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FULL RESEARCH PAPER
Cardiovascular disease

Identification and management of cardiopulmonary risk in patients with chronic obstructive pulmonary disease: a multidisciplinary consensus and modified Delphi study

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Aims Cardiovascular disease is a common comorbidity in chronic obstructive pulmonary disease. Yet, cardiovascular disease and risk are underdiagnosed in chronic obstructive pulmonary disease and are often undertreated, increasing the risk of cardiopulmonary events.

Methods and results We formed a Global Working Group of experts in chronic obstructive pulmonary disease and cardiovascular disease to produce a consensus statement detailing the identification and management of cardiopulmonary risk in patients with chronic obstructive pulmonary disease. We conducted virtual meetings supplemented by remote working and communication. The Chairs (C.P.G., M.B.) proposed a draft consensus statement, which was further developed by the Global Working Group. The selection of the final consensus statement and key points were obtained using the modified Delphi method. The consensus statement is, 'Given the high burden of fatal and non-fatal major cardiovascular and respiratory events in patients with COPD it is important that cardiopulmonary risk is assessed and managed'. Patients with cardiovascular risk factors or disease who have regular cough or expectoration, recurrent 'chest infections', a significant smoking history, or dyspnoea should complete spirometry to confirm the presence of chronic obstructive pulmonary disease. Prevalent and incident cardiovascular disease and risk in patients with chronic obstructive pulmonary disease, including heart failure, dyslipidaemia, hypertension, ischaemic heart disease, and atrial fibrillation, should be managed according to clinical guidelines. In addition, chronic obstructive pulmonary disease exacerbation risk in patients with chronic obstructive pulmonary disease should be addressed to reduce cardiopulmonary risk. Enhanced integration with specialists in cardiology, pulmonology, and primary care is recommended.

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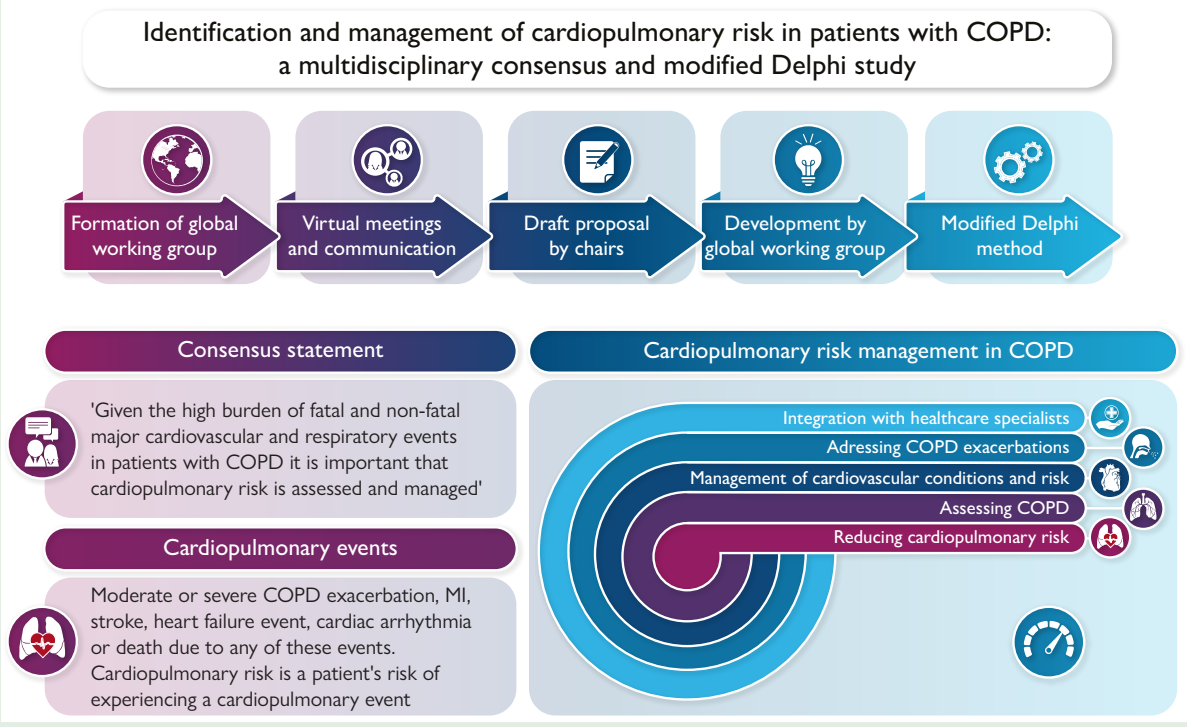
Conclusion The identification and management of cardiopulmonary risk in patients with chronic obstructive pulmonary disease are an unmet public health need that can be addressed through shared understanding and multidisciplinary working to improve cardiopulmonary outcomes.

Lay summary This paper, produced by the Global Working Group of experts in chronic obstructive pulmonary disease and cardiovascular disease, is about the identification and management of cardiopulmonary risk in patients with chronic obstructive pulmonary disease.

- Individuals with cardiovascular risk factors or disease who have a regular cough or expectoration, recurrent 'chest infections', a significant smoking history, or breathlessness should complete spirometry to confirm the presence of chronic obstructive pulmonary disease.
- Cardiovascular disease and risk in individuals with chronic obstructive pulmonary disease, including heart failure, dyslipidaemia, hypertension, ischaemic heart disease, and atrial fibrillation, should be managed according to clinical guidelines.
- Identifying cardiopulmonary risk to prevent exacerbations of chronic obstructive pulmonary disease, treat established cardiovascular disease, and reduce cardiovascular risk in patients with chronic obstructive pulmonary disease offers the prospect to improve cardiopulmonary outcomes.

Graphical Abstract



Keywords Chronic obstructive pulmonary disease • Cardiovascular disease • Cardiopulmonary risk

Introduction

Chronic obstructive pulmonary disease is a long-term respiratory condition associated with multiple comorbidities, and frequently with cardiovascular disease. Compared with individuals without chronic obstructive pulmonary disease, those with chronic obstructive pulmonary disease have a higher prevalence of ischaemic heart disease, heart failure, stroke, and arrhythmia.[1–3] This is not surprising given their shared exposures and risk factors such as smoking, air pollution, socioeconomic deprivation across the life course, diabetes, hypertension, low levels of exercise, unhealthy diet, dyslipidaemia, and the direct and indirect effects of treatment (due to systemic steroids) and exacerbations of chronic obstructive pulmonary disease.[4,5]

When cardiovascular disease coexists with chronic obstructive pulmonary disease, it carries a worse prognosis. It is estimated that one in five patients with chronic obstructive pulmonary disease die from cardiovascular disease,[6,7] and compared with age- and sex-matched controls without chronic obstructive pulmonary disease, the risk is two- to four-fold higher at three years follow-up.[8] This risk is even higher in patients with chronic obstructive pulmonary disease of moderate severity, where cardiovascular disease is the predominant cause of death.[9]

Despite the increased cardiovascular risk associated with chronic obstructive pulmonary disease, cardiovascular disease in these populations remains under-recognized, underdiagnosed, and undertreated.[10,11] Equally, chronic obstructive pulmonary disease may be under-appreciated and suboptimally managed in people with cardiovascular disease.[10,12] Shared symptoms, predominantly breathlessness, between patients with chronic obstructive pulmonary disease and cardiovascular disease may impede diagnosis and treatment. Thus, there exist substantial missed opportunities to reduce the risk of adverse cardiovascular and respiratory events—'cardiopulmonary risk'—in these populations.[10] Moreover, there is no guideline or recommendation for the identification, management, and definition of cardiopulmonary events and risk in chronic obstructive pulmonary disease.

The aim of this work is to help pulmonologists, cardiologists, primary care physicians, and other healthcare professionals understand, identify, and manage cardiopulmonary risk in patients with chronic obstructive pulmonary disease. We formed a Global Working Group of experts in chronic obstructive pulmonary disease and cardiovascular disease[13] to establish agreement on consensus statements about the identification and management of cardiopulmonary risk in patients with chronic obstructive pulmonary disease, and a standardized definition of cardiopulmonary events in chronic obstructive pulmonary disease, using a modified Delphi process. The consensus statements and sections outline a practical approach to the identification and management of cardiopulmonary risk in patients with cardiovascular disease and chronic obstructive pulmonary disease. We highlight gaps in the knowledge base and make recommendations for future research.

Of note, this document focuses on chronic obstructive pulmonary disease-associated cardiopulmonary risk and not the wider range of cardiopulmonary diseases or on the primary prevention of cardiovascular and respiratory diseases each of which are covered in separate international guidelines.[14–17]

Methods

The study comprised two stages: (i) development of statements with an online modified Delphi consensus process to determine agreement with and refinement of the statements, and (ii) section writing about fundamental aspects of cardiopulmonary risk.

Study groups

We formed a core Global Working Group comprising clinical and academic experts in chronic obstructive pulmonary disease and cardiovascular disease.[18] We also formed a wider Global Working Group comprising 100 individuals encompassing a range of disciplines.[13] Both Groups were chaired by a cardiologist (C.P.G.) and a pulmonologist (M.B.).

Delphi statements

To develop the draft consensus statements for (i) the identification and management of cardiopulmonary risk in individuals with chronic obstructive pulmonary disease, and (ii) the definition of cardiopulmonary events, the Chairs of the Global Working Groups met virtually on Teams between December 2023 and early February 2024, and used open-ended questions to provide their opinions about cardiopulmonary events in the context of chronic obstructive pulmonary disease. Discussions orientated around: (i) clinical events in individuals with chronic obstructive pulmonary disease; (ii) standardization of outcomes measures for chronic obstructive pulmonary disease clinical studies; (iii) substrates and triggers for cardiovascular and chronic obstructive pulmonary disease events in individuals with chronic obstructive pulmonary disease; and (iv) conceptualization of cardiopulmonary risk.

Modified Delphi method

We used a modified Delphi panel method to generate consensus for the final statements.[19] A draft statement for the identification and management of cardiopulmonary risk in individuals with chronic obstructive pulmonary disease was presented to 11 members of the core Global Working Group in English using SurveyMonkey (an artificial intelligence-powered feedback platform that enables online surveys) as a 4-point Likert scale for agreement, and with the option to provide free-text comments. Following this, a virtual consensus meeting was held to discuss the results of the independent voting, and to agree upon modifications to the statement. A revised statement was then circulated with a 2-point Likert scale for agreement, and with the option to provide free-text comments using SurveyMonkey. A final voting threshold of over 80% agreement (agree vs. disagree) was considered consensus and appropriate to allow incorporation of the consensus statement in the document that would be circulated to the wider Global Working Group for review.

Section writing

The lead author (C.P.G.) drafted the scope and principal sections of document. Section Chairs with specific expertise led on topics, which was coordinated and refined by the Global Working Group Chairs through online feedback. Sections Chairs were requested to list knowledge gaps and research needs.

Timelines

Over a six-month period from January 2024, we conducted a series of virtual meetings on Teams with the core Global Working Group supplemented by remote working and communication, and face-to-face meetings. The Chairs of the Global Working Groups had scheduled virtual meetings on Teams lasting 30 min each fortnight during this period.

Patients

We engaged with a patient with chronic obstructive pulmonary disease, a patient with cardiovascular disease, and the Global Airways and Allergy Patient Platform to canvas feedback about our document. The Chairs of the Global Working Group agreed that this activity would be undertaken during the later stages of development of the document.

Statistical analysis

For the current study, a threshold of over 80% agreement was used because we wished to define consensus agreement on the basis that a small group may result in higher standard deviation in responses. Descriptive statistics were used to summarize scores. All free-text responses were provided in English, evaluated by the Chairs and where applicable used to make amendments or clarifications for the consensus statement in the second round.

Results

The core Global Working Group comprised 11 members (six pulmonologists, one general practitioner, four cardiologists; representing seven men and four women across five countries). The wider Global Working Group comprised (in addition to the core group) 38 pulmonologists, 3 general practitioners, 28 cardiologists, 10 nurses, 3 epidemiologists, 1 exercise physiologist, 1 cardiopulmonary physiotherapist, 1 exercise physiologist, 1 patient group, 2 patients, and 1 medical student; in total, this represented 63 men and 37 women across 40 countries.

Modified Delphi

For the statement about the identification and management of cardiopulmonary risk, the first round of the modified Delphi process occurred between 13 December 2023 and 3 January 2024. There was full consensus from all 11 (100%) members of the core Global

Working Group, with only one comment that recommended the term 'people' rather that 'patients', which was actioned. Thus, the consensus statement was inserted into the document and progressed to the wider Global Working Group for feedback.

For the statement about the definition of cardiopulmonary events, the first round of the modified Delphi process occurred between 18 February 2024 and 24 February 2024. Following reminders to non-responders, there were eight respondents (72.7%), of whom seven (87.5%) agreed and one (12.5%) strongly agreed with the consensus statement. Four comments were submitted about the definitions of the individual components of the cardiopulmonary event composite. Following online discussion, the second round of voting occurred between 24 February 2024 and 1 March 2024. The survey was completed by eight respondents (72.7%), of whom seven (87.5%) agreed and one (12.5%) disagreed. Three comments were submitted about simplifying the statement as a whole and the definitions of the individual components of the cardiopulmonary event composite. This was actioned following review with the Chairs, and the consensus statement inserted into the document and progressed to the wider Global Working Group for feedback.

Sections

We identified 12 sections for the document representing the fundamental issues in cardiopulmonary risk in chronic obstructive pulmonary disease; (i) consensus statement; (ii) definitions; (iii) clinical presentation; (iv) estimating cardiopulmonary risk; (v) identification of cardiovascular disease in people with chronic obstructive pulmonary disease; (vi) identification of chronic obstructive pulmonary disease in people with cardiovascular disease; (vii) outcomes and prognosis; (viii) management of cardiovascular disease in people with chronic obstructive pulmonary disease; (ix) management of cardiovascular risk and cardiopulmonary risk in people with chronic obstructive pulmonary disease; (x) management of chronic obstructive pulmonary disease in people with cardiovascular disease; (xi) organization and delivery of care; and (xii) pre-chronic obstructive pulmonary disease and relevance to cardiovascular risk in chronic obstructive pulmonary disease. Knowledge gaps and research needs for cardiopulmonary risk in chronic obstructive pulmonary disease are presented in *Table 1*, and recommendations for research about cardiopulmonary risk in chronic obstructive pulmonary disease are presented in *Table 2*.

Consensus statement

The final consensus statement was, 'Given the high burden of fatal and non-fatal major cardiovascular and respiratory events in people with COPD it is important that cardiopulmonary risk is assessed and managed'.

Definitions

Cardiopulmonary events

Cardiopulmonary events is a composite term comprising the singular of moderate or severe chronic obstructive pulmonary disease exacerbation, myocardial infarction, stroke, heart failure event, cardiac arrhythmia, or death due to any of these events. While myocardial infarction,[20] stroke,[21] and heart failure event[22] have standard definitions,[23] cardiac arrhythmia is defined as the existence of atrial fibrillation, atrial flutter,[24] ventricular tachycardia, or ventricular fibrillation.[25] Cardiopulmonary events may also be employed as a study composite outcome measure. We acknowledge that composite outcome measures can provide financial and logistical efficiency to detect a minimally clinically important difference in a research study, but potentially at the expense of losing clarity over the mechanism of the effect of the intervention.[26,27] The Global Working Group also supports the notion that cardiopulmonary events that occur earlier after an index event, such as a chronic obstructive pulmonary disease exacerbation, may be more likely to be causally related to that index event.

Cardiopulmonary risk

We define cardiopulmonary risk as a patient's risk of experiencing a cardiopulmonary event. We propose that cardiopulmonary risk is modifiable and may be categorized as low, intermediate, high, and very high (*Figure 1*). However, once a patient with chronic obstructive pulmonary disease has been optimally managed in terms of their cardiovascular and pulmonary disease and risk, they may continue to be at elevated cardiopulmonary risk, albeit with a lower risk of events; we propose that this is termed residual cardiopulmonary risk. A clinical goal should be to minimize cardiopulmonary risk though lifestyle interventions and therapy. Tackling residual cardiopulmonary risk may require novel interventions and should be a priority area for research.

Clinical presentation

The manifestation of incident cardiovascular disease in people with chronic obstructive pulmonary disease is most frequently with atherosclerotic cardiovascular disease, heart failure, and atrial fibrillation, and of these three presentations, it is reported to be the highest for heart failure.[28,29] The incidence of ischaemic heart disease in people with chronic obstructive pulmonary disease is estimated to be ~70% higher than that for people without chronic obstructive pulmonary disease.[28] Furthermore, incident acute myocardial infarction is more than three-fold higher in people with chronic obstructive pulmonary disease compared to those without, and among those aged 35–44 years, it carries a more than 10-fold higher risk.[30] Among people with chronic obstructive pulmonary disease, heart failure with reduced ejection fraction is estimated to be prevalent in 10–46%,[31] and 20–70% have heart failure with mildly reduced or preserved ejection fraction[32,33] (which contrasts with the prevalence of clinically significant cor pulmonale that is estimated to be <1% in patients with chronic obstructive pulmonary disease).[34] Incident heart failure is three-fold higher for people with chronic obstructive pulmonary disease compared to those without chronic obstructive pulmonary disease. Finally, the incidence of atrial fibrillation is ~60% higher in chronic obstructive pulmonary disease with a prevalence estimated to be ~7%.[28,35] This prevalence increases with worsening chronic obstructive pulmonary disease severity, as demonstrated in a prospective study where, after adjustment for demographic and cardiovascular risk factors, lower levels of the forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were each associated with about a 20% proportional increase in risk for atrial fibrillation per 500 mL reduction in FEV1 and/or FVC.[36]

It is important to note that patients with chronic obstructive pulmonary disease may be at risk for, but not have clinically overt, cardiovascular disease, and the ways that it manifests itself may differ between men and women.[37] In addition, most common cardiovascular disease prevention risk scores (except for QR4[38]) do not include chronic obstructive pulmonary disease as a risk factor, raising the potential for underestimation of cardiovascular risk in this population (*Tables 1* and *2*).[39,40] The Global Working Group on Cardiopulmonary Risk also recognizes that chronic obstructive pulmonary disease is frequently associated with frailty,

Table 1 Knowledge gaps and research needs for cardiopulmonary risk in chronic obstructive pulmonary disease

Clinical presentation
- Contemporary and representative information about the incidence of cardiovascular disease in individuals with chronic obstructive pulmonary disease.
- The underlying pathophysiological mechanisms that convey the increased risk of cardiovascular events in patients with chronic obstructive pulmonary disease.
- The magnitude of cardiovascular risk (e.g. of cardiac arrhythmia) induced by pharmacotherapy for chronic obstructive pulmonary disease exacerbations.

Estimating cardiopulmonary risk
- The performance and clinical utility of a risk score for the prediction of cardiopulmonary events in people living with chronic obstructive pulmonary disease.

Identification of cardiovascular disease in people with chronic obstructive pulmonary disease
- The most accurate and cost-effective method(s) to assess and address cardiovascular risk factors and disease in people with chronic obstructive pulmonary disease.
- The role of natriuretic peptides (e.g. NT-proBNP) in evaluating heart failure among individuals with chronic obstructive pulmonary disease.
- Whether CT scans performed for lung cancer screening can help identify early forms of cardiovascular disease.
- Whether the use of coronary artery calcium scoring and/or CTCA and resultant treatment for coronary artery disease, as necessary, in people with chronic obstructive pulmonary disease is associated with improved clinical outcomes.

Identification of chronic obstructive pulmonary disease in people with cardiovascular disease
- The most accurate and cost-effective strategy for identification of chronic obstructive pulmonary disease in individuals with cardiovascular disease.

Outcomes and prognosis
- The association of chronic obstructive pulmonary disease and a wider range of incident cardiovascular diseases such as heart failure, ischaemic heart disease, arrhythmia, and peripheral vascular disease.
- The extent to which a cardiovascular event alters future risk of cardiopulmonary events in patients with chronic obstructive pulmonary disease.
- The impact of stratified interventions (tailoring treatments to specific phenotypes of chronic obstructive pulmonary disease) on cardiopulmonary outcomes in people with chronic obstructive pulmonary disease.
- The effect of biologics for the treatment of chronic obstructive pulmonary disease on cardiopulmonary events.
- The effect of novel investigational medicinal products for concomitant cardiovascular disease and chronic obstructive pulmonary disease on cardiopulmonary events.

Management of cardiovascular disease in people with chronic obstructive pulmonary disease
- Eligibility for and the implementation gap in established guideline-directed medical therapy among real-world populations with chronic obstructive pulmonary disease and concomitant cardiovascular disease.
- The magnitude of residual cardiovascular risk in people with chronic obstructive pulmonary disease after adjusting for treatment of cardiovascular risk factors and cardiovascular disease.
- Effect of cardiovascular therapies on pulmonary related symptoms, quality of life, and outcomes.
- Response to cardiovascular therapies in specific phenotypes of chronic obstructive pulmonary disease.
- The role of opportunistic screening by coronary calcification identified at lung CT.

Management of cardiovascular risk and cardiopulmonary risk in people with chronic obstructive pulmonary disease
- The effect of treating cardiovascular risk factors in people with chronic obstructive pulmonary disease on clinical outcomes.
- The clinical effect of intensive cardiovascular risk factor treatment to lower than standard guideline targets (as adopted in people with diabetes) among people with chronic obstructive pulmonary disease.

Management of chronic obstructive pulmonary disease in people with cardiovascular disease
- Whether optimization of chronic obstructive pulmonary disease care, including non-pharmacologic and pharmacological treatments aimed at reducing chronic obstructive pulmonary disease exacerbations and systemic steroid use, improve cardiovascular outcomes in patients with established cardiovascular disease.

Organization and delivery of care
- Whether a breathlessness pathway can provide accelerated diagnosis and treatment of chronic obstructive pulmonary disease and cardiovascular disease, and whether this is associated with reduced cardiopulmonary events.

which increases a person's vulnerability to chronic obstructive pulmonary disease exacerbations and adverse outcomes.

Estimating cardiopulmonary risk

Guideline recommended cardiovascular risk scores, including the Framingham risk sore, Pooled Cohorts' Equations (PCE), Reynolds risk score, SCORE2, JBS3, PREVENT, and QRISK3, for the estimation of future cardiovascular disease in individuals without previous cardiovascular disease, do not include chronic obstructive pulmonary disease as a predictor.[39] The QRISK3 risk score has been shown to underestimate observed 10-year cardiovascular disease among individuals living with chronic obstructive pulmonary disease. In the Canadian Cohort of Obstructive Lung Disease (CanCOLD), individuals with chronic obstructive pulmonary disease have an approximate two-fold higher risk

Table 2 Recommendations for research about cardiopulmonary risk in chronic obstructive pulmonary disease

Clinical presentation
- New estimates of incident cardiovascular disease in people with chronic obstructive pulmonary disease are required to inform the burden of disease and opportunities for prevention.
- There is a need for chronic obstructive pulmonary disease and cardiovascular guidelines to provide a practical and systematic approach to assessing cardiopulmonary risk to mitigate cardiovascular disease.
- Risk stratification for cardiovascular disease should consider chronic obstructive pulmonary disease as a predictor, and cardiovascular risk scores should be designed for the chronic obstructive pulmonary disease population.
- Mechanistic studies are needed to understand the pathophysiology of cardiovascular events in chronic obstructive pulmonary disease, to more fully identify targets for treatment or prevention.

Estimating cardiopulmonary risk
- A simple composite score that accurately predicts the risk of cardiopulmonary events in people with chronic obstructive pulmonary disease should be developed and validated.
- Levels of cardiopulmonary risk should be defined and quantified.
- People with chronic obstructive pulmonary disease should be systematically assessed for combined risk of cardiovascular disease and future chronic obstructive pulmonary disease exacerbations.

Identification of cardiovascular disease in people with chronic obstructive pulmonary disease
- Chronic obstructive pulmonary disease clinical practice guidelines should include recommendations related to the assessment of cardiovascular risk and disease.
- Develop means to assess cardiovascular risk in individuals with chronic obstructive pulmonary disease.
- The cost effectiveness of cardiovascular diagnosis and treatment approaches among people with chronic obstructive pulmonary disease should be investigated.

Identification of chronic obstructive pulmonary disease in people with cardiovascular disease
- Cardiovascular and chronic obstructive pulmonary disease guidelines and recommendations should more fully recognize the importance of identifying chronic obstructive pulmonary disease in people with cardiovascular disease.
- Studies are required to evaluate the clinical benefits associated with identification of chronic obstructive pulmonary disease in people with cardiovascular disease.

Outcomes and prognosis
- Outcomes research is needed to understand the course of chronic obstructive pulmonary disease, factors associated with cardiopulmonary events in chronic obstructive pulmonary disease, and the prognostic determinants of outcomes.
- Randomized clinical trials of patients with chronic obstructive pulmonary disease should consider including cardiopulmonary events as a pre-specified composite or individual components outcome measure(s).
- Randomized controlled trials designed to test the effect of biologics for the treatment of chronic obstructive pulmonary disease on cardiopulmonary events.
- Randomized controlled trials designed to test the effect of novel investigational medicinal therapies for concomitant cardiovascular disease and chronic obstructive pulmonary disease on cardiopulmonary events

Management of cardiovascular disease in people with chronic obstructive pulmonary disease
- Include and characterize cardiovascular disease in participants of future clinical studies of chronic obstructive pulmonary disease (e.g. cardiovascular biomarkers, 12-lead ECG, transthoracic echocardiography), along with characterization of chronic obstructive pulmonary disease in future clinical studies of cardiovascular disease [e.g. modified Medical Research Council (mMRC) dyspnoea scale, CAT, and spirometry].
- Conduct pragmatic randomized controlled trials that test the identification and treatment of cardiovascular disease in people with chronic obstructive pulmonary disease.

Management of cardiovascular risk and cardiopulmonary risk in people with chronic obstructive pulmonary disease
- Clinical practice guidelines for chronic obstructive pulmonary disease include recommendations for the identification and management of cardiovascular risk factors.
- Cardiovascular outcome trials of the effect of treating cardiovascular risk factors in people with chronic obstructive pulmonary disease.

Management of chronic obstructive pulmonary disease in people with cardiovascular disease
- Cardiovascular outcomes studies of chronic obstructive pulmonary disease treatment optimization across all stages of chronic obstructive pulmonary disease in patients with established cardiovascular disease.

Organization and delivery of care
- Implement and evaluate new models of care for patients with undifferentiated breathlessness.
- Health services research to investigate service-level performance using audit and feedback for chronic obstructive pulmonary disease care, and breathlessness pathways for efficient diagnosis of chronic obstructive pulmonary disease and cardiovascular disease.

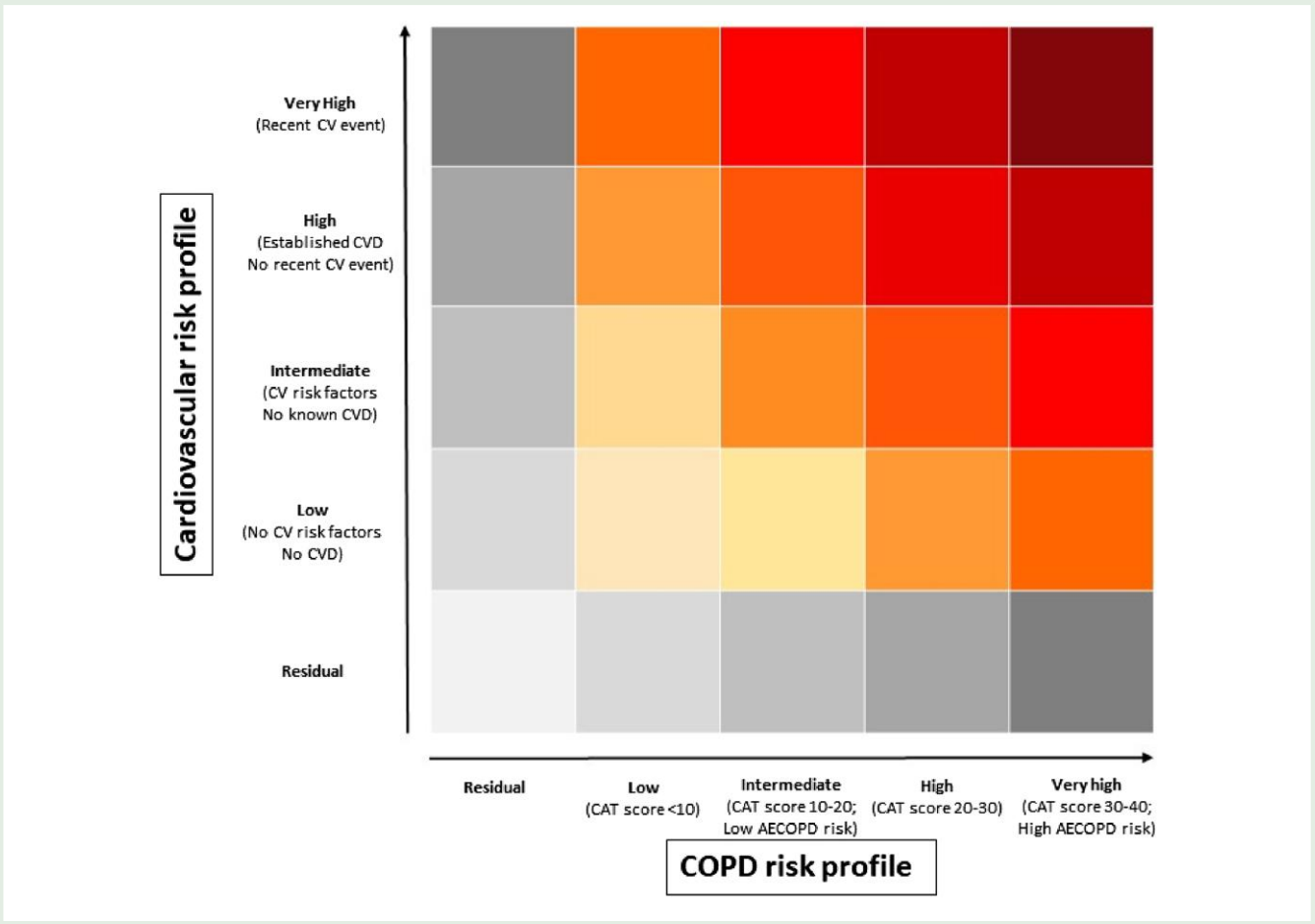


Figure 1 Conceptualizing chronic obstructive pulmonary disease-associated cardiopulmonary risk. CV, cardiovascular; CVD, cardiovascular disease; CAT, COPD Assessment Tool; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

of developing cardiovascular disease compared to individuals with normal spirometry, without evidence of improved prediction of cardiovascular events among those with impaired spirometry when the PCE or Framingham risk scores were used. In contrast, the new QR4 risk score that incorporates chronic obstructive pulmonary disease affords the ability to reclassify patients with chronic obstructive pulmonary disease into higher risk for cardiovascular disease in order to enable them to be offered lifestyle intervention and lipid-lowering therapy.[38] It does not, however, identify who with chronic obstructive pulmonary disease is at higher risk of a cardiopulmonary event.

There exists a need for a validated, accurate risk score for the prediction of cardiopulmonary events in patients with chronic obstructive pulmonary disease. Some scores have been developed to predict the risk of acute exacerbation (e.g. ADO) and survival (e.g. BODE), but neither includes comorbidities nor other forms of cardiovascular disease, and they add little over simple clinical assessment of past exacerbation history. Given that all people with chronic obstructive pulmonary disease are at elevated cardiopulmonary risk, it is important to determine which factors carry the greatest incremental risk (e.g. smoking, elevated COPD Assessment Tool (CAT) score, frequency and severity of Acute Exacerbations of COPD (AECOPD), known cardiovascular disease, high predicted risk of cardiovascular disease in those without known cardiovascular disease, hypertension, diabetes, chronic kidney disease, dyslipidaemia, obesity, and coronary artery calcification). Risk estimates may differ according to sex.[37] In a cohort of people with stable chronic obstructive pulmonary disease, after adjustment for cardiovascular risk factors, prevalent cardiovascular disease, and other established chronic obstructive pulmonary disease mortality predictors, high sensitivity troponin concentration was a predictor for all-cause mortality.

Identification of cardiovascular disease in people with chronic obstructive pulmonary disease

International respiratory guidelines and recommendations do not address the importance of identifying cardiovascular disease in people with chronic obstructive pulmonary disease. In contrast, the 2021 European Society of Cardiology Guidelines on Cardiovascular Disease Prevention in Clinical Practice recommend that all people with chronic obstructive pulmonary disease be evaluated for atherosclerotic cardiovascular disease and associated risk factors.[16]

We propose that people with chronic obstructive pulmonary disease be fully evaluated for cardiovascular disease with a cardiovascular history (noting a history of chest pain/tightness, orthopnoea,

paroxysmal nocturnal dyspnoea, palpitations, syncope, and disproportionate dyspnoea), full lipid profile, haemoglobin a1c (Hba1c), full (complete) blood count, urea and electrolytes, estimated glomerular filtration rate, thyroid function, liver function (collectively representing a basic metabolic panel), N-terminal pro-B-type natriuretic peptide (NT-proBNP), blood pressure, and a 12-lead electrocardiogram performed. At a minimum, a cardiovascular disease history and, as necessary, additional cardiovascular investigations should be performed as dictated on an annual basis.

Given the prevalence and consequence of atrial fibrillation, consideration should be given to screening for this condition in individuals with chronic obstructive pulmonary disease utilizing algorithms based on electronic health records data (such as FIND-AF), and/or photoplethysmography-based devices. Among those without known cardiovascular disease, people with chronic obstructive pulmonary disease should have their risk of cardiovascular disease estimated using QR4 (or an equivalent validated cardiovascular disease risk score, while understanding that scores may underestimate cardiovascular risk in chronic obstructive pulmonary disease). The COPDCoRi risk score estimates the risk of coronary artery disease in patients with chronic obstructive pulmonary disease. Patients should be informed of the importance of a heart-healthy diet and regular exercise. Blood pressure control, lipid-modifying therapy, oral anticoagulation for stroke prevention in atrial fibrillation, control of diabetes mellitus, weight management, and treatment of heart failure should be undertaken in accordance with clinical guidelines.[16,17] Incident and prevalent cardiovascular disease should be assessed and managed in conjunction with the person's general practitioner, cardiologist and/or specialist nurse or allied health professional. Further cardiovascular evaluation should be tailored according to the results of initial laboratory tests (*Figure 2*). This may include a transthoracic echocardiogram in the context of an elevated NT-proBNP (noting that a normal left ventricular ejection fraction in a patient with elevated NT-proBNP does not exclude heart failure) or coronary artery calcium scoring to refine atherosclerotic cardiovascular disease risk assessment. NT-proBNP levels vary in patients with chronic obstructive pulmonary disease and are higher in patients with chronic obstructive pulmonary disease exacerbations, pulmonary hypertension, and heart failure, and is associated with adverse prognosis. If the history supports a specific cardiovascular disease, then additional cardiovascular imaging could be pursued such as computed tomography coronary angiography (CTCA), functional testing, ambulatory rhythm monitoring, cardiopulmonary exercise testing, and cardiac magnetic resonance imaging. Although an increased troponin level is a strong independent predictor for cardiovascular events and mortality in stable chronic obstructive pulmonary disease, we do not recommend the routine testing of troponin in patients with chronic obstructive pulmonary disease unless there are clinical features to suggest acute coronary syndrome.

Identification of chronic obstructive pulmonary disease in people with cardiovascular disease

In the absence of clinical practice guidance related to identification of chronic obstructive pulmonary disease in people with cardiovascular disease, we propose that people with cardiovascular risk factors or disease with regular colds or bronchitis, chronic cough or recurrent expectoration, recurrent 'chest infections', dyspnoea, or a significant smoking history (more than 10 pack years) should have spirometry performed. Particular note should be drawn to patients in whom dyspnoea is not explained by cardiovascular disease. Of note, the PUMA score (comprising age, sex, pack-years smoking, dyspnoea, sputum, cough, and spirometry) has a mean accuracy of 76% for detecting chronic obstructive pulmonary disease; this and other such scores could be employed for opportunistic case finding. In a randomized strategy trial, a case finding method to identify adults in the community with respiratory symptoms without known lung disease reduced the annualized rate of participant-initiated health care utilization for respiratory illness (though was not specifically for the identification of chronic obstructive pulmonary disease in people with cardiovascular disease). Digital spirometers or handheld microspirometers could potentially serve as an initial screening strategy for people at increased risk for chronic obstructive pulmonary disease; and CTCA requested for cardiac investigation could be useful to detect chronic obstructive pulmonary disease. Because environmental and workplace exposure to pollution, chemicals, fumes, smoke, and dust can cause chronic obstructive pulmonary disease, patients with this history may warrant additional evaluation. Additional investigations should also be performed according to the results of preliminary tests, and may include gas transfer and lung volumes, and as appropriate transthoracic echocardiography and thoracic computed tomography. Patients identified as having incident and prevalent chronic obstructive pulmonary disease should have their lung-related treatment optimized according to local, national or international guidelines and recommendations (*Figure 3*).

Outcomes and prognosis

Evidence suggests that people with chronic obstructive pulmonary disease face increased risk for hospitalization and death due to cardiovascular disease.[30] Moreover, the presence of cardiovascular disease serves as an adverse effect modifier in people with chronic obstructive pulmonary disease, and conversely the presence of chronic obstructive pulmonary disease serves as an adverse effect modifier in people with cardiovascular disease. Numerous observational studies have reported the deleterious effects of chronic obstructive pulmonary disease in terms of mortality and morbidity in people with cardiovascular disease. This appears to be associated with lung function severity, exacerbation status, and use of systemic steroids for chronic obstructive pulmonary disease exacerbations. For every 10% decrease in FEV1, all-cause mortality increases by 14%, cardiovascular mortality increases by 28%, and non-fatal coronary events increase by 20%. Among people with concomitant cardiovascular disease and chronic obstructive pulmonary disease, compared with people with no exacerbation, severe chronic obstructive pulmonary disease exacerbations were associated with six-fold increase in hospitalization due to fatal or non-fatal stroke, myocardial infarction, or heart failure in the following six months. Moreover, the risk of a cardiovascular event is extended, albeit attenuated, for up to one year following a chronic obstructive pulmonary disease exacerbation. Interestingly, patients with concomitant atrial fibrillation and chronic obstructive pulmonary disease had a very poor prognosis and the temporal sequence in diagnosis was differentially associated with prognosis, where a chronic obstructive pulmonary disease diagnosis preceding an atrial fibrillation diagnosis was accompanied with a higher mortality risk compared with a chronic obstructive pulmonary disease diagnosis following an atrial fibrillation diagnosis.

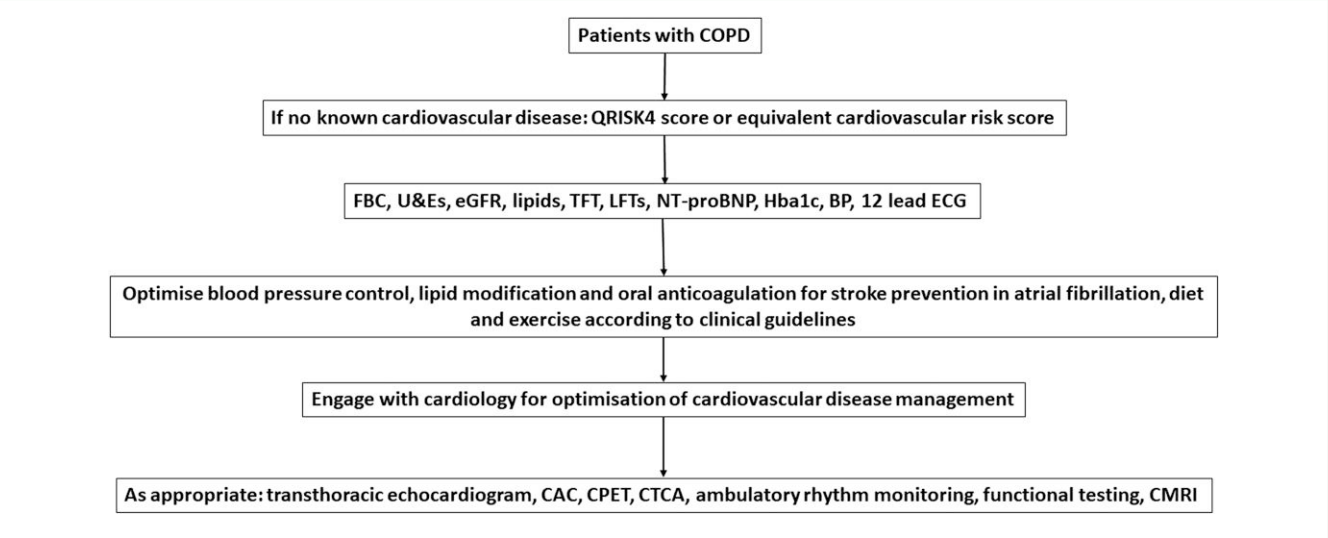


Figure 2 Identification of cardiovascular disease in people living with chronic obstructive pulmonary disease. FBC, full (complete) blood count; U&Es, urea and electrolytes; eGFR, estimated glomerular filtration rate; TFT, thyroid function tests; LFT, liver function tests; Hba1c, haemoglobin A1C (collectively representing a basic metabolic panel); NT-proBNP, N-terminal pro-B-type natriuretic peptide; ECG, electrocardiogram; CAC, coronary artery calcium score; CPET, cardiopulmonary exercise test; CTCA, computed tomography coronary angiography; CMRI, cardiac magnetic resonance imaging.

Management of cardiovascular disease in people with chronic obstructive pulmonary disease

The management of cardiovascular disease in people with chronic obstructive pulmonary disease should follow established guidelines for the respective cardiovascular disease.[16,17] Individuals who smoke tobacco and/or vape should be advised to stop smoking and be offered interventions and support to facilitate smoking cessation.

Important for both the cardiovascular and chronic obstructive pulmonary disease population is the role of vaccinations. Chronic obstructive pulmonary disease guidelines recommend for the administration of vaccines for seasonal influenza, pneumococcus, respiratory syncytial virus, and COVID-19, to reduce the risk of exacerbations. Influenza is associated with a six times increased risk of acute myocardial infarction. In the IAMI trial, influenza vaccination significantly reduced the rates of all-cause mortality, acute myocardial infarction, and stent thrombosis at 12 months. Although randomized evidence that vaccines would reduce a chronic obstructive pulmonary disease patient's cardiopulmonary risk is lacking, given that there is benefit to vaccination in both conditions, one may propose that the benefit would be extended to a chronic obstructive pulmonary disease patient to reduce their cardiopulmonary risk.

For patients with chronic obstructive pulmonary disease, cardiovascular disease is a fundamental extrapulmonary 'treatable trait' that requires specific therapy when present. Importantly, there is no contraindication to guideline-directed medical therapy for cardiovascular disease in individuals with chronic obstructive pulmonary disease. This includes beta-blockers, antiplatelet therapy, lipid-lowering therapy [such as but not limited to HMG Co-A reductase inhibitors (statins)], and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) for atherosclerotic cardiovascular disease, antiarrhythmic drugs for arrhythmia, and quadruple therapy for heart failure (sacubitril–valsartan, beta-blockers, mineralocorticoid receptor antagonists (MRA), and sodium-glucose transport protein 2 (SGLT2) inhibitors.

Concerns regarding beta-blockers in people with chronic obstructive pulmonary disease are unfounded. In systematic reviews and meta-analyses, cardioselective beta-blockers have been shown to be safe and well tolerated in even moderate and severe chronic obstructive pulmonary disease. Furthermore, a common misperception is that people with chronic obstructive pulmonary disease and established cardiovascular disease derive less benefit from cardiovascular therapies due to competing non-cardiovascular risks. However, because they have higher absolute rates of major adverse cardiovascular events and the same relative risk reduction with cardiovascular therapies, the absolute risk reduction is even greater. The undertreatment of patients at high cardiovascular risk underscores the strong observational association between cardiovascular treatments and improved outcomes in real-world populations with chronic obstructive pulmonary disease (an unhealthy non-user effect). Multidisciplinary pulmonary rehabilitation programmes including core components or physical exercise and education for people with chronic obstructive pulmonary disease have also been associated with improvements in cardiovascular risk factors.

Management of cardiovascular risk and cardiopulmonary risk in people with chronic obstructive pulmonary disease

In addition to being under-recognized, cardiovascular risk factors are also inadequately monitored, undertreated, and poorly controlled in people with chronic obstructive pulmonary disease. In a large primary care cohort in Canada, cardiovascular risk factors were prevalent in people with chronic obstructive pulmonary disease, namely hypertension (52.3%), dyslipidaemia (62.0%), diabetes (25.0%), obesity (40.8%), and

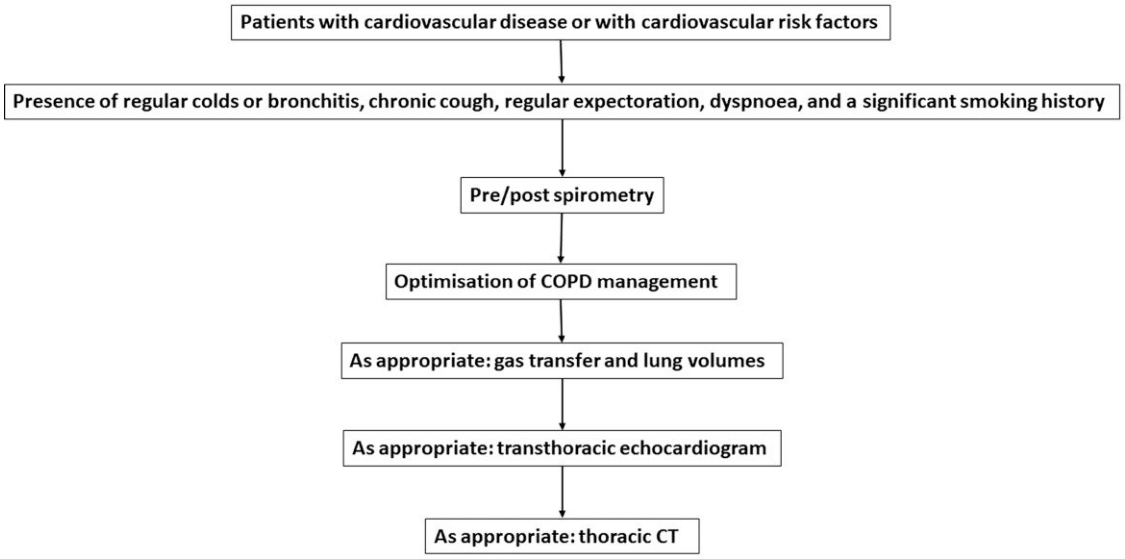


Figure 3 Identification of chronic obstructive pulmonary disease in people living with cardiovascular disease. CT, computed tomography.

smoking (40.9%). For those receiving cardiovascular risk factor monitoring, guideline recommended targets were achieved in only 60.8%, 46.6%, 57.4%, 10.6%, and 12.0%, respectively. Cardiovascular therapies including ACEI (69%), statins (69%), and smoking cessation therapies (27%) were also underused.[10] Similarly, influenza vaccination remains underutilized in chronic obstructive pulmonary disease, increasing the risk for cardiovascular events. As with established cardiovascular disease, the management of cardiovascular risk should follow established guidelines of the respective risk factors.[16,17]

Management of chronic obstructive pulmonary disease in people with cardiovascular disease

Patients with cardiovascular disease who are diagnosed with chronic obstructive pulmonary disease should have their lung disease severity evaluated beyond spirometry. Patient reported outcome measures such as the modified Medical Research Council (mMRC) dyspnoea scale or the CAT are reliable and validated tools for the assessment of chronic obstructive pulmonary disease burden and health status. A history of chronic obstructive pulmonary disease exacerbations and hospitalizations in the last 12 months should be recorded and incorporated into the patient assessment.[15] Using this and other individual demographic information, a tailored chronic disease management strategy incorporating biopsychosocial (both non-pharmacological and pharmacological) interventions can be developed and implemented. There are a number of guidelines and recommendations that exist, and the treatment for chronic obstructive pulmonary disease will depend on resources available in the clinical setting.[14,15] In patients with cardiac arrhythmia, the use of beta2-agonist bronchodilators should be minimized, and tailored according to the nature of the cardiac rhythm disturbance. For example known, rate controlled and anticoagulated atrial fibrillation would not be seen in the same context as recurrent ventricular tachycardia. Preventing exacerbations of chronic obstructive pulmonary disease that result in the use of beta2-agonist bronchodilators should be a clinical goal.

Organization and delivery of care

Given the importance of timely diagnosis and optimal management of chronic obstructive pulmonary disease in people with cardiovascular risk factors and disease, there exists a greater need to optimize coordination between primary care, cardiology, and pulmonology. Traditional, discrete models of parallel referrals from primary care to separate cardiology and pulmonology specialists who themselves do not interact may impede optimal care. Alternative models of care should be explored including: multidisciplinary team discussions and virtual review; multi-speciality clinics for people presenting with undifferentiated breathlessness; inclusion (and contracting) of cardiopulmonary risk assessment in the annual chronic obstructive pulmonary disease review; early cardiopulmonary review following a moderate or severe chronic obstructive pulmonary disease exacerbation; and dedicated cardiopulmonary risk clinics. Allied health professionals, including pharmacists, specialist nurses, and certified respiratory educators, could be upskilled to enable the identification and initial management of cardiopulmonary risk in the community as well as at cardiology and respiratory clinics. Indeed, a chronic obstructive pulmonary disease care pathway can successfully be embedded in an existing cardiology outpatient clinic infrastructure (for example using microspirometry and remote analysis of results).

Pre-chronic obstructive pulmonary disease and relevance to cardiovascular risk assessment in chronic obstructive pulmonary disease

Pre-chronic obstructive pulmonary disease defines a large subgroup of high risk ever smokers with clinical or radiological features characteristic of chronic obstructive pulmonary disease, but not meeting traditional spirometric criteria showing airflow limitation. Although still the subject

of ongoing research, including from several large cohort studies (SPIROMICS, COPDGene, UKBiobank, and ACRIN), two spirometric defined subgroups have been identified; PRISm (preserved ratio impaired spirometry) and GOLD 0 (characterized primarily by non-obstructive chronic bronchitis). These subgroups have been shown to have elevated cardiovascular and all-cause mortality, likely through an increased prevalence of features of the metabolic syndrome (diabetes mellitus, hypertension, and obesity) and co-existing airways abnormalities.

Summary and future directions

We have developed a multidisciplinary, clinically-focused, consensus-based document detailing the internationally agreed definitions of cardiopulmonary events and cardiopulmonary risk in chronic obstructive pulmonary disease, as well as providing a blueprint for the identification and management of cardiopulmonary risk in people with chronic obstructive pulmonary disease. Adoption of this will facilitate high quality clinical research and reduce the burden of premature cardiovascular events in people with chronic obstructive pulmonary disease.

Patients with chronic obstructive pulmonary disease are at high risk for fatal and non-fatal major adverse cardiovascular and respiratory events—cardiopulmonary risk. Despite the clear epidemiologic links between these conditions, cardiovascular risk factors are often underdiagnosed and undertreated in patients with chronic obstructive pulmonary disease, and chronic obstructive pulmonary disease is often underdiagnosed and suboptimally managed in patients with cardiovascular disease.[12] Recognizing the opportunity to improve care and outcomes through greater attention to the connection between chronic obstructive pulmonary disease and the cardiovascular system, the Global Working Group on Cardiopulmonary Risk[13] in patients with chronic obstructive pulmonary disease herein provides a consensus statement on the identification and management of cardiopulmonary risk in patients with chronic obstructive pulmonary disease. In particular, we: (i) call for improved cardiopulmonary risk identification and stratification in chronic obstructive pulmonary disease; (ii) provide suggested clinical pathways and integrated models for identifying comorbid chronic obstructive pulmonary disease and cardiovascular disease in patients known to have either chronic obstructive pulmonary disease or cardiovascular disease but not the other; and (iii) highlight the importance of developing novel therapies and defining optimal treatment strategies and systems of care to reduce chronic obstructive pulmonary disease-associated cardiopulmonary risk.

As there are no contemporary international specialist society-based guidelines on addressing cardiovascular disease screening and management in patients with chronic obstructive pulmonary disease or chronic obstructive pulmonary disease screening and management in patients with cardiovascular disease, this document offers several consensus recommendations based on expert opinion. This statement should be viewed as a pragmatic guide for clinicians and a call to action to better understand and treat chronic obstructive pulmonary disease-associated cardiopulmonary risk rather than a definitive set of evidence-based guidelines. From an inaugural list of researchable questions published on behalf of the Global Working Group,[18] this document suggests priorities for future research studies and randomized clinical trials, and builds on other initiatives. Moreover, as reflected by the multidisciplinary backgrounds of its co-authors, this consensus statement acknowledges the importance of cross-disciplinary collaboration to expand our understanding of chronic obstructive pulmonary disease-associated cardiopulmonary risk and to broadly improve health outcomes.

We recognize the limitations of our work. There was unanimous agreement for the statement about the identification and management of cardiopulmonary risk in people with chronic obstructive pulmonary disease. It is possible that this may have arisen because the core Global Working Group was too small and/or the voting option was binary. We appreciate that the core working group did not represent low income countries. Nonetheless a free-text comments section was provided, and the consensus statements were reviewed by the Global Working Group of 100 international experts from a range of disciplines representing the range of World Bank income groups, with no call for revision or further voting. Equally, the modified Delphi process for the statement about the definition of cardiopulmonary events generated comments and discussion, which was addressed and taken to further voting. We acknowledge that the components of the composite term cardiopulmonary event include more cardiovascular outcome measures that respiratory outcome measures, and that this weighting could impact study outcomes.[27] Conversely, should acute exacerbations occur more frequently than stroke or a heart failure events, then a study using cardiopulmonary events as a composite primary outcome measure may realize its primary endpoint through the respiratory component rather than the cardiovascular components.

To our knowledge, this is the first comprehensive study of cardiopulmonary risk in chronic obstructive pulmonary disease. Adoption of our work will provide the opportunity to advance the field and improve chronic obstructive pulmonary disease care and outcomes.

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Author contribution

C.P.G. conceived the original idea, facilitated the modified Delphi process, and produced the skeleton of the manuscript. C.P.G. drafted the early content of the article. C.P.G. and M.B. co-ordinated the manuscript development and writing. C.P.G., J.R.H., and M.B. co-ordinated the wider Global Working Group. C.P.G., J.R.H., N.M.H., R.P.Y., D.D.B., and M.B. wrote sections of the article. F.J.M., D.Sz., S.Z., T.G., D.S., D.P., D.D.M., C.S.P.L., M.K.H., and J.B. provided iterative critical review and writing. R.N. provided critical review, and facilitated journal formatting and submission. All members of the core working group (C.P.G., J.R.H., N.H., J.B., M.K.H., C.S.P.L., D.D.M., D.P., D.Sz., S.Z., D.D.B., M.B.) contributed to the content and format of the article, and provided critical feedback and helped shape the final manuscript. All members of the Global Working Group read and were able to provide comments on the article in its draft state. All members of the Global Working Group read and agreed with the content of the final article.

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Data availability

No new data were generated or analysed in support of this research.

Appendix

Names of the 100 participants of the Global Working Group on Cardiopulmonary Risk in chronic obstructive pulmonary disease:

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Luís	Alves
Sameera	Ansari
Antonio	Anzueto
Felix	Barasa
David D.	Berg
Andy	Bevan
Mohit	Bhutani
Giuseppe	Biondi-Zoccai
Jean	Bourbeau
Raffaele	Bugiardini
Daniela	Calderaro
Arturo	Cortes-Telles
Michael G.	Crooks
Diego F.	Echazarreta
Nabil	Farag
Fredrico L.A.	Fernandes
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Maria C.	Gaviria
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Kari Hanne	Gjeilo
Ty	Gluckman
Martha	Gulati
MeiLan K.	Han
Nathaniel M.	Hawkins
Jeroen M.	Hendriks
John R.	Hurst
Anh-Thu	Huynh Dang
Majdy M.	Idrees
Tobin	Joseph
Nadim	Kanj
Ee Ming	Khoo
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Leonie	Klompstra
Martha	Kyriakou
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Claudia	Münks-Lederer
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Yoko M.	Nakao
Thu	Nguyen Ngoc Phuong
Johanna	O'Callaghan
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Alberto	Papi
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David	Price
Hany I.	Ragy
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Catherine	Reynolds
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Lavanya	Saiva
Juliana	Salas Segura
Julie	Sanders
Raewyn J.	Scott
Terence	Seemungal
Dinesh	Shrikrishna
Sami O.	Simons
Dave	Singh
Yuanlin	Song
Daiana	Stolz
Abirami	Subramaniam
Yongchang	Sun
Raj	Thakkar
Frederik	Trinkmann

Izabella	Uchmanowicz
Viola	Vaccarino
Lowie E.G.W.	Vanfleteren
Rajesh	Vedanthan
Tonya	Winders
Jianhua	Wu
Robert P.	Young
Jinping	Zheng
Min	Zhou
Shelley	Zieroth

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