note of typical features of COPD patients with cardiovascular comorbidities

In COPD patients, the risk of CVD is higher than in persons of comparable age in the general population

In patients with CVD, there is a high level of underdiagnosis of COPD and vice versa

Patients with cardiovascular comorbidity are usually older, more often male, have a higher smoking index, a lower quality of life and exercise tolerance, a higher dyspnea score and a longer recovery period after an exacerbation

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

CHD

Between COPD and CHD, there is a fairly strong

epidemiological relationship, which persists regardless of statistical adjustment for the common risk factors (smoking index, cholesterol level, etc.). Both diseases are characterized by systemic inflammation, oxidative stress and coagulopathy.

The main marker of inflammation is CRP, the increased level of which simultaneously contributes to an increase in the level of bronchial resistance and an increase in the risk of CHD (43,44). At the same time, the activation of immune cells in atheromatous plaques, which occurs in CHD, stimulates the production of cytokines (interferon γ , interleukin-1, tumor necrosis factor α and interleukin-6), as well as inflammatory proteins of the acute phase (fibrinogen, CRP), which are involved in the inflammatory reaction of the airways in COPD (43,44).

Despite the close relationship, the question of the connection between the severity of COPD and the frequency of accompanying CHD remains important. It was shown that a particularly high level of angiographically-confirmed coronary artery disease (59%) was observed in patients with severe COPD awaiting pulmonary transplantation (45).

At the same time, the prevalence of COPD is high in patients with CHD, but, as in patients with CHF in cardiological practice, there is a high level of underdiagnosis of COPD (46-48). A recent study showed that airflow limitation was documented in 30.5% of patients with confirmed CHD (49).

If we compare stable COPD patients with accompanying CHD and patients without comorbidity, patients with comorbidity are characterized by: older age, of male sex, higher smoking index, lower quality of life and tolerance of physical activity, increased intensity of shortness of breath and a longer recovery period after an exacerbation (50,51).

In the acute period of the disease, patients with comorbidity may have manifestations of both diseases, and coronary events may be combined with exacerbations of COPD (52-55).

Concomitant COPD increases morbidity and mortality among patients with coronary artery disease. Signs of myocardial and endothelial damage in COPD are not always detected, which leads to the underdiagnosis of CHD. Even the presence of symptoms of simple chronic bronchitis increases the risk of death from coronary episodes by 50% (56). In addition, during the exacerbation of COPD, the risk of myocardial damage in patients with concomitant CHD increases. The presence of concomitant COPD may, in some cases, complicate the recognition of

MI and contribute to its delayed diagnosis (57).

Detection of COPD in patients with CHD requires spirometric studies to identify and document airflow limitation (9). At the same time, spirometric examination should not be performed in patients with an unstable condition of the cardiovascular system: within 1 week (or 1 month) after MI (58). Despite the simplicity of diagnostic approaches, the underdiagnosis of COPD in patients with CHD and the associated lack of appropriate therapy remains a major problem.

According to published data, approximately 1 in 12 patients with severe or very severe airflow limitation hospitalized with COPD exacerbation had chest pain and/or ECG changes in dynamics that met the MI criteria (59). Moreover, available data demonstrate that increased cardiac troponin during COPD exacerbations is an independent prognostic marker of all-cause mortality (60,61). These data suggest that episodes of exacerbation may be associated with damage to the myocardium of varying degrees, which in turn may play a role in future cardiac events (62).

It remains an open question as to whether the risk of COPD increases as the severity of CVD worsens: according to the classification of GOLD, there is a significant heterogeneity of cardiovascular risk, even in cases of one category of severity (28).

Arrhythmias (AF)

AF is the most common supraventricular arrhythmia in the general population and in patients with COPD (20). Despite the fact that the largest number of publications is devoted to the combination of COPD and AF, there are also studies that investigated the combination of COPD with other rhythm disturbances: atrial tachycardia, atrial flutter, ventricular tachycardia and conduction disorders (63,64). The prevalence of AF in patients with stable COPD ranges from 4.7% to 15% (65), with a significant increase in patients with very severe COPD (20–30%) (16).

Moreover, the frequency of AF is closely related to the major spirometric indicator of the degree of bronchial obstruction—FEV₁ (66).

On the other hand, the prevalence of COPD among patients with AF ranges from 10–15%, reaching 65% in patients older than 65 years (67,68). Exacerbations of COPD can be a trigger factor that causes AF, and, in turn, AF can cause exacerbations of COPD. The latter is a risk factor of sudden cardiac death, both in cohorts of CVD patients and in the general population.

AF in various studies was a negative prognostic factor in COPD patients with respect to quality of life and health status (69), risk of hospitalizations (45) and mortality from all causes (16,70-72).

AF in COPD with the lack of control of the ventricular contraction frequency can be accompanied by shortness of breath and pulmonary edema and is often attributed to exacerbations of COPD (54). On the other hand, impaired gas exchange, hypoxia and hypercapnia, as well as oxidative stress in exacerbations of COPD may be the causes of arrhythmias (73).

HF

According to the recent definition of the European Society of Cardiology, HF is determined as a syndrome in which patients have typical symptoms (shortness of breath, swelling of ankles, fatigue) and signs (elevated jugular pressure, crackling, peripheral edema), caused by disruption of the structure and/or function of the heart that leads to a decrease in cardiac output and/or increased intracardiac pressures at rest or during exercise (74).

The prevalence of HF among COPD patients is significantly higher (10–30%) compared to the general population (1–2%), with an estimated annual incidence of 3.7% and an OR of 2.57 [95% confidence interval (CI): 1.90–3.47; $P < 0.0001$] (11,31). COPD is also a frequent concomitant disease in patients with HF and occurs, according to different studies, in 13–39% of patients (75,76).

In addition, according to a recent meta-analysis, COPD increases the risk of mortality in patients with HF (OR: 1.24–1.7).

Patients with stable COPD and HF are slightly older than patients with COPD and lack of HF, include a higher percentage of men, have more apparent symptoms and more concomitant diseases (15,77).

Exacerbations of COPD, as well as acute HF, are caused by different trigger factors: e.g., respiratory infections and pollutants in COPD and arrhythmias; acute coronary syndrome and hypertension in acute HF (78,79). At the same time, the mechanisms of pulmonary-cardiac interaction are quite complex, and respiratory symptoms often have both pulmonary and cardiac origins (52,59). In many cases, chronic HF is not detected in patients hospitalized for exacerbation of COPD, and is a cause that makes it difficult to cancel respiratory support and worsens

the overall prognosis (80,81).

Thus, the differential diagnosis of COPD in patients with HF and vice versa may be difficult, especially in elderly patients and in smokers, with severe shortness of breath as the main symptom. In this case, spirometry can provide significant help (9,82). However, conducting a correct interpretation of the spirometric study in patients with CHF may be difficult, since spirometry cannot be performed in a patient with rapidly increasing decompensation and there is a certain risk of overdiagnosis of COPD (83). In addition, even in a stable and euvolemic state, patients with low ejection fraction (EF) can experience a 20% decrease in both FEV₁ and FVC compared to the control group. However, the FEV₁/FVC ratio does not change and remains at a high level, allowing the exclusion of bronchial obstruction (84). Body plethysmography is an important additional diagnostic tool that allows the correct identification of COPD in patients with low EF (85). Thus, the clinical decision, which requires identification of COPD in this category of patients, should be based on risk factors and spirometry conducted in the stable phase of the disease, supplemented, in certain cases, by data of body plethysmography.

On the other hand, the diagnosis of HF in COPD presents the same difficulties due to the commonality of risk factors and similar clinical manifestations (84,86,87). Reduced EF is the main criteria for the diagnosis of HF in COPD patients indicated in the literature (88).

In the absence of a decrease in EF, besides the clinical picture, it is recommended to use the following criteria:

- elevated levels of natriuretic peptides: brain natriuretic peptide (BNP) >35 PG/mL and/or its N-terminal precursor (NT-proBNP) >125 PG/mL;
- objective confirmation of structural changes in the heart: increase in LV myocardial mass index or left atrium size, or diastolic dysfunction detected by echocardiography (75).

At the same time, COPD itself can have an independent effect on cardiac function, thereby influencing the results of diagnostic tests. For example, a direct relationship between NT-proBNP and FEV₁ was established in elderly individuals without HF (21).

Echocardiography remains the most important method in the diagnosis of HF. However, a significant problem in the application of this method is a significant reduction in the size of the acoustic window due to hyperinflation in emphysema in COPD patients, leading to a poor quality of

the images obtained in 10–50% of patients (87) (*Box 4*).

Box 4 Clinical notes IV: note of COPD exacerbations and cardiovascular events

During exacerbation, patients with COPD and CVD may have manifestations of both diseases and cardiac events may combine with exacerbations of COPD

Exacerbations of COPD can be a trigger factor that causes arrhythmias, and, in turn, rhythm disturbances can cause COPD acute exacerbations

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

Treatment of COPD with concomitant CVD in pulmonological practice

The COPD management in clinical practice of recent years is guided by national and international clinical recommendations, which are currently undergoing major changes (9). Unfortunately, none of these documents pay enough attention to the problems related to the treatment of COPD patients with comorbid conditions. These problems are often faced by doctors of both specialties (cardiologists and pulmonologists).

The basis of therapy for stable COPD is (I) smoking cessation, (II) administration of short- and long-acting bronchodilators (BD) (β_2 -agonists and anticholinergics), both individually and in the form of free and fixed combinations, (III) the use of combinations of inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA), and more recently (IV) triple therapy in a single inhaler.

Cardiovascular safety of BD remains a debatable subject, especially in concomitant CVD. Whether BD increases the risk of developing HF in COPD patients or whether patients with COPD and concomitant HF have an increased risk of side effects remains an open question. For example, the results of most clinical studies indicate that LABA has a satisfactory cardiovascular safety profile (89). However, this cannot be fully transferred to patients with HF, in whom a change in the β -receptor system may be observed (for example, regulation by the type of negative feedback of β_1 receptors while maintaining the unchanged level of β_2 receptors) (90), which may lead to greater sensitivity to inotropic effects. Thus, in patients taking LABA, hospitalization or emergency care for HF may be more likely, especially in the first 2–3 weeks (91). However, in other studies, data on the increased risk of cardiovascular events and deaths in patients with HF treated by LABA were not confirmed (92,93).

Similar discussions have been conducted over the past 10 years on the safety profile of anticholinergics (94,95). Short-acting antimuscarinic agents (SAMA), such as ipratropium bromide, may slightly increase the risk of HF (96). However, with the use of long-acting antimuscarinic agents (LAMA), such as tiotropium, glycopyrronium, aclidinium, umeclidinium and even a combination of LAMA and LABA, no data on an increase in the risk of HF were obtained (97–103).

In studies on the safety of phosphodiesterase-4 inhibitor (roflumilast) and ICS, no data were obtained on the increase in the risk of HF (104–106). A recently published landmark study among COPD patients with increased cardiovascular risk—SUMMIT—confirmed the cardiovascular safety of the combination of ICS/LABA (fluticasone furoate/vilanterol) (107). However, it should be noted that patients with severe HF and low FV (<30%) were excluded from the study.

Thus, it seems that LAMA are more preferable than LABA for the treatment of COPD and HF patients with low EF (108). Careful observation of COPD patients with HF could also be recommended during the first weeks of BD treatment (91), especially those with low EF. However, to date, there is no direct evidence that COPD patients with concomitant HF should be treated differently (9).

Regarding COPD patients with concomitant CHD, it was shown that the main classes of medications (LABA, LAMA and combinations of ICS/LABA) are effective and safe (89,109,110). In addition, in the FLAME study, the incidence of fatal MI, unstable angina and coronary revascularization was practically identical between groups of patients treated with a combination of LABA-LAMA (indacaterol-glycopyrronium) and ICS-LABA (fluticasone-salmeterol) (102). The SUMMIT study demonstrated that the incidence of MI and unstable angina did not differ significantly in groups of COPD patients with increased cardiovascular risk treated with a combination of ICS-LABA (fluticasone-vilanterol), monocomponents and placebo (107).

The presence of AF in COPD patients should not have a serious impact on the therapy of the underlying disease. For many years, BD have been considered as having a potential arrhythmogenic effect. However, at present, there is a sufficient amount of evidence confirming the acceptable safety profile of LABA, LAMA and ICS (111–113). Nevertheless, short-acting β_2 -agonists and theophylline should be administered with caution: if they aggravate AF, and/or impair the control of ventricular contraction frequency (114–116), they should be stopped as soon as possible.

Oral macrolides, which are often prescribed for COPD exacerbations, can increase the duration of QT interval as well as the risk of arrhythmias and sudden cardiac death (117,118).

In conclusion, it should be emphasized that COPD patients today are a heterogeneous group of subjects with a complex multimorbidity, requiring a differentiated approach. Current available data cannot answer all the questions faced by doctors of different specialities, who encounter such patients in their daily practice. At the same time, it becomes obvious that only an integrated holistic multidisciplinary approach will achieve success in the understanding and management of this group of patients (*Box 5*).

Box 5 Clinical notes V: note of cardiovascular safety of basic COPD management

It is important to determine the significance of a particular comorbidity for the treatment of COPD

The results of most clinical studies indicate that basic COPD pharmacotherapy (LAMA, LABA, LAMA-LABA and their combinations with ICS, as well as phosphodiesterase-4 inhibitor-roflumilast) has a satisfactory cardiovascular safety profile

COPD, chronic obstructive pulmonary disease; LAMA, long-acting antimuscarinic agents; LABA, long-acting β 2-agonists; ICS, inhaled corticosteroids.

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