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Review

Cardiovascular diseases or type 2 diabetes mellitus and chronic airway diseases: mutual pharmacological interferences

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***Abstract*:** Chronic airway diseases (CAD), mainly asthma and chronic obstructive pulmonary disease (COPD), are frequently associated with different comorbidities. Among them, cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) pose problems for the simultaneous treatment of CAD and comorbidity. Indeed, there is evidence that some drugs used to treat CAD negatively affect comorbidity, and, conversely, some drugs used to treat comorbidity may aggravate CAD. However, there is also growing evidence of some beneficial effects of CAD drugs on comorbidities and, conversely, of the ability of some of those used to treat comorbidity to reduce the severity of lung disease. In this narrative review, we first describe the potential cardiovascular risks and benefits for patients using drugs to treat CAD and the potential lung risks and benefits for patients using drugs to treat CVD. Then, we illustrate the possible negative and positive effects on T2DM of drugs used to treat CAD and the potential negative and positive impact on CAD of drugs used to treat T2DM. The frequency with which CAD and CVD or T2DM are associated requires not only considering the effect that drugs used for one disease condition may have on the other but also providing an opportunity to develop therapies that simultaneously favorably impact both diseases.

Keywords: asthma, cardiovascular disease, chronic airway diseases, chronic obstructive pulmonary disease, pharmacological interferences, type 2 diabetes mellitus

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Introduction

According to current evidence from extensive studies and quantitative synthesis of published reports, chronic airway diseases (CAD), mainly asthma and chronic obstructive pulmonary disease (COPD), are frequently associated with pulmonary or extrapulmonary-related comorbidities.[1,2] This association indicates that comorbidity detection must become integral to CAD care. Furthermore, a thorough assessment of their impact is essential to ensure they are adequately treated and regulated to limit their effect on CAD.

When extrapulmonary comorbidities are added, the clinical scenario becomes considerably more challenging, as they can significantly influence the overall treatment of people with CAD. First, it is essential to assess the link between comorbidity and CAD, and to establish whether it is only a concomitant disease that has causally appeared in a patient with CAD or whether it may also result from the pharmaceutical therapies used to treat CAD.[3] If this is the case, the treatment of CAD should be reconsidered. However, it cannot be ruled out that the drugs used to treat comorbidity may have an unfavorable impact on CAD, either through a direct effect on the lungs or through a drug–drug interaction that decreases the therapeutic efficacy of the prescribed treatment for CAD.[4] Besides these negative interferences, there is growing evidence that some drugs used to treat CAD benefit comorbidity. Conversely, some of those used to treat comorbidity may reduce the severity of lung disease.[5]

Among the many comorbidities associated with asthma and COPD, cardiovascular disease (CVD)[4] and type 2 diabetes mellitus (T2DM)[6] pose problems for the simultaneous treatment of CAD and comorbidity. This is not a minor problem considering the frequency with which CAD, CVD, and T2DM coexist in the same patient. A significant prevalence of CVD has been documented in COPD patients, ranging from 28% to 70%.[2,7–10] Early-onset asthma patients had a 26% greater risk of CVD than those without asthma. In contrast, late-onset asthma patients had a 39% increased risk of CVD.[11] The incidence rate of T2DM in COPD patients was 1.26 per 100 patient-years. Still, it became 1.47 among frequent exacerbators (⩾2 treated exacerbations per year) compared to infrequent exacerbators and 1.73 for patients receiving high-dose inhaled corticosteroids (ICS) (>800 µg budesonide equivalent dose) compared to patients receiving no ICS therapy in a cohort study that used primary care data from the Clinical Practice Research Datalink.[12] Over 11 years of follow-up, individuals with hyperglycemia or T2DM had a 43% increased risk of incident asthma.[13] Furthermore, compared to those in the normal range, individuals with glycated hemoglobin in the pre-diabetic or diabetic range have 27–33% higher rates of asthma exacerbations,[14] lower lung function, and 68% higher rates of having their asthma hospitalized.[15]

In this narrative review, we aim to describe the potential risks and benefits for patients with CVD or T2DM treated with pulmonary drugs and the potential pulmonary risks and benefits for patients with CAD when taking cardiovascular or antidiabetic drugs.

Cardiovascular disease

Potential cardiovascular risks for patients with CVD when using drugs to treat CAD

A complex and varied context supports the link between CAD and CVD.[16] It has been proposed that lung inflammation spreads into the systemic circulation, generating systemic inflammation.[16] In fact, patients with CAD and concomitant CVD have increased levels of interleukin (IL)-6, C-reacting protein, and fibrinogen. Systemic inflammation, in turn, is linked to acute endothelial dysfunction of systemic blood arteries and causes arterial stiffness.[16] Moreover, hypoxemia in individuals with CAD may result in pulmonary vascular remodeling and vasoconstriction, resulting in right ventricular diastolic dysfunction.[16] Dysfunction of the right ventricle may increase pulmonary vascular resistance, causing the interventricular septum to be displaced to the left ventricle and affecting ventricular filling, stroke volume, and cardiac output. However, should only asthma and its link to CVD be considered, it is true that the two diseases share chronic systemic inflammation, but asthma is considered a type 2 disease. At the same time, CVD is often a type 1 condition. IL-4, IL-5, and IL-13 are type 2 cytokines that are pathogenic in allergic asthma but protect against possible cardiovascular damage.[17] This would predict that asthma and CVD have an ameliorative rather than a worsening association, contrary to what is observed in clinical practice.[17] However, IgE concentrations are higher in coronary events. Still, it is unclear whether this is due to their involvement in the genesis of the coronary event or to the inflammatory response caused by the tissue damage that occurred during the event.[18]

CAD treatments are generally successful and safe. It has been suggested that the severity of CAD does not appear to influence the risk of CV events (CVEs), which unexpectedly increases in people without a history of CVD when using bronchodilators.[19] Indeed, many side effects of drugs used to treat pulmonary disorders may include some degree of CV risk, particularly in some susceptible patients.[16] Physicians must take this risk into account, considering reports of adverse CVEs in patients with asthma or COPD who are using long-acting muscarinic receptor (mAChR) antagonists (LAMAs)[20] or long-acting β_2-adrenoceptors (ARs) agonists (LABAs).[21]

Those who use bronchodilators within 6 months are less likely to develop coronary vasospastic angina than those who have used them between 7 and 36 months earlier.[22] Individuals who use bronchodilators for a shorter time may be less susceptible than longer-term users because continuous use of bronchodilators may stimulate and enhance sympathetic activity and produce vasospasm.[22]

There are several pharmacological mechanisms by which bronchodilators can induce adverse CVEs. The coexistence of β1- and β_2-ARs and M_2 and M_3 mAChRs in the heart implies that

both LABAs and LAMAs can have some effect on the heart, even when they are highly selective.

β-ARs located in the heart, with 77% and 23%, respectively, in the atria and ventricles, play a crucial role in managing the CV system.[21] In normal hearts, β_1-ARs and β_2-ARs coexist, although the β_1-AR subtype predominates; however, the density of β_2-AR is 2.5-fold greater in the sinoatrial node than in the right atrial myocardium, and this is consistent with physiological studies that attribute to this receptor a role in the regulation of cardiac chronotropism.[23] Increased heart rate and palpitations are less common with the selective β_2-AR agonists than with nonselective β_1-AR and β_2-AR agonists, although even stimulation of β_2-ARs can result in vasodilation and reflex tachycardia. In any case, the heart is a non-target tissue with a lower β_2-AR density than target tissues, such as airway smooth muscle (ASM).[24] MAChRs reside in both the atria and ventricles but have a greater density in the former, with M_2-mAChRs being the predominant mAChR subtype in the heart.[25] The levels of M_2-mAChRs are comparable between the human atrium and ventricle, while the density of M_3-mAChRs appears ~10-fold higher in the ventricle than in atrium. Stimulation of the M_2-mAChRs mediates negative chronotropic and inotropic effects, and its inhibition is responsible for tachycardia. The role of M_3 mAChRs might become prominent in pathological situations, such as cardiac ischemia, pathological cardiac hypertrophy, cardiac arrhythmias, and heart failure (HF).

MAChR antagonists. Tachycardia and arrhythmia can result from reduced parasympathetic nervous system activity.[24] Heart rate mediated by β_2-AR stimulation increases in the presence of inhibition of cardiac vagal tone caused by a mAChR antagonist due to the decrease or even the absence of the influence of vagal tone on the adrenergic response in the heart.[25]

Inhaled ipratropium, a short-acting mAChR antagonist, can induce a modest risk of arrhythmia in asthmatic adolescents and young adults.[26] Concern has also been raised about the probable links between the use of tiotropium, a LAMA, and CV morbidity and mortality, at least in patients with COPD.[20] Although the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial found no significantly increased risk of mortality (HR 0.89; 95% CI 0.79–1.02) or myocardial infarction (RR 0.73; 95% CI 0.53–1.00) with tiotropium Handihaler, the pro-ischemic and pro-arrhythmic effects are consistent with the excess reported of angina (RR 1.44; 95% CI 0.91–2.26), imbalance in strokes attributable to ischemia, and rates of supraventricular tachyarrhythmias.[27] However, a *post hoc* analysis of all-cause mortality and adverse severe CVEs in patients who had cardiac arrhythmia, myocardial infarction, or HF during the UPLIFT study and completed it found that tiotropium did not increase the risk of a major or even fatal CVE.[28]

The introduction into the market of tiotropium delivered by the Respimat Soft Mist Inhaler, which releases a higher dose of fine particles and allows for more significant deposition of the drug in the lung than the aerosols produced by HandiHaler,[29] resulted in several documentations that Tiotropium Respimat increases the risk of death compared to tiotropium HandiHaler.[30–32] However, the large Tiotropium Safety and Performance in Respimat (TIOSPIR) study[33] and the results of real-life research[34] showed that tiotropium, when administered by Respimat, was not less safe than Handihaler, although it showed a trend toward an increased incidence of myocardial infarction. This conclusion has been validated by an evaluation of the safety of tiotropium Handihaler *versus* tiotropium Respimat SMI performed by a systematic review and network meta-analysis of the available clinical evidence that concluded that both devices had a low absolute risk of adverse CVEs, with a minimal but not statistically significant benefit in favor of tiotropium HandiHaler.[35] A population-based cohort study using data collected in routine clinical practice also came to the same conclusion.[36]

In this scenario, real-world studies are required to identify people possibly at high CV risk and may benefit from ECG monitoring. As each patient may respond differently to mAChR blockade, it will be crucial to make every effort to proactively identify people at high risk of adverse CVEs when treated with tiotropium or another mAChR antagonist.[35] It has been proposed that there is a subgroup of COPD patients at high risk of CAD who respond to initial therapy with LAMA by amplifying sympathetic activation or who amplify systemic inflammation after taking long-acting bronchodilators due to predisposing characteristics.[37]

β_2-AR agonists. People with asthma exhibit higher sympathetic responses to β_2-AR agonists, which may increase CV risk.[38] However, β_2-agonists differentiate into full agonists, such as isoproterenol or formoterol, which completely move the equilibrium in the activated conformation of the β_2-ARs, partial agonists, such as salmeterol or ultra-LABAs (mainly vilanterol), that bind to and activate β_2-ARs but are unable to generate the maximum possible response produced by full agonists, and inverse agonists, which are β-AR blockers, such as nadolol, that bind to the same β_2-ARs binding site as an agonist but induce a pharmacologic response opposite to that agonist, shifting the equilibrium away from the activated conformation of the β_2-ARs toward an inactive state.[23,24] Full and partial agonists can elicit similar downstream effects. Full agonists have a therapeutic benefit over partial agonists during an exacerbation because fewer spare receptors may exist.[39] In contrast, the heart has a lower β_2-ARs density than ASM, which may explain why partial agonists have a better safety profile.[24]

In patients with asthma, there can be an association between inhaled β_2-AR agonist therapy and an elevated risk of acute myocardial infarction, atrial fibrillation, congestive HF, cardiac arrest, and sudden cardiac death, with a particularly high risk in individuals with long QT syndrome.[40] In COPD, short-acting β_2-AR agonists may precipitate atrial fibrillation and worsen ventricular rate control.[41] LABAs induce an increase in heart rate and a worsening of arrhythmia mainly in patients with COPD experiencing preexisting cardiac arrhythmias and hypoxemia, and could increase the risk of HF.[21] These effects appear to be dose-dependent and based on whether the β_2-AR agonist is a full or partial agonist.[42] Nevertheless, a *post hoc* analysis of the Toward a Revolution in COPD Health (TORCH) study concluded that although a history of myocardial infarction doubled the risk of adverse CVEs, the development of new CVEs was not more common in patients who received LABA than in placebo-treated individuals.[43]

Dual bronchodilation. The development of LAMA/LABA combinations was undoubtedly a significant advancement in the treatment of COPD patients,[44] and such a therapeutic approach is currently the cornerstone of recommendations in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy.[45] However, there is evidence that dual bronchodilation treatment may also increase the prevalence of CV comorbidities in COPD patients, although with substantial differences in risk related to the LAMA/LABA combination examined.[46] Nevertheless, data from randomized controlled trials (RCTs), mainly from individuals without important CV morbidity, revealed that the different LAMA/LABA combinations used at approved doses were not significantly different from their monocomponents in cardiac safety.[47] Furthermore, an observational study conducted in the real world using primary care medical data from the UK Clinical Practice Research Datalink found that compared to long-acting bronchodilator monotherapy, LAMA/LABA combinations resulted in an equivalent 1-year risk of acute myocardial infarction, stroke, and arrhythmia.[48] However, people who added a second long-acting bronchodilator had a slightly greater risk of HF.

Inhaled corticosteroids. Regarding corticosteroids, current evidence does not document an increased risk of CVE with ICS treatment for asthma or COPD.[49] However, a study analyzing data from the Taiwan National Health Insurance database concluded that previous corticosteroid use increased the risk of coronary vasospastic angina.[32] This result could be explained by previous corticosteroid users having more severe inflammation than new corticosteroid users.[32] Furthermore, individuals undergoing high-dose corticosteroid treatment ($\geqslant$7.5 mg prednisone equivalents daily) have been reported to be at risk of developing atrial fibrillation.[50] Treatment with ICS/LABA did not change mortality or CV outcomes in people with moderate COPD and high CV risk.[51] However, in real-world COPD patients with overlapped HF, ICS alone was associated with significantly higher mortality risks than LAMA or ICS/LABA.[52] A recent meta-analysis documented that triple (ICS/LABA/LAMA) combinations significantly increased the risk of severe adverse CVEs (RR 1.29, 95% CI 1.10–1.51; $p < 0.01$) compared to ICS/LABA combinations but reduced it (RR 0.66, 95% CI 0.53–0.80; $p < 0.001$) compared to LAMA/LABA combinations.[53] In any case, the risk of severe adverse CVEs was reduced when the dose of ICS included in triple therapy was higher, while it was higher when the amount of ICS was lower.

Monoclonal antibodies. The Evaluating Clinical Effectiveness and Long-term Safety (EXCELS) study in patients with moderate-to-severe asthma, conducted in 7836 patients, showed that patients taking omalizumab, a monoclonal antibody (mAb) that targets IgE, preventing it from binding to receptors on basophils and mast cells, had higher rates of cardiovascular, cerebrovascular, and arterial thromboembolism events than untreated patients despite having much higher blood IgE levels.[54] This contrasts with the possibility that IgE plays a role in the atherosclerotic process. One possible explanation for this finding could be that patients treated with omalizumab were more severe, and the CV damage may have been a consequence of the drugs used to treat asthma, particularly oral corticosteroids, which have been associated with an increased risk for adverse CVEs.[55]

Furthermore, a French pharmacovigilance study found that omalizumab was considerably more related with hypertension, ventricular arrhythmia, and venous thromboembolism than mepolizumab, reslizumab, and benralizumab, which are anti-IL-5 mAbs.[56] However, a pooled review of 25 omalizumab-related RCTs and two extension studies found no indication of increased CV risk.[57] Until now, there have only been isolated reports of omalizumab-related arterial and venous thromboembolic events.[58]

The documentation of the rare occurrence of CV adverse events when using anti-IL-5 mAbs[56] confirms the lack of genetic evidence that might suggest that IL-5 inhibition influences the risk of cardiovascular and thromboembolic adverse events.[59] However, it contrasts with the hypothesis that IL-5 plays a protective role in atherosclerosis,[60,61] and therefore, its inhibition could theoretically increase the risk of CVD.

Potential cardiovascular benefits for patients with CVD when using drugs to treat CAD

Due to their ability to improve pulmonary function, inhaled bronchodilators can play a role in treating individuals with chronic HF, particularly those with airway obstruction, even in the absence of true COPD.[62] In effect, patients with HF may develop diffusion impairment and airway obstruction even when they are stable and uncongested and do not have CAD.[63] Airway obstruction in these patients has been associated with increased airway wall thickness caused by bronchial mucosal enlargement, peribronchial edema and fibrosis, parasympathetic-mediated bronchoconstriction, and alveolar fluid retention.[64] Reduced air trapping combined with reduced compression of the pulmonary microcirculation mediates the effects of bronchodilators on cardiac filling caused by improved perfusion.[65] The improvement of regional ventilation with these agents is a second process closely related to the first.[65]

Dual bronchodilation. Lung hyperinflation has long been associated with increased heart size and cardiac dysfunction in COPD patients.[66] A small but important study showed that 14-day treatment with LAMA + LABA induced significant lung deflation, normalized biventricular end-diastolic volumes, and improved cardiac filling in patients with moderate-to-severe COPD and pulmonary hyperinflation.[67] The cardiac and pulmonary effects were greater than expected. Dual bronchodilation improved regional ventilation and pulmonary microvascular blood flow with increased cardiac filling and cardiac output.[68] The observational COPD and Systemic Consequences–Comorbidities Network (COSYCONET) study confirmed the favorable impact on the CV system of dual bronchodilation.[69] The effects of long-term treatment with ICS, LABA + ICS, LAMA + LABA, and triple therapy on the left heart evaluated in a large COPD population by echocardiographic data were mainly on the left atrial diameter; this was true for ICS, LABA + ICS and more consistently for LAMA + LABA.

Inhaled corticosteroids. ICSs can reduce the inflammatory process in the lungs, limiting the spillover of inflammatory mediators from the lungs into the systemic circulation and reducing the systemic inflammatory process that is common in patients with obstructive airway disease.[70] Since systemic inflammation contributes to the development of endothelial dysfunction and the progression of atherosclerosis, ICSs can improve blood vessel function and lower the risk of ischemic events.[70] ICS use is associated with significantly lower CV and all-cause mortality in women with asthma.[71] It has been suggested that inhaled budesonide at a high dosage (800 $\mu g \cdot day^{-1}$) might considerably reduce ischemic heart events in smokers with moderate COPD.[72] Moreover, compared to other inhalation therapies, the administration of ICS/long-acting bronchodilator

combinations has also been shown to reduce the severity of clinical symptoms of the acute phase of ST-elevation myocardial infarction (STEMI) in patients with COPD.[73] A *post hoc* analysis of the TORCH study revealed that combining an ICS with a LABA may provide some cardioprotection.[41] However, as already mentioned, the Study to Understand Mortality and MorbidITy (SUMMIT) research found no survival advantage for fluticasone furoate/vilanterol in COPD patients with a history of CVD or risk factors.[51] However, in the pivotal phase III, 52-week Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trial, deaths from CV causes occurred in 0.5%, 0.8%, 1.4%, and 0.5% of patients in the budesonide/glycopyrrolate/formoterol fumarate 320 μg, budesonide/glycopyrrolate/formoterol fumarate 160 μg, glycopyrrolate/formoterol fumarate, and budesonide/formoterol fumarate 320 μg groups, respectively.[74]

Potential pulmonary risks for patients with CAD when using drugs to treat CVD

The drugs that are typically used to treat the various CVDs are β-AR blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 (AT1) receptor antagonists, statins, antiplatelet drugs, calcium channel blockers, and diuretics, regardless of whether the patient also has asthma or COPD.[4,5]

β-AR blockers. β-AR blockers are beneficial in treating individuals with acute coronary syndromes and in the secondary prevention of coronary events. They are also helpful in congestive HF and in the treatment of cardiac arrhythmias. Furthermore, β-AR blockers are used as hypertension medications. In patients with CAD, β-blockers may cause bronchoconstriction and neutralize the efficacy of β_2-AR agonists.[4,5] In addition, they can induce moderate and severe asthma exacerbations and increase mortality in patients with severe COPD.[4,5] However, these adverse events have only been reported in patients who received non-cardioselective selective β-AR blockers, those that affect the function of both β1- and β_2-ARs, such as propranolol, nadolol, pindolol, labetalol, sotalol, carvedilol, and timolol.[75] On the contrary, there is evidence that cardioselective β_1-AR blockers, such as metoprolol, atenolol, acebutolol, betaxolol, esmolol, bisoprolol, and nebivolol, are not associated with a significantly increased risk of moderate or severe asthma exacerbations in patients with CVD and concomitant asthma. No cases of cardioselective β_1-blockers causing asthma mortality have been reported.[76] β-AR blockers may induce a reduction in lung function during the early part of the treatment period, which is modest, does not persist, and does not predict exacerbations in COPD patients,[77] and increased mortality in patients with severe COPD.[78]

ACE inhibitors and AT1 receptor antagonists. ACE inhibitors and AT1 receptor antagonists are commonly used as first-line or add-on drugs for arterial hypertension, congestive HF, and myocardial infarction.[4,5] The mechanism of action of ACE inhibitors is based on the inhibition of ACE, the enzyme responsible for the conversion of angiotensin (Ang) I into Ang II and the degradation of many hemodynamically active peptides, such as bradykinin.[79] The latter contributes to the overall benefit of ACE inhibitor therapy by mediating vasodilation incrementally, releasing nitric oxide and increasing the synthesis of vasoactive prostaglandins. AT1 receptor antagonists directly block AT1 receptor and displace Ang II from the AT1 receptor. Thus, AT2 receptor activation is enhanced and is followed by vasodilation and natriuresis.[79]

In asthma, there is evidence that ACE inhibitors can occasionally cause bronchospasm, but coughing is a more prevalent adverse effect.[80] ACE inhibitors were associated with increased asthma morbidity, emergency department visits or hospitalizations, and the use of systemic corticosteroids in a case-control study.[81] There is documentation that those with active asthma and are older, female, and have a higher body mass index tolerate ACE inhibitors less.[82] However, the development of ACE inhibitor-induced bronchoconstriction or asthma is not universal in all asthma patients, and if a risk exists, individual predisposition should be investigated further.[83] However, AT1 receptor blockers do not produce cough or increased airway hyperresponsiveness, even in individuals unable to take an ACE inhibitor.[84] In COPD, ACE inhibitors can cause coughing and increase airflow obstruction, side effects that are generally not induced by AT1 receptor blockers.[85]

Calcium antagonists. Several studies have found that calcium antagonists did not have major side events in asthma patients.[86] On the contrary,

dihydropyridine calcium channel blockers can be harmful in COPD because they can alter ventilation/perfusion matching and exacerbate hypoxemia.[87] Still, this impact appears to be relatively moderate and neutralized by an improvement in central hemodynamics.[88]

Diuretics. Simultaneous use of β_2-AR agonists or ICSs with a diuretic, primarily a thiazide, may amplify the hypokalemia effects[89] associated with the capacity of β_2-AR agonists to force potassium into cells and the propensity of corticosteroids to enhance urine potassium excretion moderately.[90] Arrhythmias can occur due to hypokalemia.[91] The metabolic alkalosis caused by thiazide diuretics can decrease the ventilatory drive, thus increasing the degree of hypoxemia and hypercapnia in patients with COPD and persistent hypercapnia.[92] High doses of loop diuretics can cause metabolic alkalosis, with hypoventilation acting as a compensatory mechanism, which can worsen hypercapnia.[93] In addition, diuretics may affect mucus production.[94]

Potential pulmonary benefits for patients with CAD when using drugs to treat CVD

Medications that reduce the CV risk may significantly influence the clinical outcome of patients with CAD by lowering the CV component of unfavorable morbidity and mortality.[4]

β-AR blockers. Nadolol is an inverse agonist and has shown various positive benefits in asthma, but large-scale studies have not been conducted to corroborate these findings.[95] In contrast to β-AR blockers that are not inverse agonists, nadolol reduces airway hyperresponsiveness, most likely through its action on the arrestin/extracellular signal-regulated kinase (ERK) pathway.[96]

A recent network meta-analysis that evaluated the effects of β-AR blocker use in patients with COPD included 23 observational studies and 14 RCTs.[97] It found a lower incidence of COPD exacerbations, mortality, and a higher quality of life in observational studies. In contrast, propranolol was the only drug associated with decreased lung function in RCTs. However, no specific β-AR blocker was associated with a decline in lung function in the CVD subset. It has been suggested that lowering sympathetic tone and increasing expression of β_2-ARs in the lungs may reduce the demand for β_2-AR agonists and may be possible pathways through which β-AR blockers demonstrate positive pulmonary benefits in COPD patients over time.[5]

Although there is a signal that the advantages of β-blockers in patients with COPD and coexisting CVD are less evident in older patients and those with more severe disease,[98] this should not be understood as a restriction of the use of these agents in COPD, mainly if the patient is under regular β_2-AR agonist treatment.[5] Furthermore, it was found that the co-administration of a β_2-AR agonist and a β_1-AR blocker can normalize decreased β_1-AR mRNA expression and cardiac cyclic AMP levels, reduce infarct size, and influence cardiac remodeling.[99] It was also documented that lung function, overall respiratory status, and safety of dual bronchodilation were not influenced by baseline β-AR blocker treatment in patients with moderate-to-very severe COPD.[100]

ACE inhibitors and AT1 receptor antagonists. The renin–angiotensin system may play a role in the pathophysiology of CAD by generating proinflammatory mediators in the lungs, such as tumor necrosis factor-α, IL-1, IL-6, monocyte chemoattractant protein-1, IL-8, macrophage inhibiting factor, and regulated on activation normal T cell expressed and secreted (RANTES).[101] When ACE is inhibited, Ang I levels rise while Ang II levels fall, lowering Ang II-mediated salt retention, vasoconstriction, vascular development and proliferation, superoxide generation, inflammation, and prothrombotic effects.[102] AT1 receptor antagonists affect the same process by inhibiting the Ang II AT1 receptors.[101] However, ACE appears to have a larger affinity for bradykinin, which is important in regulating vasodilation, natriuresis, oxidative stress, fibrinolysis, inflammation, and apoptosis, than for AT1, implying that ACE inhibitors may be more efficient inhibitors of bradykinin breakdown than of Ang II synthesis.[103]

Therefore, chronic reduction in ACE activity can have significant long-term benefits in treating patients with CAD through effects on pulmonary inflammation, architecture and vasculature, respiratory drive and respiratory muscle function, peripheral oxygen use efficiency, and improved functional capacity of skeletal muscle despite reduced oxygen supply.[101] As a result, ACE inhibitors and AT1 receptor antagonists may

benefit people with asthma or COPD.[104] ACE inhibitors protect smokers from a rapid decrease in lung function and progression to COPD, with a stronger effect on the decline in FEV_1 than on the reductions in forced vital capacity (FVC).[105] However, there is also evidence that the use of AT1 receptor blocker is associated with an attenuated decrease in lung function, particularly in former smokers.[106] On the contrary, emphysema development is slowed by both ACE inhibitors and AT1 receptor antagonists, regardless of current or former smoking status.[106] Furthermore, ACE inhibitors and AT1 receptor antagonists are associated with a reduced risk of pneumonia in patients with COPD.[107] Even more important is the documentation that the use of ACE inhibitor/AT1 receptor antagonists before hospitalization was associated with a reduction in mortality in patients with COPD exacerbation and acute respiratory failure.[108] There is also evidence that ACE inhibitors improve exercise capacity as measured by incremental cardiopulmonary exercise testing in patients with COPD.[109]

Statins. Statins have several pharmacological properties that may be advantageous in the treatment of patients with asthma and COPD, including antioxidant, anti-inflammatory, and immunomodulatory effects.[101] An analysis of data from the Korean National Health Insurance Service-Health Screening Cohort reported that statin treatment was associated with a lower incidence of asthma-related emergency room (ER) visits, hospitalizations, and systemic steroid use among patients with asthma.[110] A recent systematic review and meta-analysis showed that although statins did not change lung function, they reduced serum hypersensitive C-reactive protein and the proportion of eosinophils and IL-6 levels in sputum and improved symptoms in subjects with asthma.[111] However, the possible advantage that statins could provide in patients with COPD is highly debated. The most recent literature denies any beneficial effect of statins on exacerbation rates or mortality in COPD patients,[112] in total agreement with the findings of the Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations (STATCOPE) trial, which found that simvastatin did not affect exacerbation rates or the time to the first exacerbation in COPD patients at high risk of exacerbation.[113] Furthermore, losartan did not prevent the progression of emphysema in people with COPD with mild-to-moderate emphysema.[114] On the contrary, simvastatin at a dose of 40 mg daily substantially delayed the time to the first COPD exacerbation and decreased the incidence of exacerbations in a single-center double-blind RCT.[115] Furthermore, case-control research found that statin usage was associated with a lower risk of COPD exacerbations that required ER visits or hospitalization.[116] Lipophilic statins had a greater protective impact against acute exacerbations than hydrophilic statins. However, 1 year of statin therapy had no impact on the occurrence of COPD in this population. The possibility that statin use may be associated with improved long-term survival in elderly COPD patients, mainly in those with an acute exacerbation of COPD (AECOPD) that requires hospitalization, has been suggested.[117]

It has been speculated that the positive effect of statins on COPD exacerbations observed in some studies may have been because in these studies, patients with established indications for statin therapy were not excluded and, as a result, the observed effect may have depended on the statin-induced reduction of cardiac or vascular risk.[118] In fact, an escalation of respiratory symptoms that mimic an exacerbation of COPD may also be caused by CVD exacerbations.[119]

Antiplatelet therapy. Platelets interact with dendritic cells to mediate allergen sensitization and with eosinophils and neutrophils to influence pulmonary recruitment and subsequent development of extracellular eosinophil and neutrophil traps.[120] Furthermore, elevated urine 11-dehydrothromboxane B2, a metabolite of the platelet activation product thromboxane A2, was associated with poorer respiratory symptoms, health status, and quality of life in patients with stable moderate-to-severe COPD.[121] Therefore, interfering with platelet activation could represent a new opportunity to modulate lung inflammatory responses.[4] However, several studies imply that platelet activation in particular inflammatory situations may differ from platelet activation during hemostasis and thrombosis.[122] A proof-of-concept, placebo-controlled, randomized, cross-over trial of 26 patients with asthma found that prasugrel, an irreversible, competitive, thienopyridine P2Y12 receptor antagonist, might decrease airway hyperresponsiveness.[123] However, in 11 patients with mild asthma, no substantial change in pulmonary function was detected with ticagrelor, a direct-acting, non-competitive, reversible, cyclopentyl-triazolopyrimidine P2Y12 receptor

antagonist.[124] Thromboxane A2 synthetase inhibitors have demonstrated beneficial effects, such as a reduction in bronchial hyperresponsiveness, in the asthmatic Asian population[125] but not in patients with acute asthma.[126]

Antiplatelet therapy has been associated with a lower 1-year death rate after hospitalization for COPD exacerbations[127] and has increased survival in patients with high oxygen reliance.[128] Antiplatelet agents may also decrease all-cause mortality in patients with COPD, regardless of the presence or absence of ischemic heart disease.[129] Daily use of aspirin is associated with a lower incidence of COPD exacerbations, less dyspnea, and a higher quality of life.[130] However, aspirin plus ticagrelor antiplatelet treatment did not work in about one-third of COPD patients without a history of CVD.[131]

Calcium channel blockers. Calcium channel blockers reduce ASM contraction, relieve bronchoconstriction caused by a range of stimuli, such as some antigens, exercise, histamine, and cold air, and produce moderate bronchodilation.[132] A systematic review with meta-analysis indicated that calcium channel blockers are beneficial in improving lung function in patients with mild asthma in terms of post-dose FEV_1 and the ΔFEV_1, particularly in exercise-induced asthma.[133] Long-term nifedipine medication might prevent a decline in cardiac output in patients with COPD and high pulmonary pressure.[134] There is also evidence of the beneficial impact of inhaled verapamil on hospitalized patients with COPD, in whom it induces a bronchodilator effect and a decrease in the dyspnea score.[135] Furthermore, inhaling verapamil improved oxygen saturation and accelerated extubation in hypoxic COPD subjects admitted to the intensive care unit.[136] There is documentation that verapamil improved *pulse oximetry* values (SpO_2) and increased FVC in outpatients with pulmonary hypertension associated with COPD, indicating its potential to address ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatch.[137]

Type 2 diabetes mellitus

Potential negative impact on T2DM of drugs used to treat CAD

The association between diabetes and CAD, specifically COPD, appears to be independent of the use of drugs to treat CAD. However, there is a slight association between the use of ICS and the presence of T2DM in patients with CAD.[138] Hyperglycemia can arise after corticosteroid use in sensitive people. ICS usage has been linked to elevated blood glucose concentrations in diabetic individuals in a dose-dependent manner,[139] mainly in patients treated with an ICS and an oral hypoglycemic agent.[140] However, a systematic review and meta-analysis has concluded that the use of ICS does not influence blood glucose and is not associated with the incidence of new-onset DM or the progression of diabetes in patients with COPD.[141] Furthermore, the influence of ICS on DM remains uncertain.[142] However, glycosylated hemoglobin levels increased considerably after 6 weeks of inhaled fluticasone therapy in a small prospective crossover study in individuals with established T2DM.[143] In any case, an analysis of the British Thoracic Society Difficult Asthma Registry showed that the association with severe oral corticosteroid-dependent asthma was strong for T2DM.[144]

β_2-AR agonists can affect glucose homeostasis by modulating insulin secretion, glucagon secretion, hepatic glucose production, and glucose absorption into muscle, increasing blood sugar levels.[145] Unless the patient is on the verge of glucose intolerance, the effects are evident but appear of little clinical significance.[146] However, due to the risk of ketoacidosis, β_2-AR agonists should be taken with caution in diabetic patients with asthma.[145]

After adjustment for age and gender, tiotropium bromide was linked with DM (OR = 1.6; 95% CI 1.0–2.5; $p = 0.034$) in a study carried out in Spain to establish the comorbidity and economic effect of tiotropium bromide therapy for COPD.[147] Furthermore, a pooled clinical trial review on the safety of tiotropium found no higher overall risk of diabetes in individuals who received tiotropium *versus* those who received placebo.[148] However, the relative risk of hyperglycemic episodes was 1.69. Recently, the cholinergic system has been shown to influence insulin secretion, and at least oral antimuscarinic agents may reduce late-phase insulin action to various degrees of diabetic state.[149]

Potential positive impact on T2DM of drugs used to treat CAD

Experimentally, β_2-AR agonists have been shown to protect against the vascular consequences of

diabetes.[150] Their protective effects appear based on a β-arrestin2/ inhibitor of nuclear factor (NF)-κB (IκB)α/NF-κB signaling pathway, resulting in a reduction in inflammatory stimuli and tissue protection.[150] Surprisingly, results of a retrospective analysis of data collected from outpatients afferent to a University Hospital suggested that the combination of a β_2-AR agonist with an ICS can reduce the probability of developing T2DM in patients with COPD.[138]

Potential negative impact on CAD of drugs used to treat T2DM

Insulin was found to increase the risk of asthma among diabetic patients.[151,152] Insulin receptors exist in the lung, and high levels of insulin binding may enhance ASM contraction and hyperresponsiveness.[153] Insulin causes a concentration-dependent contraction of the ASM, which is mediated by the production of contractile prostaglandins.[154] Furthermore, insulin stimulates the production of contractile phenotypic markers in ASM through Rho kinase and PI3-K.[155] Although the administration of a β_2-AR agonist can reduce inhaled insulin-induced bronchoconstriction, this effect is potentially harmful in patients with COPD.[6] In any case, therapeutic insulins continue to be immunogenic in humans regardless of purity and origin.[156]

Potential positive impact on CAD of drugs used to treat T2DM

T2DM is associated with impaired lung function.[157] High glucose concentrations have been shown to increase ASM response to contractile agents and intracellular calcium release in cultured ASM cells through the Rho/Rho-Associated Kinase (ROCK) pathway, and intracellular calcium mobilization and phosphorylation of myosin phosphatase target subunit 1.[158] Therefore, it is crucial to maintain glycemic management in these patients because the deterioration in lung function seen in diabetic individuals could lower the threshold for clinical signs of CAD.[6] However, there is growing evidence that the systemic inflammatory pathway is the common connection between CAD and T2DM, but the processes by which the systemic component emerges remain unknown.[6] CAD and T2DM are linked to low-grade systemic inflammation.[6] Therefore, it would be reasonable to consider a therapeutic approach that controls blood glucose and induces an anti-inflammatory effect when simultaneously treating T2DM and CAD.[159–161]

Oral hypoglycemic medications, mainly biguanides and thiazolidinediones, are now known to provide anti-inflammatory properties,[162] although thiazolidinediones cause fluid retention, which is linked to an increased risk of new or worsening HF.[163] Adults with asthma and concomitant diabetes who used metformin had lower rates of asthma exacerbations, asthma-related emergency department visits, and asthma-related hospitalizations, according to large retrospective observational cohort studies.[163,164] Furthermore, metformin improved the quality of life in patients with asthma–COPD overlap.[165] Rosiglitazone 4 mg twice daily did not increase mean FEV_1 in asthma patients challenged with allergen inhalation, but it resulted in a 15% reduction in the weighted mean late asthmatic response and lowered inflammatory markers.[166] However, pioglitazone did not reveal any meaningful improvements in lung function, asthma control, airway inflammation, or quality of life in asthma patients.[167] However, a study conducted on Taiwanese patients with T2DM revealed that pioglitazone might have a favorable effect on the incidence of COPD, especially when administered for more than 11 months.[168] This conclusion supports previous documentation that thiazolidinedione exposure was associated with a slight but substantial decrease in the incidence of COPD exacerbation in adults with diabetes and concurrent COPD.[169] Interestingly, a cohort-based case-control study using data from Taiwan's National Health Insurance Research Database found that thiazolidinedione combination medications were associated with a lower incidence of AECOPD in patients with advanced T2DM and coexisting COPD.[170] Patients who received sulfonylurea and thiazolidinedione had a lower risk of AECOPD than those who received metformin and sulfonylurea, and those who received metformin, sulfonylurea, and thiazolidinedione had a lower risk of AECOPD than a combination of metformin, sulfonylurea, and α-glucosidase inhibitors, regardless of COPD complexity.

A recent meta-analysis of large RCTs of sodium-glucose transporter 2 (SGLT2) inhibitors has suggested that this drug class can significantly reduce the occurrence of overall respiratory

disorders, acute pulmonary edema, asthma, and sleep apnea syndrome regardless of the type of underlying diseases and type of SGLT2 inhibitors, and also reduces the risks of COPD and pulmonary hypertension.[171]

Another alternative is to use an oral antidiabetic drug that exerts a direct broncholytic action.[6] Exendin-4, a glucagon-like peptide (GLP)-1 agonist, activates the GLP-1 receptor (GLP-1R) and produces bronchorelaxation through the cAMP-protein kinase A pathway in isolated human bronchi.[172] GLP-1 has also been shown to alleviate dysregulated arginine metabolism and advanced glycation end-product-mediated inflammation, both of which are common pathophysiological processes in obesity and asthma.[173] In patients with T2DM and no underlying obstructive pulmonary diseases, treatment with GLP-1R agonists improves airway function regardless of blood glucose levels.[174] In patients with T2DM and low baseline FEV_1, liraglutide, another GLP-1R agonist, lowered blood levels of surfactant protein D, which independently predicted improvements in FVC.[175] Remarkably, a retrospective study of electronic medical records from an academic medical facility discovered that individuals with T2DM and asthma who used GLP-1R agonists had much lower rates of asthma aggravation than those who took other antidiabetic medications.[176] Furthermore, among individuals with asthma and T2DM who needed intensive T2DM therapy, those who started GLP-1R agonists had fewer asthma exacerbations and symptoms within 6 months of starting the medication than those who started other antidiabetic drugs.[177]

Conclusion

Currently, no asthma or COPD guideline proposes a core CVD or T2DM examination for CAD patients, and no CVD or T2DM guideline recommends a comprehensive pulmonary evaluation for CVD or T2DM patients. This is probably why there is little specific guideline guidance for treating CAD in CVD or T2DM patients or vice versa. There is certainly a need for CAD and these comorbidities to be evaluated together. Managing patients with CAD who have comorbidities requires regular medication management and a detailed evaluation of the entire drug list at each presentation. Efforts should be taken to minimize the risk of adverse effects on the airways and organs/apparatus involved in comorbidity. However, the favorable impacts that a drug used to treat CAD may have on CVD and T2DM, or vice versa, cannot be ignored.

It is still unknown whether CAD comes first and then CVD or T2DM, or vice versa, whether the two diseases develop simultaneously on a common pathological substrate. Looking toward the future, the frequency with which CAD and CVD or T2DM are associated requires not only considering the effect that drugs used for one disease condition may have on the other but also providing an opportunity to develop drugs that have a simultaneous favorable impact on both diseases. The information emerging from preclinical studies indicates the potential for several therapeutic options, but data from prospective clinical trials that evaluated such approaches still need to be improved.

However, given the current emphasis on treating patients with chronic airway problems based on treatable traits, we should remember that comorbidities are a core extrapulmonary treatable trait that requires specific therapy when present. Therefore, in the absence of specific guidelines that would help to treat patients with CAD and CVD or T2DM, the correct approach is to treat each disease according to its respective guidelines, keeping the patient under constant observation.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Mario Cazzola: Conceptualization; Investigation; Writing – original draft.

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