Effectiveness and safety of concurrent beta-blockers and inhaled bronchodilators in COPD with cardiovascular comorbidities

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ABSTRACT Chronic obstructive pulmonary disease (COPD) is the most common chronic respiratory disease and its prevalence is increasing worldwide, in both industrialised and developing countries. Its prevalence is ∼5% in the general population and it is the fourth leading cause of death worldwide. COPD is strongly associated with cardiovascular diseases; in fact, ∼64% of people suffering from COPD are treated for a concomitant cardiovascular disease and approximately one in three COPD patients die as a consequence of cardiovascular diseases.

Inhaled bronchodilators might have adverse cardiovascular effects, including ischaemic events and arrhythmias, and beta-blockers might adversely influence the respiratory symptoms and the response to bronchodilators. For these reasons, it is important to know the safety profiles and the possible interactions between these two classes of drug, in order to prescribe them with greater awareness.

In this article, we review the literature about the epidemiology of COPD, its association with cardiovascular diseases, and the safety of concurrent use of inhaled bronchodilators and beta-blockers, as a tool for improving the approach to complex therapies in clinical practice.

Introduction

Chronic obstructive pulmonary disease (COPD) is the most common chronic respiratory disease, its prevalence is increasing worldwide, and it is currently the fourth leading cause of death worldwide (third in the USA) [1]. It results in a substantial waste of economic resources, in particular from dealing with exacerbations and hospitalisations [2, 3]. COPD is becoming more widespread in both industrialised and developing countries, with its prevalence reaching ∼5% in Western countries. In particular, in patients aged >65 years, prevalence is estimated to be >10% [1]. According to the multicentric REPOSI (Registro...
It is important to note that the prevalence of COPD has increased in women in recent decades. Although this could be explained by increased tobacco use, it has been suggested that, for the same degree of tobacco exposure, women may be more susceptible than men to smoking-induced lung injury, due to a peculiar bronchial immunoreactivity [4, 5]. COPD is also strongly associated with cardiovascular diseases. In fact, ~64% of people suffering from COPD are treated for a concomitant cardiovascular disease [6], and about one third of COPD patients die because of cardiovascular diseases [7].

Because inhaled bronchodilators cause adverse cardiovascular effects, including ischaemic events and arrhythmias, and beta-blockers could adversely influence respiratory symptoms and the response to bronchodilators, it is important to know the safety profiles and the possible interactions between these two classes of drug, in order to use them with greater awareness.

**COPD and cardiovascular comorbidities**

In the last few years, awareness of the systemic nature of COPD and about the comorbidities that contribute to its severity and mortality has grown [6]. In particular, there is a strong association among COPD, heart failure and ischaemic heart disease [2]. Other data from the literature point out that patients with COPD are at an increased risk of developing ischaemic heart disease and myocardial infarction than patients without COPD [7, 8]. Moreover, 17% of patients with myocardial infarction suffer from COPD.

The prevalence of COPD in patients with heart failure ranges from 20% to 32% of cases, and the prevalence of heart failure in COPD patients is >20% [9]. Data from the REPOSI registry indicate a prevalence of heart failure close to 30% in COPD patients aged >65 years with comorbidities [3].

The association between COPD and cardiovascular diseases varies according to different COPD phenotypes [10]. In particular, individuals with chronic bronchitis and frequent exacerbations experience more cardiovascular events (arrhythmias, myocardial infarction and heart failure) than those without exacerbations, probably because of an underlying inflammatory–hypoxic state, but also because it is not easy to distinguish between COPD exacerbations and both ischaemia and heart failure. Conversely, the emphysematous phenotype shows a stronger association with diastolic dysfunction due to lung hyperinflation, which adversely influences ventricular filling and cardiac output.

Due to increasing life expectancy and to improvements in both diagnostic and therapeutic tools, this coexistence of diseases will increase inexorably in the future. In evidence of this, a high proportion of patients with COPD (~80%) are on multiple drugs, not only for respiratory and cardiovascular conditions [6]. The β₂-agonists and anticholinergics used for the treatment of COPD have adverse cardiovascular effects, including ischaemic events and arrhythmias, and beta-blockers can adversely influence respiratory symptoms and the response to bronchodilators; therefore, it is clear how difficult it is to determine the approach and management of patients with COPD and cardiovascular comorbidities.

The concomitant presence of COPD and cardiopathy results in a greater severity of the clinical condition. Both conditions share similarities such as the age of the population affected, and both have a common risk factor in smoking, which is closely related to COPD and ischaemic heart disease and is the leading cause of heart failure in Western countries [11]. COPD also determines an increased risk of cardiovascular disease, including ischaemic heart disease and heart failure, because of the latent chronic organ-specific and systemic inflammatory state [9, 12]. Thus, the presence of these comorbidities might adversely affect the prognosis.

**Beta-blockers in COPD and cardiovascular comorbidities**

Poor prognosis in patients with heart failure and COPD is probably due to several factors, including interactions of the two conditions, diagnostic delay and the often unjustified rejection of the use of beta-blockers, which are essential for the treatment of ischaemic heart disease and heart failure. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines do not discourage their use [13]. In fact, according to all heart failure guidelines, once it has been established that there are no other contraindications, beta-blocker therapy is mandatory.

In this regard, a meta-analysis from 2012 pointed out that cardioselective beta-blocker use in COPD patients is safe and has a protective effect on all-cause mortality [14]. Consistent with this, an earlier Cochrane review in 2005 had already analysed the available data on the use of β₁-selective beta-blockers in COPD patients and concluded that, following administration of a β₁-selective beta-blocker, there was no evidence of adverse effects on respiratory function. More importantly, these beta-blockers did not adversely affect the effects of routinely inhaled β₂-agonists on bronchial smooth muscle [15]. Several
studies have demonstrated improved outcomes or a good safety profile (table 1). In particular, a cohort study using a database provided by National Health Service Scotland (Tayside Allergy and Respiratory Disease Information System (TARDIS)) evaluated 5977 patients aged >50 years, with a mean follow-up of 4.35 years [16]. Beta-blockers were cardioselective in 88% of cases, and their administration resulted in a reduction of 22% in all-cause mortality when added to established inhaled stepwise therapy, regardless of COPD severity. Furthermore, patients treated with beta-blockers reduced oral corticosteroid use and hospital admissions due to respiratory disease.

It has also been reported that, in COPD patients with ischaemic heart disease, heart failure and hypertension, beta-blocker use significantly reduces 1-year mortality and hospital admissions due to respiratory disease, compared to patients not treated with beta-blockers [2]. Moreover, it has been shown that cardioselective beta-blockers are undoubtedly better than non-selective beta-blockers. Consequently, there is no valid reason to avoid the use of $\beta_1$-selective beta-blockers in individuals with COPD and concomitant cardiac disease.

Table 2 shows the classification of the most common beta-blockers according to both selective and non-selective properties. The $\beta_1$-selective beta-blockers are also classified according to intrinsic sympathetic activity, the importance of which is discussed later in this section.

Although beta-blockers are the mainstay of treatment in patients with ischaemic heart disease and COPD, in these patients the use of inhaled long-acting $\beta_2$-agonists (LABAs) and inhaled long-acting muscarinic receptor antagonists (LAMAs) is more complex and still a matter of controversy. In this regard, a retrospective cohort study involving 220 elderly patients (mean±SD age 84.1±6.9 years) diagnosed with COPD was recently conducted [17]. The patients were divided into four groups by the use of beta-blockers, LABAs, combination therapy (LABA plus beta-blocker) and controls. N-terminal pro-brain natriuretic peptide and left ventricular ejection fraction were measured and evaluated. Over the follow-up period (>20 months), there was no significant difference in all-cause mortality among the four groups of treatment.

These data would indicate that there is no association between the use of LABAs, beta-blockers or combination therapy with cardiac function and all-cause mortality in elderly COPD patients, which means that they could be prescribed in a relatively safe manner in this population. The benefits associated with

### Table 1: Characteristics of the studies using beta-blockers in patients with chronic obstructive pulmonary disease (COPD) and cardiovascular comorbidities

| First author [ref.] | Year | Design | Population | Safety outcome |
|---------------------|------|--------|------------|----------------|
| SALPETER [15]       | 2005 | Review of data from 22 randomised, blinded controlled trials | 1567 patients with COPD | No adverse effect of cardioselective beta-blockers on lung function or respiratory symptoms compared to placebo |
| SHORT [16]          | 2011 | Retrospective cohort study using a disease-specific database of COPD patients (TARDIS) | 5977 patients aged >50 years with COPD | Reductions in mortality, exacerbations and hospital admissions; additive benefits with inhaled therapy; 88% of beta-blockers used were cardioselective |
| ETMINAN [14]        | 2012 | Systematic review and meta-analysis of nine retrospective cohort studies | 99877 patients with COPD | Protective effect of beta-blockers (selective and non-selective) with respect to all-cause mortality |
| STEFAN [2]          | 2012 | Retrospective cohort study | 35,082 patients aged >40 years with COPD and coexistent ischaemic heart disease, chronic heart failure or hypertension | $\beta_1$-selective beta-blocker therapy among chronic users appears to be safe during a hospitalisation for acute COPD exacerbation; $\beta_1$-selective beta-blockers are superior to non-selective beta-blockers in this category of patients |
| ZENG [17]           | 2013 | Retrospective cohort study | 220 elderly male COPD patients (mean±SD age 84.1±6.9 years) | No association between the use of $\beta_2$-agonists, beta-blockers or beta-blocker/$\beta_2$-agonist combination therapy with cardiac function and all-cause mortality in elderly male COPD patients |

TARDIS: Tayside Allergy and Respiratory Disease Information System.
beta-blocker treatment could be due to the reduction of cardiac frequency and the prevention of arrhythmogenesis induced by excessive use of bronchodilators during exacerbations and, in general, to the control of the deleterious effects of systemic sympathetic activation. Moreover, the improved cardiac haemodynamics due to the treatment could also have benefits on lung function, increasing exercise tolerance and preventing or mitigating chronic pulmonary hypertension [18].

Another important issue is that asthma and COPD may coexist in the same individual, leading to a condition that has been termed asthma–COPD overlap syndrome (ACOS). Ageing is associated with the coexistence of the two diseases. CASTIGLIA et al. [19] extensively reviewed this issue and raised some speculative and interesting observations. Additionally, a meta-analysis investigated the effect of cardioselective beta-blockers on the respiratory function of patients with "reactive" airway disease, defined by the authors as asthma or COPD with a reversible obstructive component [20]. This definition probably includes those patients who would nowadays be defined as having ACOS. In particular, the findings of this meta-analysis underscored that the use of β1-blockers is safe with regard to pulmonary function and respiratory symptoms, and is not associated with increased use of inhaled β2-agonists. Moreover, among β1-selective beta-blockers, those without intrinsic sympathetic activity cause a lower forced expiratory volume in 1 s (FEV1) reduction than the other categories of beta-blocker, which can be noted after the first administration [20]. Furthermore, they appear to cause an upregulation and sensitisation of β2-receptors, resulting in an increased response to exogenous β2-agonists. In patients treated with LABA plus beta-blocker without intrinsic sympathetic activity, FEV1 increased by 12% compared to those treated with placebo, while those treated with LABA plus beta-blocker with intrinsic sympathetic activity did not show any improvement in FEV1 [20].

The correct use of β1-selective blockers, in particular without intrinsic sympathetic activity, is an example of good clinical practice in patients with mild-to-moderate COPD and associated heart failure and/or coronary artery disease. Moreover, bisoprolol reduced the incidence of heart failure and/or COPD exacerbation compared with carvedilol in a retrospective longitudinal analysis [21]. Although there is a high tolerance of β1-selective blockers and certain benefits in cardioprotection, their prescription should always be preceded by a careful evaluation of each patient’s characteristics, and follow a proper and safe drug dosage.

**LABAs and LAMAs in COPD**

LABAs and LAMAs, alone or in combination therapy, represent one of the mainstays of COPD treatment. However, these drugs do not only bind lung receptors. In fact, β2-agonists bind the β2-receptors of the respiratory system with more affinity, and β1-receptors of the heart with less affinity. β2-agonists, acting on the sinus node, increase the heart rate and, acting on the myocardium, increase stroke volume, thus exerting their sympathomimetic effect. Antimuscarinic agents may bind M2 receptors of the sinus node, potentially increasing the heart rate and, consequently, the myocardial oxygen consumption. Thus, their effect should be considered in the therapy management of patients with concomitant heart disease. Several studies have been conducted to clarify the extrapulmonary effects of LABAs and/or LAMAs, mainly focusing on their use in patients with cardiac comorbidities (table 3).

A 2015 meta-analysis, conducted to assess the safety profile of LABAs and LAMAs for severe arrhythmias (including atrial fibrillation and other tachyarrhythmias), showed no statistically significant differences.

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**TABLE 2 Classification of the most common beta-blockers according to selective and non-selective properties**

| Non-selective β1- and β2-blockers | α- and β-blockers | ISA-Selective | ISA+Selective |
|-----------------------------------|------------------|--------------|---------------|
| Propranolol 40–280 mg twice daily | Labetalol 200 mg twice daily | Atenolol 25–100 mg once or twice daily | Nebivolol 5–10 mg once daily |
| Sotalol 80–160 mg twice daily | Carvedilol 12.5–50 mg twice daily | Metoprolol 100 mg once or twice daily | Acebutolol 200–800 once daily |
| Nadolol 40–320 mg once daily | | Bisoprolol 2.5–10 mg once daily | |
| | | Esmolol 50–200 μg·kg⁻¹·min⁻¹ | |

Data are presented as usual dosage in clinical practice. ISA: intrinsic sympathetic activity.
among all the agents [22]. Salmeterol showed a lower cardiovascular mortality risk versus placebo and tiotropium (Respimat Soft Mist Inhaler; Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany). Tiotropium was associated with higher cardiovascular mortality risk. However, in another context, tiotropium was shown to be more effective in reducing exacerbations than salmeterol and indacaterol, regardless of association with inhaled corticosteroids [27, 28]. Moreover, the UPLIFT study (Understanding Potential Long-term Impacts on Function with Tiotropium), a double-blind, randomised, placebo-controlled clinical trial conducted on >6000 patients (followed up for 4 years), revealed a reduced acute myocardial infarction and cardiovascular mortality incidence versus placebo [29]. Thus, tiotropium is considered the gold standard drug as monotherapy. The TIOSPIR study (TIOtropium Safety and Performance In Respimat) also showed that different formulations of tiotropium (Respimat at a dose of 2.5 or 5 μg and HandiHaler at 18 μg; both from Boehringer Ingelheim GmbH) had a similar risk of death [30]. Furthermore, the risk of exacerbation and major adverse cardiovascular events did not differ significantly among the three treatment groups [30], or upon switching patients from tiotropium HandiHaler to tiotropium Respimat [31].

Current evidence supports the safety of aclidinium [32] and glycopyrronium [33, 34], with no substantial differences with other LAMAs.

The aforementioned 2015 meta-analysis revealed no significant differences in cardiovascular safety profile between combination therapy with LAMA plus LABA and monotherapy [22]. Several reviews and meta-analyses assessing the effectiveness and safety of LAMAs and LABAs in COPD patients have demonstrated that dual bronchodilation is effective and safe, with no increase in adverse events when compared with monotherapies [24, 25, 35]. Moreover, the FLAME study (which studied the effect of indacaterol–glycopyrronium versus salmeterol–fluticasone on COPD exacerbations) showed no evidence of significant cardiovascular death or cardiac pump failure, supporting a good safety profile of the LABA (indacaterol)/LAMA (glycopyrronium) association [36].

Unfortunately, these studies often involve a selected patient population. Since patients with COPD and other significant comorbidities are not included in these studies [24], these pieces of evidence may not reflect real-life clinical scenarios.

### TABLE 3 Characteristics of studies using long-acting β-agonists (LABAs) and/or long-acting muscarinic receptor antagonists (LAMAs) in patients with chronic obstructive pulmonary disease (COPD) and cardiovascular comorbidities

| First author [ref.] | Year | Design | Population | Safety outcome |
|---------------------|------|--------|------------|----------------|
| TRICCO [22]         | 2015 | Systematic review and network meta-analysis of 208 randomised clinical trials | 134 692 adults with COPD | No statistically significant differences in risks of serious arrhythmia across any of the compared agents |
| TASHKIN [23]        | 2015 | Post hoc analysis of all-cause mortality and serious cardiac adverse events using data from the UPLIFT study | 6562 patients with COPD with recent myocardial infarction, heart failure or unstable rhythm disorder | Risk of cardiac events, mortality or SAEs was not increased by tiotropium versus placebo in patients experiencing cardiac events |
| OBA [24]            | 2016 | Systematic review and network meta-analysis of 23 trials | 27 172 patients older than 35 or 40 years with a diagnosis of COPD | Combination therapy had similar effects on safety outcomes, including mortality, total SAEs, cardiac SAEs and dropouts, compared with monotherapy |
| CALZETTA [25]       | 2016 | Systematic review and meta-analysis of 22 randomised clinical trials | 23 168 with a diagnosis of COPD | No evidence of any significant difference concerning the cardiac safety profile of combination therapy compared with monocomponents |
| LAHOUSSE [26]       | 2016 | Review of 93 studies about cardiac safety of bronchodilator therapy in COPD | >700 000 patients with a diagnosis of COPD | LAMAs and/or LABAs are safe when used in the appropriate dose in adherent patients with COPD without uncontrolled cardiovascular disease or other notable comorbidities; cardiac safety is less evident when used inappropriately (e.g. overdosing) or in patients with COPD and substantial cardiovascular disease, prolonged QTc interval or polypharmacy |

UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium; SAEs: severe adverse effects.

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It is possible to infer that a LAMA or LABA alone, or in combination therapy, are safe if proper doses are administered in compliant patients with COPD, well-controlled cardiovascular diseases and no other relevant comorbidities. However, LAMA and LABA cardiovascular safety is reduced if they are not used correctly (i.e. overdose) or are used in patients with COPD and other significant cardiovascular diseases, QTc interval prolongation or who are on multiple drugs [24]. Therefore, they should be used with caution in these categories of patient.

Conclusions
This review shows that, although cardioselective beta-blockers may be used more extensively and properly in COPD patients with cardiovascular comorbidities, bronchodilators should be used with more caution in a particular subset of patients with cardiovascular comorbidities. Further pragmatic real-world-based clinical trials are required to assess the safety of these classes of drugs in COPD patients with cardiovascular comorbidities.

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