

## **Title**

Major adverse cardiovascular events in COPD: Addressing Cardiopulmonary Risk

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### **An unhealthy partnership**

Both chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are major global public health burdens, responsible for 74.4 million and 393 disability-adjusted life years, respectively in 2019.(1)(2) Given shared exposures and risk factors such as but not limited to smoking, socioeconomic deprivation, diabetes, hypertension, low levels of exercise, and dyslipidaemia it is not surprising that many people living with COPD have CVD and vice versa. Patients with COPD are two to five times more likely to develop CVD compared with the general population.(4) When coexistent, CVD is associated with adverse prognosis in COPD, and it is estimated that about one in five patients with COPD will have a cardiovascular cause of death.(3) Unscheduled hospitalisation because of a cardiovascular event is not infrequent in patients with COPD. Notably, the magnitude of the association of cardiovascular hospitalisation with acute myocardial infarction, heart failure and angina is greater with increasing severity of COPD.(4)

Given the frequent co-existence of COPD with other multiple long-term conditions such as CVD, it has been proposed that a syndemic approach to COPD is undertaken. That is, a clinical approach that moves away from single disease management to an integrated care model where COPD is considered part of a multimorbid disease state(5) and a wider perspective on risk factors and disease are addressed to improve healthy longevity.

### **Exacerbating cardiovascular events**

Exacerbations of COPD are associated with cardiovascular events in COPD, and underlying CVD increases the severity of COPD exacerbations.(7) Indeed, the most frequent non-respiratory adverse outcome during and after an exacerbation of COPD is a cardiovascular event.(6) Early after an exacerbation the risk of myocardial infarction increases by over two fold, with a 30% increased risk of stroke within the 49 days after an exacerbation.(7) This highlights the importance of acknowledging and mitigating the risk of cardiovascular events in patients with COPD.

### **Gaps in the knowledge base**

There are fundamental gaps in knowledge that must be filled using robust clinical studies in order for us to improve the care and cardiovascular outcomes of patients with COPD. A

systematic and patient facing approach to the study of cardiovascular outcomes in COPD is recommended. Table 1 displays an inaugural list of key research questions that could catalyse advances in the management of patients with COPD to reduce major adverse cardiovascular events (MACE).

### **Cardiopulmonary risk in COPD**

Higher resolution insights into the MACE experienced by patients with COPD can only be realised if we consider adverse events in both the lung and cardiovascular system as a disease specific entity. Given that patients with COPD also experience major pulmonary events –exacerbations - it is recommended that the term cardiopulmonary risk is used to emphasise the need to identify and manage patients with COPD such that cardiovascular and pulmonary sequelae are minimised in parallel. Cardiopulmonary risk is the chance that a patient with COPD has of experiencing a major adverse cardiovascular and/or respiratory event, including but not limited to acute coronary syndrome, heart failure, arrhythmia (such as atrial fibrillation and ventricular tachycardia), stroke, cardiovascular death and exacerbation of COPD. Cardiopulmonary risk could be classified as high, medium, low, and residual for patients with COPD according to phenotype and concurrent treatment. Understanding the extent and nature of major adverse cardiovascular and respiratory events in COPD (and therefore identifying scientific and clinical approaches to reduce cardiopulmonary risk) is central to reducing the cardiovascular sequelae of COPD.

However, this opportunity has not been realised, Typically, guideline recommended risk scores, including the Framingham risk score, Pooled Cohorts' Equations (PCE), Reynolds risk score, SCORE, JBS3 and QRISK3, for the estimation of future CVD in individuals without previous CVD, none of which include COPD as a predictor.(8–11) Moreover, a UK nationwide incident COPD cohort study of 13208 patients found the observed 10-year risk of CVD was 52% higher than that predicted by QRISK3, indicating that even when CVD risk is assessed, its magnitude is underestimated. The Canadian Cohort of Obstructive Lung Disease CanCOLD found that people with COPD were on average at a two-fold higher risk of developing CVD compared to individuals with normal spirometry, and the PCE or Framingham risk score did not improve the prediction of CVD among those with impaired spirometry despite it being an independent risk factor for CVD.(12) Although scores have

been developed to predict the risk of exacerbation, neither the ADO score or BODE includes co-morbidities and CVD, and there is a lack of validated and accurate risk score tools for the prediction of future cardiopulmonary events in patients with COPD.(13,14)

### **COPD is a multimorbid disease associated with MACE**

Healthcare professionals must consider COPD as a multimorbid disease, closely associated with MACE, in the same way as is achieved for people with diabetes or chronic kidney disease. Ultimately, smoking prevention and smoking cessation will reduce the incidence of COPD and CVD, and this should be the foundation of any strategy to reduce cardiopulmonary risk and MACE. Aligned to this is the need to decrease levels of indoor and outdoor air pollution and increase healthy lifestyles and aerobic exercise (for example with rehabilitation). Early and accurate prediction, detection, diagnosis and treatment of cardiovascular risk factors such as hypertension, dyslipidaemia, diabetes, obesity and atrial fibrillation will actively contribute to improved cardiovascular outcomes in patients with COPD. Indeed, each clinical review with a patient with COPD is a touchpoint offering an opportunity to holistically estimate cardiopulmonary risk, identify and mitigate cardiovascular risk factors, optimise COPD treatment and manage established CVD. Furthermore, the rising health care burden of COPD reflects only those patients with physician-diagnosed disease. Data suggest the true impact of COPD may be largely underestimated, and consequently exacerbation events likely contribute much more than previously thought to the overall burden of COPD and CVD.(15) Shared pathways across cardiology and respiratory medicine with a greater awareness in primary care will afford this. Guidelines for the care of patients with COPD should draw a wider perspective to address CVD and the prevention of cardiovascular events.

### **Tackling COPD together**

Addressing MACE in patients with COPD requires a multidisciplinary approach, investing in and integrating expertise from primary care, pulmonologists and cardiologists. Importantly, it is patients with mild to moderate COPD who are at greatest risk for cardiovascular related deaths, suggesting that the integrated care model be initiated at COPD diagnosis outset. Nonetheless, such an approach would be inefficient without a parallel effort from research funding organisations and policy makers. Healthcare professionals provide a key role in the

early detection and treatment of COPD, and this may be extended to the assessment and management of cardiopulmonary risk. Delivering integrated care models that consider both COPD and CVD will help achieve this outcome. Increased funding directed to multidisciplinary research about CVD in COPD is long overdue, and without which novel therapeutic approaches cannot be accomplished. Policy level interventions are essential to ban smoking, promote healthy lifestyle interventions, deliver cardiopulmonary rehabilitation, facilitate comprehensive COPD care, and accelerate integrated care models between primary care, cardiologists and pulmonologists.

**Table 1.** Researchable questions to address the cardiovascular sequelae of COPD.

Researchable question	Design
<i>Measuring and predicting cardiovascular risk in COPD</i>	
Do acute cardiovascular events increase the risk and severity of a future exacerbation of COPD?	Retrospective cohort study linked to clinical outcomes Prospective cohort study linked to clinical outcomes
What is the natural course of incident comorbidity and cardiovascular risk in people with COPD?	Longitudinal study
Is the onset of atrial fibrillation in smokers and people with COPD a surrogate marker for COPD/COPD stage and or subsequent cardiovascular events, or is incident atrial fibrillation a standalone disease in smokers and people with COPD?	Longitudinal study Retrospective cohort study Imaging study Prospective cohort study
What proportion of patents with COPD have undetected CVD, and if detected are under treated?	Prospective cohort study linked to clinical outcomes
What are the modes of death in patients with COPD, does this vary by stage of COPD, and can this be predicted?	Mechanistic study Longitudinal study Retrospective cohort study linked to clinical outcomes
What proportion of patients with CVD have undetected COPD, and if detected under treated?	Longitudinal study Prospective cohort study linked to clinical outcomes
Can we quantify and categorise levels of cardiopulmonary risk in patients with COPD?	Retrospective cohort study linked to clinical outcomes Longitudinal study

	Real world study
To what extent is COPD a cardiovascular risk equivalent, and what COPD phenotypes correspond to which levels of cardiovascular event risk?	Retrospective cohort study linked to clinical outcomes
<i>Biological mechanisms driving increased cardiovascular risk in COPD</i>	
What are the anatomical and functional characteristics of people with COPD who develop major cardiovascular events, and vice versa?	Imaging study Longitudinal study
Can we detect early sub clinical features of heart failure in patients with COPD?	Imaging study Biomarker study
Can we identify biomarkers that predict cardiovascular events in COPD?	Biomarker study
<i>Intervening to reduce cardiovascular events in COPD</i>	
Can we identify and manage sub optimally treated high risk COPD to reduce exacerbations and MACE?	Randomised controlled trial
Can a risk score to predict cardiovascular events be developed using routinely collected primary care data, and does its implementation change practice and benefit outcomes?	Retrospective cohort study linked to clinical outcomes Prospective cohort study linked to clinical outcomes Randomised clinical trial
Does cardiac intervention on lung CT identified coronary calcification reduce cardiovascular events in patents with COPD?	Prospective cohort study linked to clinical outcomes Randomised clinical trial
Can a breathless pathway be designed and implemented that efficiently diagnoses COPD and or CVD to enable earlier treatment?	Prospective cohort study linked to clinical outcomes Randomised clinical trial



Does triple therapy with an inhaled corticosteroid reduce cardiovascular events in patients with COPD?	Randomised clinical trial
Does profiling hospital performance with audit and feedback for COPD care reduce admissions with CVD?	Prospective cohort study linked to clinical outcomes
Does treatment with biologics reduce cardiovascular events in patients with COPD?	Randomised clinical trial
Does optimising cardiovascular risk improve COPD outcomes?	Prospective cohort study Randomised clinical trial
Do specific endotypes or phenotypes of COPD exhibit varied responses to pharmacological therapy for CVD?	Randomised clinical trial Prospective cohort study

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