REVIEW ARTICLE

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Treating Hypertension in Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) affects 174 million people worldwide, a number expected to rise over the next several decades as a result of the increased prevalence of smoking in developing countries and markedly aging populations in higher-income nations.[1] Approximately 1.13 billion people worldwide have hypertension,[2,3] the most common concurrent disease among patients with COPD.[4,5] Furthermore, hypertension may be more prevalent among patients with asthma–COPD overlap syndrome, a subgroup of patients with COPD who have asthma-related symptoms for which asthma therapeutics may be effective.[6] Like hypertension, COPD and impaired lung function have been independently associated with an increased risk of cardiovascular events.[7,8] The frequent presence of hypertension in patients with COPD may compound the risk of cardiovascular events.[5,7,8]

This review focuses on recent studies relevant to the management of hypertension in patients with COPD. Contemporary evidence concerning the effects of antihypertensive-drug classes on COPD exacerbations, hospitalizations, and adverse pulmonary outcomes is included, along with a brief update regarding the use of cardioselective beta-blockers in patients who have COPD and hypertension with concomitant heart failure or coronary artery disease. Adequate management of hypertension in patients with COPD requires an understanding of appropriate drug-therapy choices in view of other common, coexisting diseases in such patients.

COPD, Hypertension, and Associated Cardiovascular Disease

Patients with chronic lung disease are at increased risk for cardiovascular events.[7,9] Both COPD and cardiovascular disease are characterized by chronic systemic inflammation, which plays an overlapping and central role in the pathogenesis of the two diseases (Fig. 1).[7,10,11] In addition, increased oxidative stress caused by endogenous and exogenous mechanisms can lead to endothelial dysfunction in patients who have both COPD and hypertension.[12] Both sympathetic nervous system overactivation and the presence of proinflammatory cytokines may lead to an increased risk of atherosclerosis and autonomic dysfunction, heightening arterial vascular stiffness.[13] Smoking, a powerful risk factor for cardiovascular disease, also appears to contribute to increased arterial stiffness in COPD.[10] Arterial stiffness increases with the frequency of COPD exacerbations, further contributing to systemic hypertension. All these observations provide persuasive reasons for controlling hypertension in patients with COPD.[14]

Many patients with COPD, particularly those with severe disease, have evi-

KEY CLINICAL POINTS

TREATING HYPERTENSION IN PATIENTS WITH CONCOMITANT COPD

- Hypertension affects many patients with underlying COPD, and the number of patients concomitantly affected is increasing.
- Patients with COPD and hypertension commonly have coexisting conditions such as obesity, heart failure, and coronary artery disease; practitioners should assess cardiovascular risk and address concurrent diseases to ensure adequate management.
- The benefits of antihypertensive therapy and the risk of adverse pulmonary effects or interaction with medications used for pulmonary control are specific to the antihypertensive drug class.
- Contemporary data on the pulmonary effects of antihypertensive therapy are limited.
- Management of hypertension in most patients with COPD is similar to hypertension management in the general population, with specific exceptions.
- Pharmacokinetic and pharmacodynamic factors should be considered in choosing antihypertensive agents for patients with COPD, along with any coexisting conditions.

dence of systemic inflammation, even when the disease is stable, probably placing them at heightened risk.[15,16] For example, in one study with 3 years of follow-up, persistent systemic inflammation (as measured by biomarkers such as the white-cell count and levels of C-reactive protein, interleukin-6, interleukin-8, fibrinogen, and tumor necrosis factor α [TNF-α]) was found in 281 of 1755 patients with COPD (16%) and was associated with increased all-cause mortality, as compared with patients who did not have systemic inflammation.[16] In a study of more than 8600 patients with COPD, inflammatory biomarkers were associated with an increase by a factor of 2 to 4 in the risk of coexisting conditions, including ischemic heart disease, myocardial infarction, and heart failure.[17] Coexisting disorders such as hypertension, heart failure, and diabetes were associated with elevations in markers of systemic inflammation in a cohort of 2164 patients with clinically stable COPD.[18] Even after adjustment for confounders, fibrinogen levels remained significantly elevated in patients with hypertension. These findings suggest that systemic inflammation has an important influence on the progression of disease in patients with COPD and coexisting conditions.[16,18] Thus, one might speculate that control of hypertension in patients with COPD has important clinical implications.

ANTIHYPERTENSIVE TREATMENT IN PATIENTS WITH COPD

Neither contemporary nor traditional hypertension guidelines have identified COPD as a compelling indication for certain antihypertensive therapies.[19] Despite this lack of guidance, the clinician should be mindful of factors influencing control of both illnesses. The definition of hypertension was recently changed by the American College of Cardiology–American Heart Association to a systolic arterial pressure of more than 130 mm Hg, a diastolic pressure of more than 80 mm Hg, or both (Table 1), which means more persons will be considered to have hypertension.[19] Since hypertension is the most common concurrent disorder among patients with COPD, the clinician is often faced with making treatment decisions about both illnesses. Furthermore, in the context of obesity, COPD and hypertension coexist more frequently with other metabolic diseases such as diabetes and obstructive sleep apnea, further complicating treatment and the monitoring of underlying illness.[20] Knowledge of the pulmonary side effects of different classes of antihypertensive therapies, as well as interactions between antihypertensive drugs and agents used for pulmonary control, is essential for successful management.

Contemporary data on specific outcomes of antihypertensive therapy in patients with COPD are limited. The risks and benefits of antihypertensive therapy in such patients have been summarized previously, yet consensus has been limited by lack of solid outcome evidence. Recommendations for treatment have traditionally been based on the theoretical risks of the drug therapy in patients with COPD.[21,22] Pharmacokinetic and pharmacodynamic factors should be considered in choosing antihypertensive agents for patients with COPD, along with underlying lung function and any additional coexisting conditions. In general, antihypertensive drug therapy should follow guideline-directed approaches,

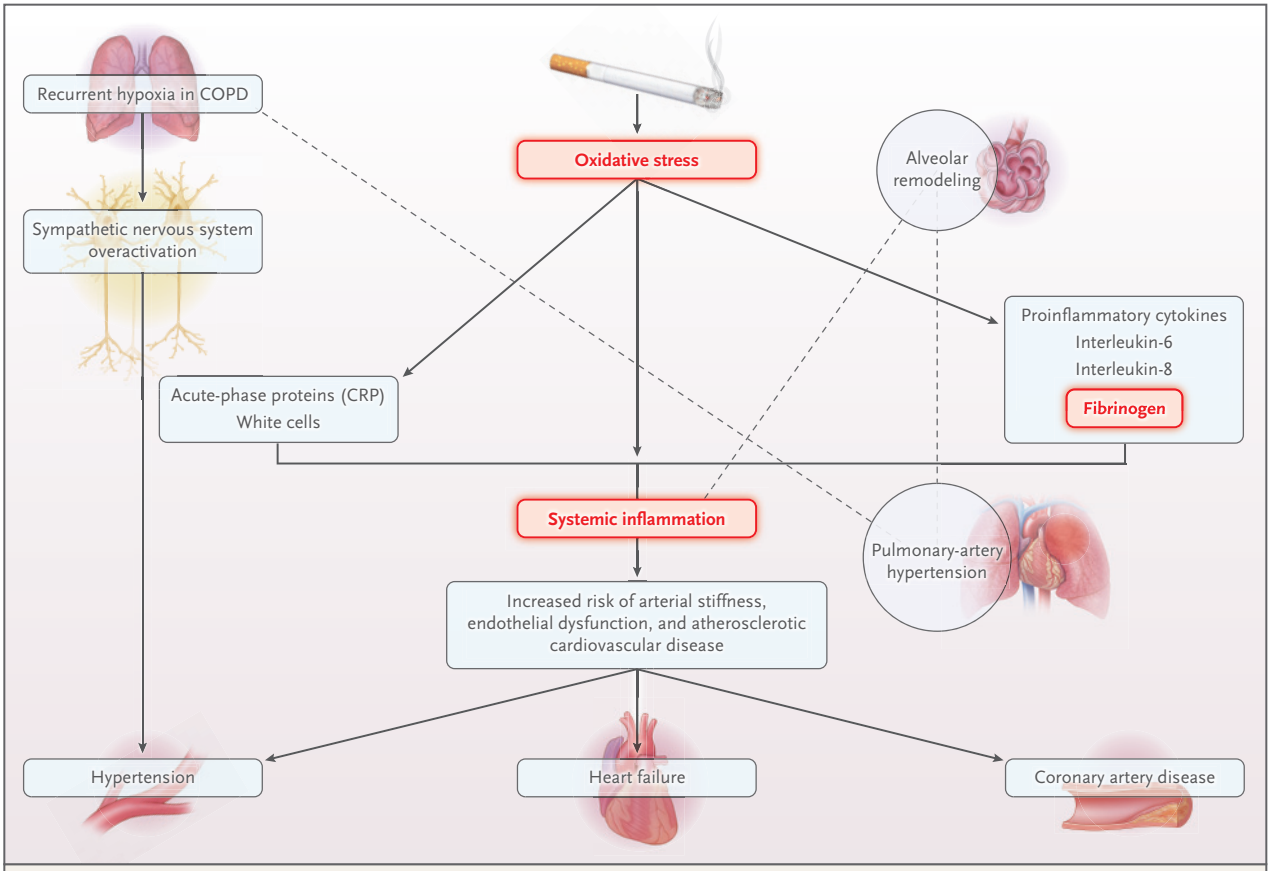

Figure 1. Potential Mechanisms for the Association of Chronic Obstructive Pulmonary Disease (COPD) with Hypertension and Other Cardiovascular Diseases.

Increased oxidative stress caused by endogenous and exogenous mechanisms in patients with COPD can lead to increased risk of hypertension and other cardiovascular diseases. The dashed lines denote lung-related changes in pulmonary diseases that contribute to chronic systemic inflammation. CRP denotes C-reactive protein.

Table 1. New Diagnostic and Treatment Criteria for Hypertension in Adults Living in the United States.*

Blood-Pressure Category	Blood Pressure	Treatment†
	mm Hg	
Normal	<120 systolic and <80 diastolic	Promote good lifestyle habits
Elevated	120–129 systolic and <80 diastolic	Promote lifestyle modifications for 3–6 mo before initiating drug therapy
Hypertension	≥130/80	Promote lifestyle modifications and initiate drug therapy, according to degree of blood-pressure elevation and 10-yr ASCVD risk
Stage 1	130–139 systolic or 80–89 diastolic	If 10-yr ASCVD risk is <10%, promote lifestyle modifications for 1 month before initiating drug therapy to reach target blood pressure of <120/80 mm Hg; if risk is ≥10%, initiate drug therapy and promote lifestyle modifications
Stage 2	≥140 systolic or ≥90 diastolic	Initiate drug therapy and promote lifestyle modifications

* Diagnostic and treatment criteria are from Whelton et al.[19]
† ASCVD denotes atherosclerotic cardiovascular disease.

with some minor exceptions.[19] Thus, angiotensin-converting–enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), calcium-channel blockers, and thiazides are all options for initial antihypertensive therapy, as long as racial differences in treatment response are taken into consideration and COPD symptoms can be adequately controlled with the addition of these therapies.[19] Age alone is not an indicator for specific drug therapy, but frailty at baseline and the degree of pulmonary impairment may influence the benefits and risks of particular antihypertensive therapies, as outlined in the sections below.

DIURETICS

We suggest that thiazide diuretics be considered as first-line antihypertensive medications in patients with COPD. To our knowledge, there is no evidence that thiazides exacerbate pulmonary impairment in such patients, although data from prospective, randomized studies in this patient population are lacking. A retrospective study examining the effectiveness of thiazide diuretics used concomitantly with other antihypertensive medications in 7140 veterans with COPD and hypertension showed no increase in COPD exacerbations with thiazide use, as compared with combination antihypertensive therapy that did not include a thiazide diuretic.[23] In fact, for patients who did not have a history of heart failure, antihypertensive therapy combined with a thiazide diuretic was associated with a reduced risk of future hospitalizations for heart failure.

Despite historical concerns, contemporary evidence suggests that thiazide diuretics have no negative effects on airway function.[21,22] However, electrolyte abnormalities can become problematic when therapies such as inhaled β_2-adrenergic receptor agonists, which shift potassium intracellularly, and glucocorticoids, which can increase urinary potassium excretion, are coadministered.[21,24] Hypokalemia during thiazide therapy is dose-dependent and will increase with escalating doses.[19] Arrhythmias are rare but remain a concern in any patient with hypokalemia (potassium level, <3.5 mmol per liter), and patients with COPD should therefore be monitored periodically for electrolyte abnormalities, especially when glucocorticoid or bronchodilator doses are being introduced or increased.

Loop diuretics have minimal antihypertensive effects but are often used in patients with heart failure and volume overload or those with an estimated creatinine clearance of less than 30 ml per minute per 1.72 m^2 of body-surface area.[25] Electrolyte monitoring is prudent in such patients, since hypokalemia may be more common with loop diuretics than with thiazide diuretics. More important, loop diuretics may contribute to metabolic alkalosis and hypercapnia in patients with COPD. Data from a recent retrospective cohort study involving administrative claims for 99,766 older patients with COPD linked a new 30-day prescription of a loop diuretic to increases in emergency department visits (hazard ratio, 1.62; 95% confidence interval [CI], 1.38 to 1.90) and hospitalization for a COPD exacerbation or pneumonia (hazard ratio, 1.36; 95% CI, 1.16 to 1.60), as well as increased mortality (hazard ratio, 1.31; 95% CI, 1.13 to 1.51).[26] In that cohort, adverse respiratory effects were observed with loop diuretics but not with new prescriptions for thiazides, ACE inhibitors, or ARBs. Although confounding data cannot be excluded from this observational data set, it does suggest a signal for increased adverse respiratory outcomes when loop diuretics are prescribed in a real-world cohort with COPD. Therefore, limiting loop diuretics in the general management of hypertension in patients with COPD would appear to be prudent.

ACE INHIBITORS AND ARBS

Although both ACE inhibitors and ARBs are considered first-line antihypertensive agents for the general population because they are associated with reductions in cardiovascular and cerebrovascular events,[19] when these agents are prescribed for patients with COPD, the risks and benefits must be considered in light of certain pulmonary issues.

Theoretical benefits of ACE inhibition include attenuation of pulmonary-artery inflammation and positive effects on pulmonary alveolar gas exchange, respiratory drive, and pulmonary-muscle function.[27] With high levels in lung capillaries, ACE is responsible for the conversion of angiotensin I to angiotensin II, as well as bradykinin breakdown. There are at least two types of angiotensin II receptors: angiotensin II type 1 (AT_1) receptors increase vascular tone when activated, whereas vasodilatation occurs when angio-

tensin II binds and activates type 2 (AT_2) receptors. In patients with marked pulmonary fibrosis, the ratio of AT_1 to AT_2 receptors is increased, and the forced expiratory volume in 1 second (FEV_1) is decreased.[27] This inverse relation might suggest a pathophysiological role of the renin–angiotensin–aldosterone system (RAAS) in patients with allergic airway inflammation and COPD.[28] Furthermore, since lung and skeletal tissues express ACE, the RAAS is considered to be involved in the pathogenesis of pulmonary and extrapulmonary symptoms of COPD. The RAAS contributes to the pathophysiology of COPD through proinflammatory cytokines such as interleukin-6 and TNF-α. Lung-tissue injury is potentially mediated through RAAS effects on the T-cell response, and AT_1-generated reactive oxygen species contribute to mitochondrial dysfunction, further promoting oxidative stress and endothelial dysfunction.[29]

The findings in observational cohort studies suggest that ACE inhibitors or ARBs may provide both cardiovascular and pulmonary protection in patients with COPD.[30,31] In one uncontrolled study, the use of ACE inhibitors or ARBs after hospitalization of patients for COPD exacerbation was associated with a significant reduction in 90-day mortality.[32] Confirmatory data from randomized, controlled trials are lacking.

Finally, it has been proposed that the use of ACE inhibitors in patients with COPD is helpful in pulmonary rehabilitation. Epidemiologic evidence favors an effect of ACE inhibition on muscle mass, leg strength, and walking speed in patients with hypertension who do not have COPD.[33,34] Evidence from randomized, placebo-controlled studies involving patients with hypertension in the general population argues that inhibition of the RAAS influences skeletal-muscle function and peak work-rate response during exercise; however, relevant randomized studies involving patients with COPD are limited with respect to study size and duration of follow-up.[35,36]

Despite the promise of a pulmonary benefit, adverse events associated with ACE inhibitor therapy may limit its use. Cough is generally the most common adverse event during therapy (occurring in 5 to 35% of patients).[37] ACE inhibitor–induced angioedema is rare in the general population (occurring in 0.2 to 0.7% of patients receiving such treatment), but the incidence is higher among persons older than 65 years of age, smokers, and persons taking concomitant calcium-channel blockers, antihistamines, or systemic glucocorticoids.[37-41] Both ACE inhibitor–induced cough and bronchospasm, as well as angioedema, are considered to be related to the elevation in bradykinin levels that occurs when ACE is inhibited.[38] Furthermore, unacceptable adverse events are more common in patients with allergies and in those who use antihistamine and antiasthma medications.[41] Nevertheless, the reductions in morbidity and mortality from the use of these agents, as observed in clinical trials evaluating the agents for the treatment of hypertension in the general population, make them appropriate for patients with COPD in whom drug-induced symptoms do not develop. ARBs may be preferable to ACE inhibitors in patients with COPD because ARBs are easier to tolerate and are associated with a lower risk of cough.[19] Unlike thiazide diuretics, ACE inhibitors and ARBs may increase potassium levels, which may offset the risk of hypokalemia from the frequent use of inhaled β_2-agonists. Thus, either an ACE inhibitor or an ARB would be the preferred antihypertensive agent in patients known to be at risk for hypokalemia.

BETA-BLOCKERS

Current hypertension guidelines do not recommend beta-blockers for the general treatment of hypertension unless ischemic heart disease or heart failure is present.[19] However, for patients who have hypertension with heart failure or have had a recent myocardial infarction, cardioselective beta-blockers such as bisoprolol and metoprolol may reduce the risk of death.[25,42-45] Beta-blockers may also be useful for additional control of angina symptoms in patients with hypertension and coronary artery disease.[19] With a low initial dose and careful dose escalation, the safety of cardioselective agents in patients with pulmonary disease has been well documented.[46,47] The use of noncardioselective beta-blockers such as carvedilol or propranolol, however, is not recommended in any clinical scenario involving reactive airway disease.[19]

Use of cardioselective agents in patients with COPD and additional compelling indications for beta-blockade should be strongly considered if a survival benefit from beta-blockers has been established (Table 2).[25,45,48] Cardioselective beta-

Table 2. Considerations for Beta-Blocker Use in Patients with COPD.

Use of beta-blockers in patients with COPD should be limited to cardioselective agents for both initial and long-term management of hypertension.
Cardioselective beta-blockers are underused in patients with COPD who have compelling indications (e.g., heart failure or recent myocardial infarction).
Cardioselective beta-blockers reduce exacerbations of COPD and mortality among patients with COPD and additional compelling indications.
Vigilance is required to avoid the use of noncardioselective beta-blockers in patients with COPD who present with heart failure, acute myocardial infarction, or unstable angina.

blockers are remarkably underused in patients with COPD who also have heart failure or coronary artery disease.[42,44,49-52] Only approximately half of patients in three studies received cardioselective beta-blockers despite indications for such treatment.[42,49,50] Several observational studies suggest that cardioselective beta-blockers reduce the risk of death among patients with COPD.[43,45,48,53-55] In a recent randomized trial involving patients with COPD who did not have an established indication for beta-blocker use, metoprolol did not prevent COPD exacerbations.[56] Cardioselective beta-blockers have been successfully used in patients hospitalized for exacerbations of COPD.[57] A small, prospective cohort study suggested that use of these agents may even improve survival after coronary-artery bypass grafting in patients with COPD.[58] Likewise, in a recent study involving 6770 patients who were hospitalized for acute myocardial infarction, patients with COPD (28.3% of the study population) were less likely than other patients to receive evidence-based therapies such as beta-blockers, coronary angiography, and coronary-artery bypass grafting.[59] Underuse of evidence-based management was associated with higher mortality.[59]

Although the use of cardioselective beta-blockers in patients with COPD is not generally associated with bronchospasm, our suggestion is to use small initial doses in all patients, with slow dose escalation to minimize the risks of hypotension and bradycardia. Clinicians must be vigilant in order to avoid inadvertent worsening of pulmonary symptoms when beta-blocker therapy is initiated or the dose is increased — for instance, in patients with an underappreciated history of asthma, with asthma–COPD overlap, with undiagnosed reversible airway obstruction, or with an increased blood eosinophil count (which would suggest coexisting asthma).[60] Such caveats are of particular importance in hypertension-related emergencies, when intravenous therapy might be used. Intravenous labetalol and sotalol should be avoided in such circumstances, whereas esmolol may be considered in low-to-moderate doses, since it selectively blocks the β_1-adrenergic receptor and is unlikely to cause bronchospasm when used at relatively low doses. However, higher doses may affect lung function.[19]

OTHER ANTIHYPERTENSIVE AGENTS

Treatment with calcium-channel blockers for the management of hypertension is supported by studies of such treatment in the general population. These agents are generally associated with reductions in cardiovascular mortality.[19] The use of calcium-channel blockers in patients with asthma has been proposed on the basis of theoretical data, but data from a specific evaluation of their effect on pulmonary function in patients with COPD are lacking.[19,21] Observational data suggest that calcium-channel blockers are associated with a decreased risk of death when used in patients with COPD and right heart failure.[61] Our opinion is that this drug class is a viable first-line option for the management of hypertension.

There are no specific concerns regarding the use of potassium-sparing diuretics or aldosterone-receptor antagonists in patients with COPD. However, these agents are generally not prescribed in lieu of thiazides for the initial management of hypertension.[19]

The reasons for using other antihypertensive agents vary. Alpha-blockers, which are commonly used in patients with benign prostatic hypertrophy, are not associated with adverse pulmonary events and, specifically, are not associated with reported adverse events in patients with COPD.[62] Centrally acting agents such as clonidine may increase bronchial hyperresponsiveness if inhaled histamine has been given first and should therefore be used cautiously in patients with underlying lung disease.[62] There is little information about the pulmonary safety of vasodilators such as hydralazine, but hydralazine has generally not been associated with reported adverse events and has a long history of use.[63]

ACHIEVING HYPERTENSION CONTROL IN COPD

Evidence-based hypertension guidelines support lowering blood pressure to less than 130/80 mm Hg, which represents a clinical challenge even in the general population.[19] The coexistence of COPD and hypertension complicates this effort, as reflected by lower rates of achieving therapeutic blood-pressure targets in this subpopulation of patients.[64] Several factors influence blood-pressure control in patients with COPD, including coexisting conditions such as obesity and severe pulmonary disease, which may require additional drug therapy that may counteract efforts to lower blood pressure. Furthermore, psychosocial issues such as depression or substance use disorders, which are common in patients with chronic disease, can affect adherence to treatment regimens.[65]

When blood pressure is not adequately controlled in patients with COPD, the use of concomitant medications should be thoroughly assessed once adherence to the antihypertensive regimen has been verified. In addition to systemic glucocorticoids, as well as over-the-counter oral and intranasal decongestants, which can cause hypertension, drug interactions may adversely affect blood-pressure control and predispose patients to adverse outcomes.[66-71] In a randomized, double-blind trial involving 314 patients with acute exacerbations of COPD, the incidence of hypertension from oral glucocorticoid therapy (40 mg of prednisone daily) did not differ significantly between patients receiving a conventional course of prednisone (14 days) and those receiving a short-term course (5 days). However, blood-pressure elevations developed or worsened in more than 10% of all patients receiving glucocorticoids (11.6% of patients in the 5-day group and 17.8% of those in the 14-day group, $P=0.22$).[66] Although one cross-sectional study suggests that high-dose inhaled glucocorticoids may be associated with hypertension, prospective investigations with larger patient populations are needed to confirm this observation.[67] Inhibitors of cytochrome P-450 3A4 greatly increase serum levels of inhaled glucocorticoids and cause adrenocortical suppression.[68] For example, inhibition of the metabolism of inhaled glucocorticoids by ritonavir may result in hypertension along with numerous other adverse effects.[68]

In patients with COPD and concomitant allergic rhinitis, the use of oral decongestants, particularly those containing pseudoephedrine, may increase blood pressure.[69,70] For most patients, decongestants have little effect on hypertension control, yet inadvertently excessive doses of topical intranasal agents have resulted in systemic hypertension.[71,72] If the blood-pressure goal is not reached despite adherence to the antihypertensive regimen, and other drug-induced causes of hypertension have been ruled out, antihypertensive treatment should be intensified, since patients with concomitant rhinitis are at elevated risk for COPD-related hospital readmission.[73]

Finally, since systemic inflammation is increased in patients with hypertension and COPD, assessment of cardiovascular risk is important in every patient. In a recent nested case–control study involving 284,220 patients with COPD, 70% of whom had hypertension at baseline, the estimated risk of a major cardiovascular event within the first 30 days after the initiation of therapy with an inhaled long-acting bronchodilator was increased by a factor of 1.5.[74] Cardiovascular events included inpatient care or emergency-department visits for coronary artery disease, heart failure, ischemic stroke, and arrhythmia. Since long-acting muscarinic antagonists and long-acting β_2-agonists are mainstay therapies for long-term management of COPD,[4] further study of this increased risk at therapy initiation is necessary. Clinicians are encouraged to monitor patients with COPD for cardiovascular symptoms during the initiation of any therapy.[74]

Intensifying antihypertensive therapy while addressing lifestyle modifications is generally recommended for all patients at least monthly until blood-pressure goals are achieved.[19] When antihypertensive therapy is initiated or changed in patients with COPD, baseline pulmonary function or status should be documented, and agents known to exacerbate or increase pulmonary and extrapulmonary adverse events should be avoided (Table 3). Subsequent monitoring should include an assessment for changes in pulmonary function, and discontinuation of an antihypertensive drug may be warranted if pulmonary symptoms worsen after the initiation of therapy.

Table 3. Practical Considerations for the Management of Hypertension in Patients with COPD, According to Drug Class.

Drug Class	General Considerations	Disease-Related Considerations	Drug-Related Considerations
Thiazide diuretics	Safe and effective as first-line antihypertensive agents[19] Hypertension guidelines favor chlorthalidone[19] Chlorthalidone is twice as potent as hydrochlorothiazide[19]	Decreased risk of COPD-related hospitalization[23] Lower risk of heart failure–related hospitalization among patients with COPD and heart failure[23] Consider use in frail patients or in those with osteoporosis, since thiazides are bone-protective[75]	Historical concern about thiazide-induced metabolic alkalosis, yet no contemporary evidence suggests suppression of ventilatory drive[21,22] or worsening of acid–base abnormalities[21,76] Increased risk of hypokalemia when used alone (dose-dependent effect) or in combination with inhaled β_2-agonists and glucocorticoids[21,22]* Monitor potassium level routinely; treat hypokalemia as appropriate[19] Monitor for glucose, lipid, and electrolyte abnormalities[19]
Loop diuretics	Use should be limited in patients with COPD unless required for patients with heart failure	Increased risk of metabolic alkalosis and hypercapnia[21] Increased emergency department visits and hospitalization for COPD or pneumonia[26]	Increased risk of elevated urinary calcium excretion when used alone or in combination with long-term glucocorticoids[21]* Use cautiously in patients at risk for bone fragility[75] Monitor for hypercapnia and oxygen levels according to disease severity[26]
Angiotensin-converting–enzyme inhibitors	Safe and effective as first-line antihypertensive agents[19]	Greater potential for angioedema[38] Decreased mortality among patients hospitalized with COPD exacerbations[30-32] Improvement in pulmonary rehabilitation[33-36]	Risk of cough higher than in the general population[37,38] Use with caution in patients with reactive cough[37,77] Avoid in patients who smoke tobacco[38] Offsets the risk of hypokalemia from thiazides, β_2-agonists, and glucocorticoids* Monitor for changes in potassium level or renal function[19]
Angiotensin-receptor blockers	Safe and effective as first-line antihypertensive agents[19]	Minimal safety concerns in patients with COPD Well tolerated in patients with stage III or IV COPD[31]	Offsets the risk of hypokalemia from thiazides, β_2-agonists, and glucocorticoids* Monitor for changes in potassium level or renal function[19]
Calcium-channel blockers	Safe and effective as first-line antihypertensive agents[19]	No pulmonary effects Both dihydropyridine and other agents in this class are considered safe in patients with COPD[21,22] Avoid verapamil and diltiazem in patients with heart failure and reduced ejection fraction[25]	Caution is advised with diltiazem and verapamil, owing to increased drug levels due to CYP-450 3A4 enzyme inhibition[68] No routine monitoring required[19]
Beta-blockers	Reserve for patients with compelling indications[19] Benefits of cardioselective agents outweigh risks in concomitant treatment of heart failure and COPD in patients with atherosclerotic cardiovascular disease[43,45,48,53-55]	Bronchospasm with noncardioselective agents and in rare cases with high doses of cardioselective agents[25] Indicated for patients with heart failure and reduced ejection fraction, recent myocardial infarction, or angina[19,25]	Avoid use of noncardioselective agents[19] Cardioselective agents should be initiated at lowest possible dose and increased slowly[60] Monitor for new symptoms such as dyspnea, exercise intolerance, cough, or increased use of rescue inhaler[46,47]

* Patients should be monitored judiciously for drug-induced pulmonary changes when antihypertensive therapy is initiated or modified. There is a risk of interaction with long-term medications used for pulmonary control.

CONCLUSIONS

Many patients with COPD also have hypertension, and the pathophysiological features of the two disorders overlap. An increased risk of cardiovascular events provides a rationale for the control of hypertension in patients with COPD. Drug therapy for hypertension should be based on approaches recommended in general guidelines for the treatment of hypertension, with special consideration of the given patient's underlying lung function and any coexisting conditions, since the pulmonary effects of antihypertensive therapy vary according to the drug class. Despite the paucity of data from randomized studies of hypertension management in patients with COPD, the limited contemporary evidence supports the use of ACE inhibitors, ARBs, and thiazides after consideration of the risks of adverse effects and interactions with medications used for pulmonary control.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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