

AMERICAN THORACIC SOCIETY DOCUMENTS

A Research Agenda to Improve Outcomes in Patients with Chronic Obstructive Pulmonary Disease and Cardiovascular Disease An Official American Thoracic Society Research Statement

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THIS OFFICIAL RESEARCH STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED MAY 2024

Abstract

Background: Individuals with chronic obstructive pulmonary disease (COPD) are often at risk for or have comorbid cardiovascular disease and are likely to die of cardiovascular-related causes.

Objectives: To prioritize a list of research topics related to the diagnosis and management of patients with COPD and comorbid cardiovascular diseases (heart failure, atherosclerotic vascular disease, and atrial fibrillation) by summarizing existing evidence and using consensus-based methods.

Methods: A literature search was performed. References were reviewed by committee co-chairs. An international, multidisciplinary committee, including a patient advocate, met virtually to review evidence and identify research topics. A modified Delphi approach was used to prioritize topics in real time on the basis of their potential for advancing the field.

Results: Gaps spanned the translational science spectrum from basic science to implementation: 1) disease mechanisms;

2) epidemiology; 3) subphenotyping; 4) diagnosis and management; 5) clinical trials; 6) care delivery; 7) medication access, adherence, and side effects; 8) risk factor mitigation; 9) cardiac and pulmonary rehabilitation; and 10) health equity. Seventeen experts participated, and quorum was achieved for all votes (>80%). Of 17 topics, ≥70% agreement was achieved for 12 topics after two rounds of voting. The range of summative Likert scores was –15 to 25. The highest priority was “Conduct pragmatic clinical trials with patient-centered outcomes that collect both pulmonary and cardiac data elements.” Health equity was identified as an important topic that should be embedded within all research.

Conclusions: We propose a prioritized research agenda with the purpose of stimulating high-impact research that will hopefully improve outcomes among people with COPD and cardiovascular disease.

Keywords: chronic obstructive pulmonary disease; cardiovascular disease; research priorities

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Supported by the American Thoracic Society.

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A data supplement for this article is available via the Supplements tab at the top of the online article.

Am J Respir Crit Care Med Vol 210, Iss 6, pp 715–729, Sep 15, 2024

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Overview

People with chronic obstructive pulmonary disease (COPD) often have comorbid cardiovascular disease and die of cardiovascular-related causes. Beyond smoking as a shared risk factor, complex pathophysiologic mechanisms are at play between the lungs and the heart. Because people with comorbid cardiovascular conditions are often excluded from COPD trials, our ability to provide evidence-based care to these individuals is hindered. Our goal was to summarize existing evidence and use consensus-based methods to prioritize a list of research topics related to the diagnosis and management of patients with COPD and common cardiovascular diseases, such as heart failure, atherosclerotic cardiovascular disease, and atrial fibrillation. After performing a literature search on comorbid COPD and cardiovascular disease, we convened an international, multidisciplinary committee including a patient member and experts in the field to review the evidence and identify research gaps.

- The research gaps spanned the following 10 domains across the translational science spectrum from basic science to implementation research: 1) mechanisms of disease; 2) epidemiology; 3) subphenotyping; 4) diagnosis and management; 5) clinical trials; 6) care delivery; 7) medication access, adherence, and side effects; 8) risk factor mitigation; 9) cardiac and pulmonary rehabilitation; and 10) health equity.
- A modified Delphi approach was used to prioritize the research topics in real time on the basis of their potential to advance the field and ultimately improve the lives of patients with COPD and comorbid cardiovascular disease. The topic that was voted to be top priority was “Conduct pragmatic clinical trials with patient-centered outcomes that collect both pulmonary and cardiac data elements,” such as real-world effectiveness trials of the polypuff or polypill in the COPD patient population

with concurrent cardiovascular disease. In addition, health equity was emphasized by the panel as cross-cutting all the domains and an important gap that should be embedded within all research proposed by the panel.

This research statement sets forth a prioritized research agenda that is based on expert opinion with the purpose of stimulating high-impact research for the optimal management of COPD and cardiovascular disease.

Introduction

The burden of COPD is significant, affecting 479 million individuals worldwide in 2020 (1). The global burden of COPD is projected to increase by 23% between 2020 and 2050 (1). Cardiovascular disease is a leading cause of death worldwide (2). Comorbid cardiovascular conditions are common in patients with COPD (3–9). Compared with the general public, patients with COPD are ~2.5 times more likely to have cardiovascular disease (7). Across cohorts, the prevalence of heart failure (7–42%), ischemic cardiovascular disease (2–18%), and arrhythmia (3–21%) is consistently high in people with COPD (3–9). Approximately 35% of deaths among patients with COPD are attributed to cardiovascular events (10–12), irrespective of airflow obstruction (13), which means that optimally treating cardiovascular disease in patients with COPD could have significant benefit at the population level.

There is growing recognition of the importance of multimorbidity, which is a shift in clinical medicine and patient care (14), that is, treating the whole patient rather than the individual diseases in isolation. COPD and cardiovascular diseases are intertwined in many complex ways (4, 15–17), including the following:

1. Both share smoking as a significant risk factor (18). Smoking activates the same underlying inflammatory pathways

(TNF- α , IL-6, CRP, etc.) and aging pathways (telomere shortening, cellular senescence) in COPD and cardiovascular disease (19, 20). Smoking leads to acute inflammation, oxidative stress, protein imbalance, elastin degradation, hypoxia or hypercapnia, endothelial dysfunction, thrombogenicity, atherosclerosis, and arterial stiffness (19, 21, 22), resulting in direct damage to both lung and heart tissue.

2. The two organs are interconnected anatomically and physiologically, as the pulmonary vasculature is situated between the ventricles, resulting in closely tied structure and function (23). It is well established that hypoxemia induces vasoconstriction in the arteries in the lung, leading to chronic pulmonary hypertension (type 3) and right heart failure. As the right heart chamber and muscle enlarge, there is ventricular interdependence, leading to the obstruction of left ventricular filling and poor cardiac output. This causes pulmonary vascular congestion and pulmonary congestion, which worsen respiratory failure. This interconnection between the lung and heart is cyclical and reciprocal. A more recent example is preliminary evidence showing that certain cardiovascular parameters (oxygen pulse and pulse pressure) improve after lung volume reduction surgery in emphysema (24).
3. Exacerbations in one organ system can perturb the other organ system. The risk of cardiovascular events dramatically increases in the 30 days after a COPD exacerbation and persists up to one year (25–28), which suggests that systemic inflammation caused by one disease process (COPD) directly affects other organs, such as the heart.
4. Inactivity due to fatigue or hypoxemia from COPD can increase the risk of coronary artery disease.
5. Medications to treat one condition can negatively affect the other organ system (19, 29). For example, on the pulmonary

side, treating patients with COPD exacerbation with azithromycin is associated with a small increase in the risk of cardiovascular death compared with no antibiotics or amoxicillin, which was most pronounced for patients at highest risk of cardiovascular events (30).

6. The presence of a comorbidity might alter clinicians' risk:benefit ratio to provide evidence-based care for the first condition. Patients with COPD and heart failure might not be given β -blockers, although it is an evidence-based indication for a β -blocker, out of concern for bronchoconstriction, even though the absolute risk with cardioselective (B1) β -blockers is inconsequential (31–36). At the population level, this practice pattern of not receiving guideline-concordant care for heart failure likely contributes to excess deaths and represents a translation gap.
7. It can be diagnostically challenging to differentiate COPD from cardiovascular disease, because they present with similar symptoms, such as shortness of breath and fatigue, in both the acute and chronic states (15, 37, 38). Without a thorough review of systems, physical examination, laboratory workup (brain natriuretic peptide and differential diagnosis), patients with COPD with worsening shortness of breath might be treated with escalating bronchodilator therapy, when they are in fact developing heart failure and/or arrhythmias. Similarly, patients with COPD who present to acute care with shortness of breath and wheezing may be treated with nebulizers and antibiotics because the suspicion for COPD exacerbation is so high, whereas pulmonary vascular congestion might in fact be the driving etiology.

These complexities have limited our ability to affect the disease course of COPD. Risk factors for cardiovascular disease are well known and modifiable (cholesterol, blood pressure control, etc.), and mortality from ischemic heart disease has trended downward over time. Meanwhile, mortality from COPD has not (39). Trials to treat patients with COPD using new combinations of inhalers have not decreased mortality, which could be because patients are not

being treated optimally for all of their comorbid conditions. Understanding the complex interplay between the heart and lungs could open new avenues for population health management and new therapeutics (40). After performing a literature review, we used consensus-based methods to prioritize research topics related to the diagnosis and management of common comorbid cardiovascular conditions that exist in patients with COPD. For the purposes of this workshop, we defined "cardiovascular disease" as heart failure, atherosclerotic cardiovascular disease, and atrial fibrillation, using the clinical framework of pump, ischemia, and rhythm. This research statement is a call to action with the goal of expediting research that will have the greatest impact on patients with COPD and cardiovascular disease.

Methods

Committee Composition

This project was approved by the American Thoracic Society (ATS) Program Review Subcommittee. The co-chairs (L.C.M., M.D., V.G.P.) convened a multidisciplinary, international committee of members representing internal medicine, pulmonology, cardiology, geriatrics, nursing, pharmacy, drug development, quality improvement and policy, learning health systems, patient experience, and patient advocacy. Members represented urban and rural healthcare settings, academic and nonacademic institutions, and professional societies. Before confirming the final roster, potential conflicts of interest were disclosed and managed per the policies and procedures of the ATS.

Literature Search and Review of Existing Evidence

The lead co-chair (L.C.M.) performed a literature search with help from a Kaiser Permanente librarian. The search methodology is described in Figure E1 in the data supplement. Using Medical Subject Headings "Cardiovascular Diseases/therapy" (MAJR) AND "Pulmonary Disease, Chronic Obstructive/therapy" (MAJR) together with filters for adults ≥ 18 years of age and published in the past 5 years, separate queries were done for articles related to 1) diagnosis, 2) management, and 3) rehabilitation. Articles were reviewed to inform the agenda for Day 1.

Meetings and Modified Delphi Rounds

Two separate meetings were held virtually (September 5, 2023, and September 27, 2023). The first day was a 6-hour session comprising six presentations and four discussions that were led by experts in the field. Presentations focused on existing literature and identifying existing gaps related to three cardiovascular conditions common in COPD (heart failure; atherosclerotic cardiovascular disease, which includes vessels in the heart, brain, and periphery; and atrial fibrillation). These three conditions were chosen using the clinical framework of "cardiovascular pump, ischemia, rhythm." Content and discussion spanned the outpatient to inpatient care spectrum and addressed the complex relationships that exist between COPD and cardiovascular disease. Discussion of drugs were done at the class level. A patient representative with COPD and cardiovascular disease (C.G.) participated and provided the patient perspective. She stressed the importance of developing new technologies (drugs and devices) to facilitate the care and day-to-day management of COPD, streamline the care of patients with COPD who have multimorbidity to prevent siloed management among specialists, limit polypharmacy, decrease cost for patients, and improve adherence to guideline-based therapies. Twenty-two experts attended the first session. The audio file was transcribed using the TranscribeMe service and loaded into a word cloud that examined the frequency of words and their proximity to one another. The co-chairs generated a list of 10 domains of gaps from Day 1's discussion that mapped onto the framework for the translational science spectrum, courtesy of the National Heart, Lung, and Blood Institute (41).

The second day was a 2-hour session to review the proposed list of research topics that were generated by the co-chairs and to perform a modified Delphi process in real time to prioritize the list (42, 43). Eighteen experts attended the second session. Seventeen of the 18 experts voted in all polls; the remaining person (co-chair V.G.P.) facilitated the Delphi rounds and was reserved to break a tie (if needed). Participants were given an opportunity to fully read the list of research topics before voting to prevent bias based on the order in which topics were listed. For each topic, participants were asked whether the topic should be considered a top priority, which

was defined as holding significant potential for advancing the field and ultimately improving the lives of patients with COPD and cardiovascular disease. Participants voted via Zoom poll using a five-point Likert scale (strongly disagree, disagree, neutral, agree, and strongly agree). Participants were limited to using a vote of strongly agree or agree a maximum of five times to facilitate generating a prioritized list with a gradient. The anonymized results were displayed in real time after each round. If $\geq 70\%$ agreement was not achieved after the first round (agreeing that the topic is either a priority or not a priority), a short (<10-min) discussion ensued to highlight key strengths and limitations of the proposed topic. A second and final poll was then launched. Additional details about the polling are provided in the data supplement.

Document Development

A co-chair (M.D.) performed the data analysis. The summative Likert score from the final round was calculated, where strongly disagree was assigned a score of -2 , disagree was assigned a score of -1 , neutral was assigned a score of 0 , agree was assigned a score of $+1$, and strongly agree was assigned a score of $+2$. The final list of prioritized topics was then ordered by the summative Likert score from the final round. Results were sent to participants electronically for feedback. The lead co-chair (L.C.M.) drafted the initial version of the manuscript, which was then circulated to the full committee and iteratively revised. The ATS Board of Directors approved the final document. This document does not include clinical treatment recommendations.

Results

Committee members were diverse in terms of sex, race and ethnicity, geographic location, medical specialty, clinical discipline, research experience/expertise, and perspective (Table 1). The literature search for COPD and cardiovascular disease yielded 97 articles (34 for diagnosis, 43 for management, and 20 for rehabilitation). The key citations that informed Day 1's content are highlighted in Table 2.

One important and controversial point of discussion from Day 1 was the concept of COPD as a potential "risk-enhancing factor" for atherosclerotic cardiovascular disease. In the cardiovascular prevention guidelines

(44, 45), certain clinical conditions characterized by systemic inflammation, such as rheumatoid arthritis, have been identified as risk-enhancing factors. When a risk-enhancing factor is identified, more intensive primary prevention goals are indicated, because patients' risk of developing cardiovascular disease is significantly higher. COPD is well known to cause systemic inflammation and increase the risk of cardiovascular disease (46) but is not currently listed as a risk-enhancing factor for primary prevention (45). Experts on the committee believed that research on how to translate existing knowledge about the risk of developing cardiovascular disease in COPD into clinical practice is warranted. They believed that it was a potential missed opportunity not to intensively manage cardiovascular disease risk, which likely explains why so many patients with COPD die of cardiovascular disease.

The 10 domains of gaps identified on Day 1 were mapped along the translational science spectrum from basic and preclinical research to clinical and population science research to knowledge translation and implementation science research (Figure 1). These included 1) mechanisms of disease; 2) epidemiology; 3) subphenotyping; 4) diagnosis and management; 5) trials; 6) care delivery; 7) medication access, adherence, and side effects; 8) risk factor mitigation; 9) cardiac/pulmonary rehabilitation; and 10) health equity. A word cloud that reflects the frequency of the words said during the meeting on Day 1 by the size of the font can be seen in Figure 2. The locations of the words in the word cloud reflect how they were used in relation to other words.

On Day 2, the committee unanimously agreed to reposition the two disparity-related topics from the list as ones that cross-cut all other topics. The two specific topics were: 1) reduce disparities in the diagnosis and management of patients with COPD and cardiovascular disease (age, gender, race/ethnicity, low literacy, payer), including appropriate and timely diagnosis and adherence to guideline-based recommendations, and 2) expand trial recruitment to include, and potentially focus directly on, patients with COPD and cardiovascular disease, especially those with low socioeconomic status.

After removing the 2 disparity-related topics, the remaining 17 topics underwent Delphi rounds for prioritization. We achieved $>80\%$ to fulfill quorum for all

rounds of voting, with no one abstaining from voting. Of the 17 topics that were voted on, agreement of $\geq 70\%$ was achieved for 10 topics in the first round of voting and 2 additional topics in the second round of voting. Figure 3 shows the distribution of responses for each topic during the final round of voting. Table 3 contains a full description of the prioritized list of topics, ordered from high to low summative Likert score from the final round of voting. The range of summative Likert score was -15 to 25 . The topic that was overwhelmingly voted to be the top priority was "Conduct pragmatic clinical trials with patient-centered outcomes that collect both pulmonary and cardiac data elements." Examples are listed in Table 3 to highlight the types of trials that the committee believed would be most useful.

Discussion

Our expert committee identified and prioritized research topics regarding the diagnosis and management of patients with COPD and cardiovascular disease, specifically heart failure, atherosclerotic cardiovascular disease, and atrial fibrillation. Spanning the full translational science spectrum, the gaps encompassed the following 10 domains: 1) mechanisms of disease; 2) epidemiology; 3) subphenotyping; 4) diagnosis and management; 5) clinical trials; 6) care delivery; 7) medication access, adherence, and side effects; 8) risk factor mitigation; 9) cardiac and pulmonary rehabilitation; and 10) health equity. The committee believed strongly that consideration of disparities should be part of research done across all topics. For the remaining 17 topics, we used robust methods (a modified Delphi consensus-building approach) and successfully achieved quorum for all and agreement for the majority (12 of 17 topics after two rounds of Delphi).

The topic with the highest priority score was "Conduct pragmatic clinical trials with patient-centered outcomes that collect both pulmonary and cardiac data elements." A pragmatic trial is a clinical trial that tests an intervention in a real-world setting (47). Although multimorbidity is common in COPD (5, 48, 49), patients with comorbid cardiovascular diseases are often excluded from trials in the COPD population (50–52), which hinders our ability to provide evidence-based care to patients in the community. Several examples do exist,

Table 1. The International Multidisciplinary Committee for Prioritizing Research Topics in the Field of Chronic Obstructive Pulmonary Disease and Cardiovascular Disease

Committee Member	Institution	Role	Area of Expertise
Laura Myers, M.D.	Kaiser Permanente Northern California	Co-chair, host	Overlap of COPD and cardiovascular disease, COPD readmissions, patient quality, safety, and policy
Valerie G. Press, M.D., M.P.H.	University of Chicago	Co-chair, Delphi facilitator	COPD medications, treatment adherence, health literacy, COPD readmissions
Miguel Divo, M.D., M.P.H. Jennifer Quint, M.D., Ph.D.	Harvard University Imperial College London, United Kingdom	Co-chair, speaker, data analyst Member, speaker	COPD and multimorbidity Epidemiology of COPD and cardiovascular disease
Peter Lindenauer, M.D. Nirupama Putcha, M.D., M.H.S. Alan Hamilton, Ph.D.	Baystate Health Johns Hopkins Medicine COPD Foundation	Member, speaker Member, speaker Member, speaker	COPD and pulmonary rehabilitation Multimorbidity, health disparities Pharmacological and nonpharmacological interventions for COPD, behavior change for patients with multimorbidity, regulatory drug approval
Nathaniel M. Hawkins, M.D., M.P.H. Caroline Gainer J. Michael Wells, M.D., M.S.P.H.	University of British Columbia, Canada Patient University of Alabama at Birmingham	Member, speaker Member, speaker Member, discussion moderator	Heart failure, cardiac arrhythmias, comorbidities Patient experience and advocacy COPD and pulmonary vascular disease; mechanisms of inflammation and vascular remodeling
David Mannino, M.D.	COPD Foundation	Member, discussion moderator	Epidemiology of COPD, environmental exposures, inflammation
R. Graham Barr, M.D., Dr.P.H.	Columbia University	Member, discussion moderator	Prospective cohort studies, epidemiology, cardiopulmonary interactions
Mark Dransfield, M.D.	University of Alabama	Member, discussion moderator	COPD, clinical trials, mechanisms of disease, health system leadership, leadership in multicenter randomized clinical trials
Sadiya S. Khan, M.D., M.Sc.	Northwestern University Feinberg School of Medicine	Member	Preventive cardiology, screening for comorbidities, epidemiology, prospective cohort studies, member of the American Heart Association
Sagar Shah, M.D.	Kaiser Permanente Northern California	Member	General internal medicine, referrals to specialists, polypharmacy
Allan Walkey, M.D.	University of Massachusetts	Member	COPD, practice patterns, health services research, learning health systems
Surya P. Bhatt, M.D.	University of Alabama at Birmingham	Member	COPD, clinical trials of medications
Andrea S. Gershon, M.D.	Sunnybrook Research Institute, Canada	Member	COPD outcomes, health services research
Todd Lee, Pharm.D., Ph.D.	University of Illinois	Member	Pharmacology, COPD medications, polypharmacy
Huong Q. Nguyen, R.N., Ph.D.	Kaiser Permanente Southern California	Member	COPD, frailty, patient-centered outcomes
Leah Witt, M.D.	University of San Francisco	Member	Geriatrics, multimorbidity
Richard Mularski, M.D.	Kaiser Permanente Northwest	Member	COPD and patient-centered outcomes, leadership of clinical trial networks

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

Table 2. Key Citations That Informed the Content of the Committee’s First Meeting

Topic	Summary of Key Points
Burden, impact and complexities of cardiovascular comorbidities in COPD	<ul style="list-style-type: none"> • Cardiovascular disease is common among individuals with COPD (3–9). For instance, the prevalence of heart failure (7–42%), ischemic cardiovascular disease (2–18%), and arrhythmia (3–21%) is consistently high across cohorts over decades (3–8). • There is underdiagnosis and underprediction of cardiovascular disease in patients with COPD (66, 67). • Approximately 35% of deaths among individuals with COPD are attributed to cardiovascular disease (10–12). • Patients with COPD have markedly increased risk of cardiovascular events in the 30 d after an exacerbation that persists for up to 1 yr (25–28). • Many patients with COPD with only mild to moderate obstruction by FEV₁ are dying of cardiovascular outcomes (13, 68, 69). • Confirmatory testing for COPD is less common than confirmatory testing for heart failure in patients with both conditions (70–72). • It is diagnostically difficult to tease apart a COPD exacerbation vs. heart failure exacerbation or cardiac ischemia (36, 38, 73–75).
Mechanisms and implications of cardiovascular disease in COPD	<ul style="list-style-type: none"> • Control of cardiovascular risk factors in patients with COPD remains poor (57). • Patients with COPD have certain phenotypes that tend to have more or less risk of cardiovascular disease in addition to the historical binary classification of “blue bloater” and “pink puffer” (49, 76, 77). • Cardiovascular events in patients with COPD increase with number of exacerbations and symptoms of breathlessness but not with FEV₁ decline (13, 78–80). • Incident heart failure in patients with COPD is associated with a 3× increase in mortality at 1 yr (81), but risks of mortality and hospitalization have not been quantified by heart failure severity (i.e., how low the ejection fraction is). • COPD promotes the occurrence of atrial fibrillation, progression, recurrence after cardioversion, reduced efficacy of catheter-based antiarrhythmic therapy, and worse outcomes (8, 82). • Smoking, in addition to occupational exposures and lifestyle habits such as diet and exercise, is believed to be the common underlying cause of many of the comorbidities seen in COPD, including cardiovascular disease (18). • The biological pathways underlying COPD and cardiovascular disease include inflammation (TNF-α, IL-6, CRP, fibrinogen, amyloid, surfactant) and accelerated aging (telomere shortening, cellular senescence, reduced cell proliferation) (19, 20). • The mechanisms underlying COPD and cardiovascular disease include acute inflammation, oxidative stress, protein imbalance, elastin degradation, hypoxia/hypercapnia, endothelial dysfunction, atherosclerosis, and arterial stiffness (19, 21, 22).
Evidence for use of medications in treating coexisting cardiovascular disease in COPD	<ul style="list-style-type: none"> • COPD treatments affect the cardiovascular system (LABAs, LAMAs, azithromycin) and treatments of cardiovascular disease affect the lung (β-blockers, amiodarone) (19, 29). Some effects may be beneficial, such as the antiinflammatory properties of statins, and others may be detrimental, such as the pulmonary toxicity from amiodarone. • Pulmonary medications <ul style="list-style-type: none"> ○ Inhaled β-agonists do not increase cardiovascular events in trials of patients with COPD, but many trials exclude patients with cardiovascular disease. Historically, there has been concern because β-agonists cause tachycardia (61, 83). ○ In meta-regression, inhaled steroid therapy was associated with lower risk of cardiovascular events compared with long-acting bronchodilator therapy, regardless of cardiovascular history (61). However, in randomized clinical trials of patients with COPD, groups receiving inhaled steroid did not have fewer cardiovascular events (SUMMIT comparison groups were ICS, LABA, LAMA, and triple therapy; IMPACT comparison groups were ICS/LABA, LAMA/LABA, and triple therapy) (59, 60). Cardiovascular outcomes were not the primary outcomes of either trial; the primary outcomes were mortality in SUMMIT and annual rate of moderate to severe COPD exacerbations in IMPACT. ○ A 5-d course of azithromycin, which is commonly used in COPD patients to treat exacerbation, was associated with a small absolute increase in the risk of cardiovascular death compared with no antibiotics or amoxicillin, which was most pronounced for patients at highest risk of cardiovascular events (30). • Cardiac medications <ul style="list-style-type: none"> ○ Statins do not lower risk of COPD exacerbations or cardiovascular events, though the major trial was done in patients without cardiovascular disease or diabetes (84, 85). ○ Cardioslective (B1) β-blockers alleviate symptoms and improve survival in patients with heart failure but are underused in patients with concurrent COPD because of fear of bronchoconstriction (32–35).

(Continued)

Table 2. (Continued)

Topic	Summary of Key Points
Patient-centered outcomes for patients with COPD with cardiovascular disease	<ul style="list-style-type: none"> ○ β-Blockers should not be used to prevent COPD exacerbations in patients who do not have cardiac indications (55). ○ There were fewer cardiovascular events in patients with COPD with acute myocardial infarction if treated with P2Y₁₂ receptor antagonists vs. thienopyridine (86). ○ Amiodarone causes direct lung toxicity, which can manifest in the form of interstitial pneumonitis, organizing pneumonia, acute respiratory distress syndrome, and diffuse alveolar damage (31). ○ Certain treatments (e.g., SGLT2i) might have a larger benefit in the COPD subgroup with heart failure, though further research is needed to assess if there is truly heterogeneity of treatment effect (54). <ul style="list-style-type: none"> ● Patient-centered outcomes should be incorporated into current clinical trials. The working definition of treatment benefit is a favorable effect on a meaningful aspect of how a patient feels or functions in their usual life. Examples include respiratory symptoms, quality of life, and functional capacity. ● Research activities should engage patients in active, meaningful, collaborative interaction across any and ideally all stages of the research process, where decision making is guided by patients' contributions as partners, recognizing their specific experiences, values, and expertise (87). ● Physician/hospital payment models and research funding are geared toward managing a patient with one condition as "principal discharge diagnosis," which is not patient-centric, practical, or reflective of the complexity of their comorbidity profile.
Patient perspective	<ul style="list-style-type: none"> ● New technologies (drugs and devices) should be developed to facilitate the care and day-to-day management of COPD. An example is an oxygen support device that automatically titrates to oxygen saturation to promote patient mobility and exercise. ● Care of patients with COPD who have multimorbidity should be streamlined to prevent siloed management among specialists, limit polypharmacy, decrease cost for patients, and improve adherence to guideline-based therapies.
Evidence for rehabilitation in patients with COPD with cardiovascular disease	<ul style="list-style-type: none"> ● There are strong published clinical recommendations for the following patients to undertake pulmonary rehabilitation, with choice of telerehabilitation: 1) those with stable COPD and 2) those who have been hospitalized for COPD exacerbation (88, 89). ● Patients with high comorbidity burden, such as those with heart failure, are unlikely to participate in pulmonary rehabilitation (90). ● The goals of pulmonary and cardiac rehabilitation are similar (education, exercise, lifestyle modification, and behavior change), but little is known about combined cardiopulmonary rehabilitation programs among patients with COPD and cardiovascular disease.
Health equity in diagnosing and treating patients with COPD and cardiovascular disease	<ul style="list-style-type: none"> ● Disparities exist in both the diagnosis and management of patients with COPD and multimorbidity. Numerous factors are important to consider, such as race, socioeconomic status, sex, and urban/rural residence (91–97). ● Guideline-concordant statin care is less common in patients with both COPD and cardiovascular disease than those with cardiovascular disease alone (98). ● Patients with ischemic heart disease are less likely to receive β-blockers and revascularization if they have COPD (38, 99). ● There is variability in comorbidity profile among patients with COPD of different races (96). For example, hypertension and history of stroke are more common in non-Hispanic Black patients, whereas dyslipidemia and history of myocardial infarction are more common in non-Hispanic White patients. ● There are differences by gender in the prevalence of cardiovascular comorbidities in patients with COPD (97). Women with COPD tended to have more heart failure and hypertension and less ischemic heart disease compared with men with COPD.

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; IMPACT = Informing the Pathway of COPD Treatment; LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; SGLT2i = sodium-glucose cotransporter-2 inhibitors; SUMMIT = Study to Evaluate the Effect of Fluticasone Furoate/Vilanterol on Survival in Subjects With Chronic Obstructive Pulmonary Disease.

though, in which both COPD and cardiovascular disease were addressed: 1) One trial comparing inhaler regimens in patients with COPD specifically enrolled patients with and those without stable cardiac disease, which the investigators defined as no myocardial ischemic event in 6 months, no hospitalization for advanced heart failure, and no life-threatening

arrhythmia in 12 months (53). 2) An important lesson was gleaned from a *post hoc* subgroup analysis of a trial that enrolled patients with COPD with cardiovascular disease; the results suggested that among patients with heart failure, those with COPD had similar relative risk reduction with sodium-glucose cotransporter-2 inhibitors compared with those without COPD, but the

absolute risk reduction was greater in those with COPD, likely because of the higher frequency of cardiovascular events in this population (54). 3) A trial randomized patients with moderate to severe COPD who did not already have indications for β -blockers to receive metoprolol and showed no difference in time until exacerbation (55).

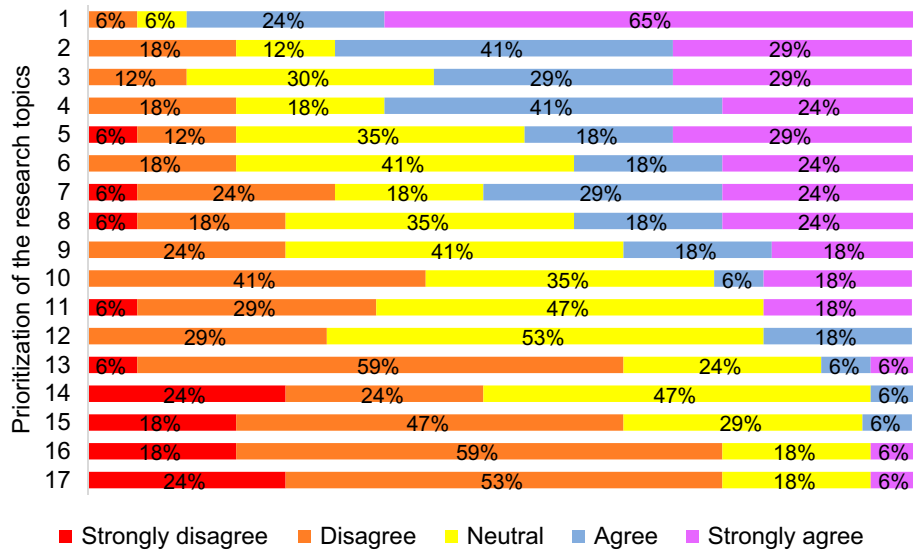


Figure 3. Breakdown of responses for prioritization of the research topics in final Delphi round across the five-point Likert scale. If a color/percentage is missing along a row, that means that the value was zero, such as strongly disagree for priority 1. The text of each of the 17 prioritized topics is listed in Table 3. Briefly, they are 1) pragmatic trials with patient-centered outcomes, 2) cost-effectiveness of cardiac and respiratory tests, 3) phenotyping, 4) cardiac and pulmonary rehabilitation, 5) knowledge translation about COPD as a risk-enhancing diagnosis, 6) epidemiology of subgroups, 7) leverage lung cancer screening computed tomography scans, 8) simplified inhaler regimens that are accessible, 9) mechanisms of disease, 10) clinician awareness about evidence-based risks of cardiovascular treatments on lung function, 11) optimal roles of clinicians that prioritizes patients' needs, 12) leverage technology, 13) longitudinal studies following stable and exacerbated patients with cardiac rhythm monitors, 14) risks and benefits of conservative medication management versus advanced cardiac testing/catheterization in patients with COPD with troponin leak, 15) impact of using active language to describe COPD exacerbation, 16) environmental triggers, and 17) performing spirometry in hospitalized patients. COPD = chronic obstructive pulmonary disease.

organizations, and reflect the real-world effectiveness of the medications. Ideally, trials that address the real-world effectiveness of medications in patients with COPD and cardiovascular disease, especially those that limit the burden of taking multiple pills or inhalers per day (polypill or polypuff), should be prioritized. Pairing qualitative analysis with quantitative analysis to understand patient perspectives is critical, as well as a focus on vulnerable patient populations. Patients with low literacy and English as a second language should be able to access the medications being tested, so designing the trials to successfully engage with diverse populations is crucial. Given that smoking underlies much of the risk of developing COPD and cardiovascular disease, interventions related to smoking cessation are an important target, as well as research that seeks to understand the differential uptake of smoking cessation tools (56). In addition, trials are needed that examine the benefit of newer medications, such as sodium-glucose cotransporter-2 inhibitors, which could have pleiotropic effects on other organs and, therefore, provide benefit in patients with COPD and multimorbidity

who have approved indications for the drugs (type 2 diabetes, heart failure, chronic kidney disease).

After some deliberation, the committee believed that the concept of COPD as a risk-enhancing factor was important. Because patients with COPD are so much more likely than the general population to develop atherosclerotic cardiovascular disease (7), the consensus was that screening and aggressive mitigation of atherosclerotic cardiovascular risk factors in the long term (cholesterol, blood pressure, etc.) might improve outcomes. However, a definitive study has not demonstrated this. Given that this research statement is not intended to make clinical recommendations, the committee believed strongly that the statement should at least call for research to quantify the benefit of treating individuals with COPD and concomitant cardiovascular disease with aggressive risk factor control. Trials that examine cardiac risk screening and aggressive risk factor management strategy would likely strengthen the evidence in favor of treating COPD as a risk-enhancing factor and inform future iterations of clinical guidelines. Patients with COPD and cardiovascular disease should not be

excluded from receiving guideline-directed primary and secondary prevention for cardiovascular disease (38, 57).

A recent article in the *Journal* proposes a shift in the guideline-based paradigm of how to choose which inhalers to initiate first in stable patients with COPD (58). Instead of the 2023 Global Initiative for Chronic Obstructive Lung Disease paradigm of A-B-E classification by Modified Medical Research Council Dyspnea Scale score, COPD Assessment Test score, and number of exacerbations, the authors suggest adding a third dimension (E+ and B+), whereby patients with COPD and known cardiovascular disease should be initiated on triple therapy first. This is based on some evidence, albeit not completely consistent (59), that patients with COPD and cardiovascular disease have better outcomes on inhaled corticosteroid-containing therapy (60, 61). Expert clinical consensus is needed to adjudicate whether the body of evidence exists to support this proposed paradigm.

There are policy implications affecting patients with COPD and cardiovascular disease. For instance, the Centers for Medicare and Medicaid Services has a

Table 3. Prioritized List of Research Topics to Fill the Most Urgent Gaps in the Field of Chronic Obstructive Pulmonary Disease and Cardiovascular Disease

Priority	Research Topic	Number of Rounds	Degree of Agreement in Final Round	Summative Likert Score in Final Round
1	<p>Conduct pragmatic clinical trials with patient-centered outcomes that collect both pulmonary and cardiac data elements.</p> <p>Specifically:</p> <ul style="list-style-type: none"> • Use pragmatic clinical trial designs to expedite the recruitment and retention of patients with COPD and cardiovascular disease, especially those with low health literacy and poor access to medications. • Ensure that pulmonary-related data (mMRC, CAT, spirometry) are reported in prospective trials focused on cardiovascular drugs, and cardiac-related data (biomarkers, echocardiographic studies) are reported in prospective trials focused on pulmonary drugs. • Integrate patient-centered outcomes into trials with the pairing of qualitative and quantitative methods to evaluate the impact of medications and interventions on patients' symptoms. • Conduct real-world effectiveness trials of medications in the broad COPD population with concurrent cardiovascular disease, especially medications that decrease the burden of taking multiple inhalers and pills per day (i.e., polypuff, polypill). • Conduct stepped-wedge implementation trials in large health systems, to examine the benefit of newer medications, such as SGLT2i, in patients with COPD who have indications to receive this class of medication (type 2 diabetes, heart failure, chronic kidney disease). 	1	95%	25
2	Determine the cost-effectiveness and other measures of benefit (NNT) of cardiac diagnostic tests (Cardiac Injury Score on ECG, biomarkers [natriuretic peptides, troponin], and echocardiography) in stable and exacerbated patients with COPD. Determine the cost-effectiveness and other measures of benefit (NNT) of spirometry with diffusion capacity to assess lung function among patients with cardiovascular disease.	1	82%	14
3	Refine our knowledge of phenotypes within the COPD population with the goal of understanding patients' individualized risk of different cardiovascular diseases (i.e., which phenotype predisposes to heart failure, atherosclerotic cardiovascular disease, and atrial fibrillation). Determine the appropriate screening studies and treatments for the different phenotypes.	2	87%	13
4	Identify and further develop the key elements of pulmonary and cardiac rehabilitation programs that specifically help patients with both COPD and cardiovascular disease, potentially aiming for an integrated cardiopulmonary program.	2	83%	12
5	Improve knowledge translation by increasing clinicians' adherence to guidelines on the primary and secondary prevention of cardiovascular disease in patients with COPD and raise awareness of COPD as a "risk-enhancing diagnosis," which requires more stringent lipid and blood pressure management.	2	82%	9
6	Define the incidence, prevalence, characteristics, and prognosis of major cardiovascular diseases in patients with COPD using contemporary definitions, including heart failure subtypes (preserved and reduced ejection fraction), acute coronary syndrome subtypes (type 1 and 2 events) and various arrhythmias (both atrial and ventricular).	2	83%	8
7	Determine the best approach to leverage cardiovascular disease seen on lung cancer screening CT scans (coronary calcium, enlarged aorta, pulmonary artery, atherosclerosis, etc.).	2	71%	7
8	Develop and test simplified medication and inhaler regimens that are low cost and accessible to those with low literacy who have COPD and cardiovascular disease. Examine the impact of different pricing strategies of medications on patients' behavior to be adherent with the goal of changing health policy to improve patients' access.	2	77%	6
9	Elucidate the mechanisms underlying the relationships between COPD and cardiovascular disease, such as congestive heart failure, atherosclerotic cardiovascular disease, and atrial fibrillation, which are common and affect patients' long-term trajectory, with the goal of finding targeted therapies that prevent or slow both diseases.	2	77%	5

(Continued)

Table 3. (Continued)

Priority	Research Topic	Number of Rounds	Degree of Agreement in Final Round	Summative Likert Score in Final Round
10	Raise awareness among clinicians about the evidence-based risks of cardiovascular treatments on lung function (such as statins, β-blockers) and pulmonary treatments on cardiovascular function (such as inhaled steroids, β-agonists).	1	59%	0
11	Define the optimal roles of primary care physicians, hospitalists, pulmonologists, and cardiologists in treating patients with COPD and cardiovascular disease in both the outpatient and inpatient settings with the goal of prioritizing patients' needs.	1	65%	-1
12	Leverage technology to improve various aspects of care for patients with COPD and cardiovascular disease, such as delivery of supplemental oxygen that is automatically titrated to oxygen saturation with movement and participation in telerehabilitation programs.	1	71%	-2
13	Conduct longitudinal studies following stable and exacerbated patients with cardiac rhythm monitors to examine the risk of undetected or recurrent AF and response to therapy (pharmacologic and ablation).	1	36%	-9
14	Determine the risks and benefits of conservative medical management versus advanced cardiac testing or catheterization in patients hospitalized with COPD who have elevated troponin.	1	53%	-11
15	Determine the impact of using active language to describe COPD exacerbation (e.g., "lung attack), given the significantly elevated cardiopulmonary risk over time and specifically in the postexacerbation period.	1	35%	-13
16	Examine how environmental triggers, such as air pollution, mediate the relationship between COPD and cardiovascular disease.	1	24%	-14
17	Evaluate the impact of performing spirometry in hospitalized patients with cardiopulmonary symptoms to differentiate between airflow obstruction and other common conditions that cause dyspnea, such as congestive heart failure.	1	24%	-15

Definition of abbreviations: AF = atrial fibrillation; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; CT = computed tomography; ECG = electrocardiography; mMRC = Modified Medical Research Council Dyspnea Scale; NNT = number needed to treat; SGLT2i = sodium-glucose cotransporter-2 inhibitors.

Seventeen participants voted on all questions. Participants were allowed to vote strongly agree or agree on only 5 of 17 priorities to facilitate generating a prioritized list with a gradient. The degree of agreement is the percentage of respondents who voted strongly disagree/disagree or neutral/agree/strongly agree about whether the gap should be considered a top priority, which was defined as significant potential for advancing the field and ultimately improving the lives of patients with COPD and cardiovascular disease. The last column is the summative Likert score, from which the final round was calculated, where strongly disagree was assigned -2, disagree was assigned -1, neutral was assigned 0, agree was assigned +1, and strongly agree was assigned +2. The final list of priorities was then ordered by the final-round summative Likert score.

Hospital Readmission Reduction Program that financially penalizes hospitals for excess readmissions after index admissions for diseases including COPD, acute myocardial infarction, and heart failure (62). Since the penalties were implemented, evidence has shown potential inverse relationships between reduced readmissions and mortality for both COPD and heart failure (63, 64). Understanding the interplay between these two diseases and, ultimately, how hospitalizations related to COPD and heart failure can be prevented is important for reimbursement for hospitals (65).

There are several benefits to the modified Delphi approach we took, but there are also limitations. The virtual Delphi approach allows a large number of experts

from distant places to participate. Because we made sure that voting results were anonymous, the group could not be swayed by the votes of individuals. However, the ideas presented in this research statement are based on expert opinion. Also, the committee believed that all of the topics identified are important and worthy of further investigation. Because the goal was to prioritize the topics on the basis of urgency and potential impact, we limited to five the number of votes experts could cast for agreeing or strongly agreeing with a topic being a priority to create a gradient for prioritization. We tried to engage as many stakeholders as possible but did not engage payers (insurance agencies) or pharmaceutical representatives.

Conclusions

This research statement sets forth a prioritized research agenda with the purpose of stimulating high-impact research and improving the lives of patients with COPD and cardiovascular disease. Although topics with lower priority ratings were still deemed to be important by the committee, pragmatic clinical trials with patient-centered outcomes that address health disparities were deemed to be the most urgent. ■

Acknowledgment: The authors thank Rachel Kaye from the ATS for facilitating the Zoom meetings, specifically the voting during the Delphi rounds. The authors also acknowledge the Behavioral Science and Health Services Research and Clinical Problems assemblies of the ATS for the opportunity to convene this committee.

This official research statement was prepared by an *ad hoc* subcommittee of the ATS Assembly on Behavioral Science and Health Services Research.

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Subcommittee Disclosures: L.C.M. holds stock in Amgen. J.K.Q. served as a consultant for AstraZeneca, Chiesi, GlaxoSmithKline, and Insmad; and received research support from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Health Data Research, Insmad, the Medical Research Council, NIHR, and Sanofi. N.M.H. served as a consultant, speaker, and received research support from AstraZeneca. N.P. served on an advisory board and as a consultant for GlaxoSmithKline and Verona; and received research support from NIH/NIEHS. A.H. served as a consultant for the COPD Foundation. P.L. served as a consultant for Kivo Health. J.M.W. served on an advisory board for GlaxoSmithKline and Takeda; served on an endpoint review committee for AstraZeneca and Bavarian Nordic; holds patent PCT/GB2021/050658 with Mereo BioPharma; received research support from Alpha-1 Foundation, ARCUS-Med, Department of Veteran Affairs, GlaxoSmithKline, Grifols, InhibiX, Medscape, Mereo BioPharma, NIH/NHLBI, Takeda, and Verona Pharma; and holds stock in Alveolus Bio. L.J.W. received honoraria from Curbsiders Podcast, Elsevier, and Medscape/WebMD; received research support from the Health Resources and Services Administration; and received royalties from McGraw Hill. H.N. served on an advisory board for NIH/UCSF; and received research support from NIH and PCORI. A.W. received research support from NIH/NHLBI; and received royalties from UpToDate. D.M.M. served as a consultant for AstraZeneca, Genentech, GlaxoSmithKline, Regeneron, and UpToDate; served as an expert witness for Schlesinger Law Firm; served in a leadership role for the COPD Foundation; received

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