

Exacerbating the burden of cardiovascular disease

Shrikrishna, Dinesh; Taylor, Clare J; Stonham, Carol; Gale, Chris P

DOI:

[10.1093/eurheartj/ehad669](https://doi.org/10.1093/eurheartj/ehad669)

License:

Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Shrikrishna, D, Taylor, CJ, Stonham, C & Gale, CP 2023, 'Exacerbating the burden of cardiovascular disease: how can we address cardiopulmonary risk in individuals with chronic obstructive pulmonary disease?', *European Heart Journal*. <https://doi.org/10.1093/eurheartj/ehad669>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.


Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Global Spotlights

Exacerbating the burden of cardiovascular disease: how can we address cardiopulmonary risk in individuals with chronic obstructive pulmonary disease?

Dinesh Shrikrishna ^{1*}, Clare J. Taylor², Carol Stonham^{3,4}, and Chris P. Gale^{5,6,7}

¹Department of Respiratory Medicine, Musgrove Park Hospital, Somerset NHS Foundation Trust, Parkfield Drive, Taunton TA1 5DA, UK; ²Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK; ³Primary Care Respiratory Society (PCRS), London, UK; ⁴NHS Gloucestershire Integrated Care Board, Gloucester, UK; ⁵Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; ⁶Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK; and ⁷Leeds Institute for Data Analytics, University of Leeds, Leeds, UK

Received 21 September 2023; accepted 26 September 2023

Cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) often co-exist.^{1,2} This is not surprising given their shared risk factors including, but not limited to, smoking, hypertension, dyslipidaemias, atrial fibrillation, physical inactivity, and air pollution. Evidence from the EURObservational Research Programme Heart Failure Long-Term Registry showed that prevalence of diagnosed COPD amongst individuals admitted with heart failure may be up to 19%, based on analysis of 6920 individuals hospitalized with heart failure.¹ Similarly, there is a reciprocal association with CVD in individuals with COPD. Data from the Julius General Practitioners' Network, a collaboration of nearly 70 general practices in the Netherlands with ~370 000 registered patients, demonstrated a 3-fold increased incidence of heart failure and 1.7-fold increased incidence of ischaemic heart disease in individuals with COPD.² In reality, these figures are likely to be underestimated because in the UK alone, reports estimate that there could be up to 2 million individuals with undiagnosed COPD,³ suggesting that many patients with potentially high CVD risk remain undetected and untreated.

In individuals with coexisting CVD and COPD, the risk of adverse clinical events is increased above that of each comorbidity in isolation. Mortality risk among those with both conditions is increased by up to 90% compared with those who have COPD alone,⁴ and approximately one-third of all COPD deaths could be cardiovascular in origin. It is well documented that acute exacerbations of COPD (AECOPDs) accelerate lung function decline and increase the risk of further acute events and premature mortality. An AECOPD also increases the risk of major

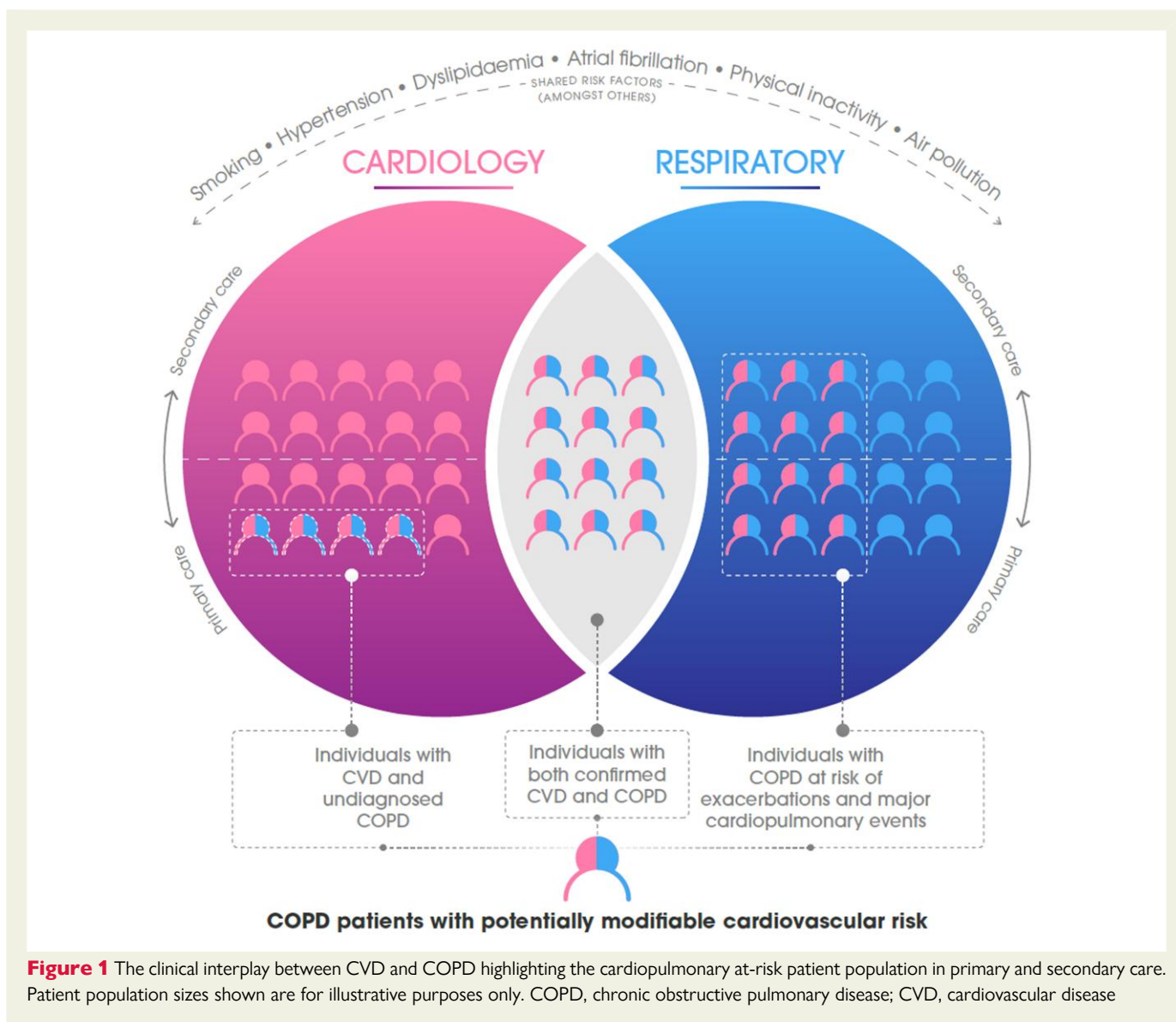
cardiovascular events in patients; up to 5 days following a moderate AECOPD, the risk of myocardial infarction (MI) is doubled, and at 6–10 days, the risk of stroke is reported to be increased by 40%.⁵ Moreover, it is estimated that in the first 30 days following a moderate or severe AECOPD, the risk of any cardiovascular event may be increased by up to four times and persists for a year, albeit attenuating over time.⁶ Recent data from the retrospective EXAcerbations of COPD and their OutcomeS on CardioVascular diseases (EXACOS-CV) US healthcare claims database of individuals with COPD ($n = 355\,978$), found that the risk of acute cardiovascular events in the first 30 days following an AECOPD of any severity may be increased by over 30% compared with those who did not have an AECOPD.⁷ Whilst the mechanisms underpinning how an AECOPD contributes to elevated cardiovascular risk require further research, it is clear that exacerbating individuals are at significant risk of both major pulmonary and cardiovascular events (cardiopulmonary risk). Optimized management of this group presents an important opportunity to improve COPD outcomes and reduce cardiovascular morbidity and mortality at a population level.

Despite the burden of COPD and impact of even a single moderate AECOPD on short- and long-term outcomes, current COPD care remains suboptimal with care pathways that are often reactive rather than proactive in approach. Less than a quarter of patients in the UK receive all five of the National Institute for Health and Care Excellence fundamentals of COPD care (smoking cessation, vaccination, pulmonary rehabilitation, personalized self-management planning and optimized

* Corresponding author. Tel: +01823 342146, Email: dinesh.shrikrishna@nhs.net

© The Author(s) 2023. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com



comorbidity treatment).³ Additionally, over a third of patients hospitalized with a first severe AECOPD are discharged without appropriate maintenance treatment.⁸ This is concerning given that two recent randomized clinical trials have demonstrated improvement in cardiopulmonary risk in individuals with COPD with a history of AECOPDs, reporting a reduction in mortality in those allocated to single-inhaler triple therapy with an inhaled corticosteroid (ICS), long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA) vs. dual therapy with a LABA/LAMA.^{9,10} Of note, data from the ETHOS trial suggested that this mortality reduction may be driven by a decline in cardiovascular deaths.⁹ Post hoc analysis also showed a lower major adverse cardiac event (MACE) incidence with ICS-containing therapy (1.4%) vs. therapy without ICS (2.1%). This difference in MACE rates on fatal cardiovascular events and non-fatal MI was more pronounced with a higher baseline eosinophil count.¹¹ Post hoc analysis of the IMPACT trial has also demonstrated a reduced risk of cardiopulmonary composite events (including exacerbations, pneumonia, cardiovascular events, and death) in individuals allocated to single-inhaler triple therapy vs. LABA/LAMA.¹⁰ Notably, this growing body of evidence has been reflected in the 2023

international consensus from the Global Initiative for Chronic Obstructive Lung Disease that recommends targeting mortality reduction in individuals with COPD.

The recent Lancet Commission on COPD outlined objectives to eliminate the disease and argued for a 'fundamental change' in thinking about COPD.¹² Notwithstanding the importance of treating tobacco dependency and other contributing pulmonary and cardiovascular risk factors in COPD, increased prioritization and treatment optimization to prevent AECOPDs and associated cardiopulmonary risk presents an important target for healthcare improvement (Figure 1). More evidence from real-world and randomized clinical trials could reinforce existing findings and generate new insights into how cardiovascular events may be reduced in AECOPDs.

Strategies to achieve this may include increased awareness and advocacy for treatment optimization for individuals with confirmed comorbid disease; identifying and investigating individuals with CVD who are suspected to have comorbid COPD; and proactive identification and treatment of individuals with COPD at risk of an AECOPD. Enhanced interdisciplinary working between cardiovascular,

respiratory, and integrated primary care services is also key to transforming COPD care pathways. Collaborative working has already seen success across cardiovascular, renal, and metabolic disciplines, and a similar partnership approach should be adopted across cardiology and respiratory care. This could improve patient outcomes with shared-goal treatment pathways across COPD and CVD.

Acknowledgement of this unmet need has inspired partnership working in the UK (The UK Cardiopulmonary Taskforce) to develop collaborative links between a multidisciplinary group of cardiac and respiratory healthcare professionals from primary and secondary care to understand and manage cardiopulmonary risk in COPD. This approach will help inform future clinical, academic, and policy approaches to improve cardiovascular care and outcomes for people with COPD—setting the scene for European initiatives to reduce premature deaths from cardiovascular disease.

Acknowledgements

The UK Cardiopulmonary Taskforce is supported by AstraZeneca. Medical writing support including formatting of figure schematic was provided by Lucid Group and funded by AstraZeneca.

Declarations

Disclosure of Interest

D.S.: Consultancy and speaker fees from AstraZeneca, GSK, Boehringer Ingelheim, Chiesi, Pfizer, and Teva. C.J.T.: Consultancy fees from Roche, AstraZeneca, and Bayer. C.S.: Unconditional honoraria via Ltd company for delivery of education from AstraZeneca, Bedford, Boehringer Ingelheim, Chiesi, GSK, Teva, and Trudell. C.P.G.: Consultancy work/advisory board/speaker fees from Al Nexus Inc., Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Cardiomatics, Chiesi, Daiichi Sankyo, GPR1 Research B.V., iRhythm, Medisetter, Menarini, Organon, Raisio Group, Wondr Medical, and Zydus; grants from the British Heart Foundation, National Institute for Health Research, Horizon 2020, Abbott Diabetes, and Bristol Myers Squibb; Deputy Editor for *European Heart Journal Quality of Care and Clinical Outcomes*, Oxford

University Press; leadership roles: NICE Indicator Advisory Committee, Chair ESC Quality Indicator Committee, and Chair Data Science Group, EuroHeart; and patent in consideration: FIND-AF D.

References

- Canepa M, Straburzynska-Migaj E, Drozd J, Fernandez-Vivancos C, Pinilla JMG, Nyolczas N, et al. Characteristics, treatments and 1-year prognosis of hospitalized and ambulatory heart failure patients with chronic obstructive pulmonary disease in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur J Heart Fail* 2018;**20**:100–10. <https://doi.org/10.1002/ehf.964>
- Groenewegen A, Zwartkruis VW, Smit LJ, de Boer RA, Rienstra M, Hoes AW, et al. Sex-specific and age-specific incidence of ischaemic heart disease, atrial fibrillation, and heart failure in community patients with chronic obstructive pulmonary disease. *BMJ Open Respir Res* 2022;**9**:e001307. <https://doi.org/10.1136/bmjresp-2022-001307>
- Asthma + Lung UK. *COPD in the UK: Delayed Diagnosis and Unequal Care*. Available at: <https://www.asthmaandlung.org.uk/sites/default/files/2023-03/delayed-diagnosis-unequal-care.pdf> (September 2023, date accessed).
- Miller J, Edwards LD, Agustí A, Bakke P, Calverley PMA, Celli B, et al. Comorbidity, systemic inflammation, and outcomes in the ECLIPSE cohort. *Respir Med* 2013;**107**:1376–84. <https://doi.org/10.1016/j.rmed.2013.05.001>
- Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010;**137**:1091–7. <https://doi.org/10.1378/chest.09-2029>
- Kunisaki KM, Dransfield MT, Anderson JA, Brook RD, Calverley PMA, Celli BR, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT randomised clinical trial. *Am J Respir Crit Care Med* 2018;**198**:51–7. <https://doi.org/10.1164/rccm.201711-2239OC>
- Daniels K, Tave A, Neikirk A, Nordon C, Rhodes K, Mannino DM, et al. Incidence of severe cardiovascular events following acute exacerbation of chronic obstructive pulmonary disease in a large claims database. *Am J Respir Crit Care Med* 2023;**207**. https://doi.org/10.1164/ajrccm-conference.2023.207.1_MeetingAbstracts.A3331
- Janson C, Nwaru BI, Wiklund F, Telg G, Ekström M. Management, and risk of mortality in patients hospitalised due to a first severe COPD exacerbation. *Int J Chron Obstruct Pulmon Dis* 2020;**15**:2673–82. <https://doi.org/10.2147/COPD.S276819>
- Martinez FJ, Rabe KF, Ferguson GT, Wedzicha JA, Singh D, Wang C, et al. Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for chronic obstructive pulmonary disease. A randomised, double-blind, multicenter, parallel-group study. *Am J Respir Crit Care Med* 2021;**203**:553–64. <https://doi.org/10.1164/rccm.202006-2618OC>
- Wells JM, Criner GJ, Halpin DMG, Han MK, Jain R, Lange P, et al. Mortality risk and serious cardiopulmonary events in moderate-to-severe COPD: post-hoc analysis of the IMPACT trial. *Chronic Obstr Pulm Dis* 2023;**10**:33–45. <https://doi.org/10.15326/jcopdf.2022.0332>
- Bafadhel M, Rabe KF, Singh D, Jenkins M, Dorinsky P, Patel M. The relationship between eosinophils and reduction in major adverse cardiac events in ETHOS. *Eur Respir J* 2021;**58**:R208. <https://doi.org/10.1183/13993003.congress-2021.R208>
- Stolz D, Mkorombindo T, Schumann DM, Agustí A, Ash SY, Bafadhel M, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet* 2022;**400**:921–72. [https://doi.org/10.1016/S0140-6736\(22\)01273-9](https://doi.org/10.1016/S0140-6736(22)01273-9)