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COPD as a Risk Factor for Cardiovascular Disease: A View from the SUMMIT

John R. Hurst (1)

Don D. Sin (2)

1. UCL Respiratory Medicine, University College London, London, UK
2. Centre for Heart Lung Innovation, St. Paul's Hospital & Division of Respiratory Medicine, University of British Columbia, Vancouver, BC, Canada

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Cardiovascular diseases (CVDs) are a common co-morbidity among patients with chronic obstructive pulmonary disease (COPD) with prevalence estimates ranging from 30 to 60% in "real-world" studies (1). CVDs have adverse consequences for COPD patients by reducing their quality of life, increasing their risk of exacerbations, prolonging exacerbations and hospitalizations and contributing to their premature mortality (2). Indeed, most large studies suggest that 30 to 50% of deaths in patients with COPD are primarily driven by the patients' underlying CVDs, though establishing clear causality of deaths is extremely challenging (3, 4). Furthermore, it is recognized that people living with COPD do not always benefit from effective primary and secondary prevention including the appropriate use of beta-blocker drugs (1).

While the importance of CVDs in COPD has been well established, COPD as a risk factor for CVDs is less well known. Not surprisingly, most major CVD consensus guidelines do not list COPD as an important risk factor for CVDs (5). Whilst some cardiovascular (CV) risk prediction such as QRISK (https://qrisk.org/) include selected chronic inflammatory conditions such as rheumatoid arthritis, COPD is not included (6). Although previous studies have shown that reduced lung function is associated with future risk of CV events including myocardial infarction (MI), heart failure, and sudden deaths even among life-time non-smokers, how (and why) this occurred is largely unknown (7). Kunisaki and colleagues performed a secondary analysis of the Study to Understand Mortality and MorbidITy (SUMMIT) trial to fill in some critical gaps in knowledge regarding the relationship of COPD with CVDs (8). They showed that CVD events occurred mostly during periods of acute exacerbations (AECOPD) with the highest risk occurring within the first 30 days of AECOPD (relative risk, RR, 3.8) and with the risk returning to baseline levels at 1 year post-AECOPD. The risk was particularly notable when the presentation of the AECOPD event – a composite of the severity of the underlying COPD and of

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the trigger - was severe enough to warrant a hospitalization. Remarkably, with these serious AECOPDs, the RR of a CV event was 10-fold higher in the first 30 days post-hospitalization.

Although such associations have been previously reported (9), there were strengths to the SUMMIT trial that addressed many of the concerns of previous epidemiological and clinical studies that have been published on this topic (1). First, SUMMIT's sample size was impressively large (n=16,485) and international and the investigators enrolled patients with co-existing CVD or who had a high risk of CVD, which provided sufficient power to dynamically estimate the risk of CV events following AECOPDs. Second, there was careful follow-up of patients with a face-to-face review, which occurred every 3 months over a median follow-up of 1.5 years, ensuring complete and accurate ascertainment of CV events and AECOPD. Third, the investigators used a well-established and accepted definition of AECOPD and most importantly objectively adjudicated all CV events using standardized protocols, which minimized the risk of misclassification that could have biased the results. Fourth, the investigators enrolled patients with COPD using well-accepted spirometric and clinical criteria dissimilar to many previous large studies that relied on reduced lung function alone (without exposure or symptoms) or on physician or self-reported diagnosis of COPD, which could have led to diagnostic misclassification.

SUMMIT also has had some limitations. The most notable was that SUMMIT was not powered on CVD events; it was a clinical trial, powered on total mortality. As such, some important information regarding AECOPD was not captured. Although SUMMIT and other studies considered AECOPD as a distinct entity, in reality, the causes of AECOPDs are heterogeneous. Viral respiratory tract infections are thought to be the most common triggers for AECOPD; however, in a large number of cases, the etiology of AECOPD is non-infectious or unknown.

Indeed, it is possible that some of the AECOPD events in SUMMIT could have been due to congestive heart failure or myocardial ischemia. To this end, data on cardiac troponins, or brain natriuretic peptide along with information on sputum cultures and thoracic computed tomography scans (to rule out pulmonary embolism or pneumonia) would have been invaluable in determining the etiology of symptom deteriorations labelled as AECOPDs in SUMMIT. In addition, SUMMIT only recruited people with COPD between FEV_1 50 and 70% predicted limiting generalizability, especially in those admitted to hospital. Finally, these data do not inform on the underlying mechanism of interaction between AECOPD and CVD events. Only by understanding this – systemic inflammation, pro-coagulant status or hypoxia to name but three possibilities – can we hope to design rational trials to mitigate this risk.

Notwithstanding these limitations, Kunisaki and colleagues' analysis provides compelling evidence that COPD is a significant risk factor for CV events, especially during AECOPDs. We postulate that the risk of CV in COPD is, at least in part, due to persistent airway inflammation, which increases sharply during AECOPDs that are driven by viral or bacterial infections. Using a large health database in Ontario, Canada, Kwong et al showed that acute viral respiratory tract infections especially from influenza was associated with a 6 to 10-fold increase in the risk of MI during the first 7 days of infection compared to baseline (non-infectious) periods (10). These data are also consistent with those of Smeeth et al which showed increased risk of MI and stroke following respiratory tract infections (either viral or bacterial) (11). These epidemiological data are supported by experimental results, which showed that acute airway exposure of lipopolysaccharide (LPS), a bioactive component of cell wall of gram negative bacteria, which have also been implicated in AECOPD, in mice leads to acute atherosclerotic plaque rupture (12). In this study, inhibition of neutrophils or its component, myeloperoxidase, prevented plaque

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rupture related to acute intratracheal LPS exposure, suggesting a crucial role of neutrophil activation in this process.

What have we learned from this SUMMIT analysis and, more importantly, how do we improve health outcomes of our patients with COPD using this information? The SUMMIT data raise the possibility that by preventing or reducing the severity of AECOPDs, we may be able to reduce CV events, though it was disappointing that neither inhaled corticosteroids (ICS) nor long-acting beta 2 agonists (LABA) by themselves or in combination significantly reduced CV events or mortality in this trial. Nevertheless, reducing AECOPD should be a primary goal for patients with frequent exacerbations. To this end, annual influenza vaccination, which reduces both AECOPD and CV events, should be rigorously recommended for all patients with COPD (13). SUMMIT also raises the possibility of using cardioprotective medications such as aspirin, statins or beta-blockers for patients with COPD and co-existing CVDs or at high risk of CVDs. Several studies are currently underway to address this critical question. Until these results are available, we believe that all patients with COPD should be assessed for cardiovascular risk (if they do not already have a coexisting CVD) and be treated with appropriate cardio-protective medications when the risk is deemed sufficiently high. Furthermore, given the high prevalence of coexisting CVD in the COPD patient population in the real-world, these patients should not be excluded in any therapeutic trials to ensure that the results are applicable to these patients.

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