Cardiovascular disease and COPD: dangerous liaisons?

Klaus F. Rabe1,2, John R. Hurst3 and Samy Suissa4,5

Affiliations: 1Dept of Medicine, University of Kiel, Kiel, Germany. 2Lung Clinic Großhansdorf, Airway Research Center North (ARCN), Großhansdorf, Germany. 3Centre for Inflammation and Tissue Repair, Division of Medicine, University College London, London, UK. 4Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada. 5Dept of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada.

Correspondence: Klaus F. Rabe, LungenClinic Großhansdorf, Airway Research Center North, Woehrendamm 80, Großhansdorf 22927, Germany. E-mail: k.f.rabe@lungenclinic.de

CVD and COPD are often comorbid. Their pathophysiology and treatment may affect each other and health outcomes.

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ABSTRACT Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) frequently occur together and their coexistence is associated with worse outcomes than either condition alone. Pathophysiological links between COPD and CVD include lung hyperinflation, systemic inflammation and COPD exacerbations. COPD treatments may produce beneficial cardiovascular (CV) effects, such as long-acting bronchodilators, which are associated with improvements in arterial stiffness, pulmonary vasoconstriction, and cardiac function. However, data are limited regarding whether these translate into benefits in CV outcomes. Some studies have suggested that treatment with long-acting β2-agonists and long-acting muscarinic antagonists leads to an increase in the risk of CV events, particularly at treatment initiation, although the safety profile of these agents with prolonged use appears reassuring. Some CV medications may have a beneficial impact on COPD outcomes, but there have been concerns about β-blocker use leading to bronchospasm in COPD, which may result in patients not receiving guideline-recommended treatment. However, there are few data suggesting harm with these agents and patients should not be denied β-blockers if required. Clearer recommendations are necessary regarding the identification and management of comorbid CVD in patients with COPD in order to facilitate early intervention and appropriate treatment.

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disorder characterised by chronic airflow limitation and an increased inflammatory response of the lung [1]. COPD is associated with many comorbidities [2, 3] (figure 1) and can be one of multiple chronic or acute diseases and medical conditions present within one person [4]. In particular, cardiovascular disease (CVD) and COPD share similar risk factors such as ageing, history of cigarette smoking (or other exposures) and a sedentary lifestyle, and frequently coexist [2, 3, 5].

Historically, many terms and definitions have been inconsistently used to describe the co-existence of diseases [6]. Recently, it was proposed that the term “index disease” should be used to describe the main condition of interest and “comorbidity” for any other medical conditions present at diagnosis of the index disease or later [6]. By contrast, “multimorbidity” is defined simply as the co-existence of two or more chronic diseases [6, 7].
Patients with comorbid COPD and CVD experience high rates of morbidity, including worse quality of life, dyspnoea and exercise tolerance [8], and a higher risk of hospitalisation for COPD and for CVD [9]. In addition, the presence of CVD or cardiovascular (CV) conditions (such as heart failure (HF), ischaemic heart disease (IHD), diabetes or atrial fibrillation (AF)) increases the risk of frequent exacerbations [10] and mortality [2, 8, 11] (figure 2). Further, COPD exacerbations and lung function decline are associated with increased CV risk and mortality [12, 13]. To minimise the risk of poor outcomes, it is therefore important to ensure that patients with comorbid COPD and CVD are managed effectively. However, drug therapies for COPD could have both beneficial and potential adverse effects on CVD and vice versa.

In the current review we provide a brief overview of key pathophysiological mechanisms, which may help explain comorbid COPD and CVD and inform the rationale for treatment. In the light of the plethora of recent literature considering the CV risks of pharmacotherapy in patients with COPD [14–18] we then provide a synthesis of the research from clinical trials and observational studies to establish the evidence for the main classes of drugs used to treat COPD and CVD. Finally, reflecting on our findings, we make some recommendations for the management of COPD patients with CVD.

Pathophysiological links between COPD and CVD
The mechanisms which underlie the association between COPD and CVD are not well understood but several processes are thought to be important and may interact with each other [19, 20]. These include...
lung hyperinflation, hypoxaemia, pulmonary hypertension (PH), systemic inflammation and oxidative stress, exacerbations, shared risk factors and shared genetics (figure 3), as well as COPD phenotype.

Hyperinflation, characterised by abnormally elevated residual gas in the lungs following spontaneous exhalation [21], is a major driver of COPD burden and mortality [1]. It is the cardinal pathophysiological mechanism affecting the mechanics of breathing and can be either static (resulting from destruction of the lung parenchyma and subsequent loss of lung elastic recoil) or dynamic (occurring when a patient inhales...
before exhaling fully, trapping air with each additional breath) [21]. Hyperinflation significantly reduces the efficiency of the respiratory muscles [22] and is increasingly recognised as a major cause of dyspnoea (shortness of breath) [23].

Abnormal lung function, including hyperinflation, is also thought to compromise cardiac function through various means [24]. Notably, airflow limitation caused by lung hyperinflation may cause increased pressures in the cardiopulmonary system, right-ventricular dysfunction, impaired left-ventricular filling and reduced cardiac output (QT) [25–29]. Emphysema is associated with static hyperinflation [30] and hyperinflation may therefore be a key risk factor for CVD in patients with emphysema-predominant COPD. In addition, progressive airflow limitation and emphysema in COPD lead to ventilation/perfusion mismatch that is a key contributor to the development of hypoxaemia, which can be further exacerbated by exercise and sleep disordered breathing [31]. Hypoxaemia in patients with COPD can lead to pulmonary vasoconstriction and vascular remodelling, resulting in right-ventricular diastolic dysfunction [32]. Indeed, PH, common in patients with severe COPD, can lead to right HF, which is in turn associated with left HF [33, 34]. In addition, altered cardiac repolarisation in patients with COPD may be related to hypoxaemia and could increase the risk of ventricular arrhythmias and sudden cardiac death [35].

Chronic or intermittent hypoxia may also increase systemic inflammation, which is known to play a role in the pathogenesis of CVD [36, 37] and has been linked to the development of arterial stiffness which has a strong predictive value for CV events [38]. Markers of pulmonary inflammation (such as surfactant protein D) and of systemic inflammation (such as C-reactive protein (CRP)) are elevated in patients with stable COPD [8, 39–41], while patients with COPD and CVD have higher blood concentrations of inflammatory markers, such as fibrinogen, interleukin (IL)-6 and IL-8, than those without CVD [8]. Moreover, coronary artery calcification scores (a marker of coronary atherosclerosis) correlate with markers of systemic and pulmonary inflammation, such as IL-6, IL-8, surfactant protein D and peripheral blood neutrophil count, in patients with COPD [42]. These findings suggest that COPD is either a systemic inflammatory state or that inflammatory processes spill over from the lungs into the systemic circulation [43], contributing to the development of CVD.

The occurrence of COPD exacerbations has been shown to increase the risk of subsequent CV events in patients with CVD or CV risk factors [44]. This may be related to lung inflammation which is heightened during COPD exacerbations [24]. Furthermore, lower respiratory tract infections, a common cause of COPD exacerbation, are associated with increased inflammatory markers such as fibrinogen and IL-6 which are linked with thrombosis and CV events [12, 45]. High levels of inflammation and oxidative stress that occur during and after an exacerbation may reduce circulating CD34+ cells (which are involved in vascular repair) and increase platelet activation and arterial stiffness [45–49]. Of note, the sudden increase in airway resistance increases that occurs during an exacerbation further limits expiratory flow and lung emptying. Consequently, patients experiencing an exacerbation tend to adopt a rapid, shallow breathing pattern, resulting in a vicious cycle of diminishing lung emptying time and increasing dynamic hyperinflation [22].

The source of CVD risk may be associated with the dominance of either chronic bronchitis or emphysema within the COPD disease profile. The presence of emphysema may reflect accelerated ageing of the lung, which may also result in HF due to downregulation of anti-ageing molecules such as sirtuins [50], while the presence of chronic bronchitis could reflect a distinct inflammatory subtype of COPD requiring specific anti-inflammatory interventions. The genetic background of chronic bronchitis and emphysema also differ, which may influence the processes underlying the association between COPD and CVD [51].

The physiological effects of CVD, for example HF-associated dyspnoea (due to pulmonary oedema) and reduced exercise capacity (due to reduced QT and impaired perfusive and diffusive oxygen transport) [52, 53] may add to the effects of COPD caused by “pulmonary” mechanisms (dyspnoea due to hyperinflation and resulting exercise avoidance and deconditioning [1]). In HF, cardiomegaly may be involved in causing a restrictive lung pattern and reduced alveolar volume [54], with alveolar gas diffusion progressively worsening due to reduction in the lung tissue participating in gas exchange [55]. Ventilatory response to exercise is greater than normal for a given metabolic rate, due to an increase in physiological dead space to tidal volume ratio (driven by high ventilation/perfusion mismatching, increased carbon dioxide production relative to oxygen uptake from lactate buffering and a decrease in partial pressure of carbon dioxide) [56]. The clinical consequences are illustrated in a study in which patients with COPD and IHD had significantly worse health status, dyspnoea and exercise capacity than those without IHD; additionally, although exacerbations were not more frequent, recovery time was longer in those with IHD [57]. CVD is also a leading cause of hospitalisation and mortality in patients with COPD [9].
Although the causal or consequential role of associated systemic inflammation is still not clear in COPD [58, 59], as described earlier, there are a number of mechanisms by which COPD-associated systemic inflammation could contribute to CVD and low-grade systemic inflammation in patients with airflow obstruction has been associated with increased risk of cardiac injury [40]. Systemic inflammation is also a feature of CVD, likely playing a role in its development and progression [60]. While the effect of COPD-associated systemic inflammation on COPD is unknown, a study in COPD patients with and without hepatitis C found a steeper decline in lung function with hepatitis C versus controls [61], suggesting an effect on the lungs due to systemic inflammation. Furthermore, risk factors of systemic and vascular inflammation, such as visceral obesity, diabetes and inactivity are also associated with reduced pulmonary function, airway hyper-reactivity and eventually COPD [58], supporting the idea that systemic inflammation associated with CVD may affect COPD.

In summary, many of the pathophysiological mechanisms underlying COPD may increase the risk of CVD and vice versa; however, more studies are needed to provide evidence that the mechanisms uncovered are relevant to the clinical manifestations of these diseases when they occur together.

Pharmacological management of COPD and CVD
With the close association between COPD and CVD, it is possible that treatments for one condition may influence the other and appropriate treatment of all conditions is therefore essential. Improvements in survival following hospital discharge for acute COPD exacerbation have been attributed to better management of COPD and associated comorbidities, including the use of CV therapies such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers and statins [62]. However, the treatment of CV conditions in patients with COPD is associated with therapeutic challenges, most notably the co-administration of (selective) β1-blockers and β2-agonists. β-blockers are widely prescribed in the treatment of CVD and β-agonists represent a cornerstone of COPD treatment; however, the two have opposing pharmacological actions and physicians may be concerned that treatment of one condition may worsen the other [63].

A number of randomised controlled trials (RCTs) and observational studies provide insight into the effect of COPD treatments on CVD and vice versa, although both study types are subject to limitations. For instance, results from observational studies may be affected by lack of blinding of study treatments and confounding bias [64]. Also, observational studies are often reliant upon patient databases, which may lack accuracy (for instance, the definition of COPD and the presence of comorbidities such as asthma) [64–66]. In addition, a number of observational analyses discussed below rely upon prescription data, which may not accurately reflect current medication intake [65, 66]. Conversely, RCTs are associated with limitations of their own, such as their limited size and duration of exposure, as well as a lack of generalisability to the general COPD population due to stringent inclusion criteria and trial setting [64]. Moreover, RCTs may introduce bias due to the deleterious effect of treatment withdrawal at randomisation, the inclusion of a run-in period, the use of untreated placebo groups and by truncating follow-up at treatment discontinuation [67–69].

Effects of COPD treatments on CV risk
Among COPD patients, CV causes are the second most common cause of death (following pulmonary causes) [70]. In this section, we discuss the effects of different classes of COPD treatment on CV risk and mortality, followed by the effects of different classes of CV treatment on COPD. Details from key studies [27, 65, 66, 71–124] are summarised in tables 1 and 2.

Bronchodilators
There is conflicting evidence regarding the CV safety of bronchodilators. An increased CV risk has been observed with bronchodilators in some studies [72, 76, 84, 125], whereas others found no evidence of increased risk or even some evidence of CV risk reduction [89, 126].

β2-agonists
While a systematic review of long-acting β2-agonists (LABAs), in combination with inhaled corticosteroids (ICS), concluded that ICS/LABA products may have a good CV safety profile in asthma patients [127], evidence for the CV safety of LABAs in COPD is less definitive. LABAs have been associated with an increased risk of CV events, possibly due to stimulation of sympathetic drive [72, 84], which may also increase the risk of arrhythmias and myocardial ischaemia in patients with CVD (particularly HF). In clinical trials, β2-agonists have been shown to increase heart rate, reduce potassium concentrations and increase the risk of CV events versus placebo in patients with obstructive airways disease [72]. Furthermore, studies of Canadian healthcare databases indicate that new use of LABAs is associated with an elevated rate of cardiac arrhythmia in patients with COPD [82, 83]. In addition, a recent analysis of
### TABLE 1 Effects of chronic obstructive pulmonary disease (COPD) treatments on cardiovascular (CV) risk

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<tr>
<th>Author/study</th>
<th>Design and participants</th>
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<td><strong>β₂-agonists</strong></td>
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<td><strong>SUSSA</strong> (2003) [71]</td>
<td>Population-based, nested case-control (n=12 090)</td>
<td>Follow-up to 1999</td>
<td>Newly diagnosed patients with COPD aged &gt;55 years (identified from the Saskatchewan Health Services databases, 1980–1997)</td>
<td>SABAs</td>
<td>Cases of acute MI occurring during cohort follow-up</td>
<td>1127 evaluable patients identified with fatal or non-fatal acute MI</td>
<td>SABA use not associated with increased risk of acute MI (rate ratio for any use: 1.06, 95% CI 0.92–1.23)</td>
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<td><strong>SALPETER</strong> (2004) [72]</td>
<td>Meta-analysis of randomised and placebo-controlled trials 13 RCTs of single-dose treatment (n=232) 20 trials of longer treatment duration (n=6623)</td>
<td>Mean of 4.7 months (range: 3 days to 1 year)</td>
<td>Patients with obstructive airway disease [COPD or asthma] Mean age 56.6 years (single-dose) and 52.2 years (longer treatment studies)</td>
<td>β₂-agonists versus placebo</td>
<td>Short-term effect on heart rate and potassium concentrations</td>
<td>Single-dose β₂-agonist versus placebo increased heart rate by 9.12 bpm and reduced potassium concentration by 0.36 mmol·L⁻¹</td>
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<td><strong>CAZZOLA</strong> (2007) [27]</td>
<td>Randomised, double blind, double dummy (n=20)</td>
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<td>COPD and sPAP &gt;20 mmHg (rest)</td>
<td>Salmeterol 50 µg Formoterol 12 µg</td>
<td>Acute haemodynamic response</td>
<td>Mean sPAP significantly decreased versus baseline at 15, 30 and 60 min post-inhalation (p&lt;0.05)</td>
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<td><strong>SANTUS</strong> (2015) [73]</td>
<td>Randomised, double blind, placebo controlled, crossover (n=40)</td>
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<td>COPD (FEV₁ ≤70% pred; RV &gt;135% pred) Absence of CV comorbidities Age 50–85 years</td>
<td>Indacaterol 150 µg versus placebo [1:1]</td>
<td>Effect of reduction of right-ventricular and FRC on right heart systolic/diastolic functional indices</td>
<td>Significant improvements in right-ventricular compliance/cardiac performance with indacaterol versus placebo (p≤0.05 after 180 min treatment) as follows: 1) TAPSE: 0.41 mm versus 0.02 mm 2) DT-TR: 11.9 ms versus 3.8 ms 3) Heart rate: −2 bpm versus 0.6 bpm</td>
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<td><strong>Muscarinic antagonists</strong></td>
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<td><strong>Kesten</strong> [2006] [74]</td>
<td>Pooled safety analysis of 19 randomised, double blind, placebo controlled trials (including two asthma trials) (n=7819)</td>
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<td>Tiotropium 18 µg once daily (n=4435) Placebo (n=3384)</td>
<td>AE occurring during the study</td>
<td>Tiotropium not associated with increased risk of serious cardiac events versus placebo. Data as follows: 1) CV mortality (relative risk 0.57, 95% CI 0.26–1.26) 2) Cardiac arrest (relative risk 0.90, 95% CI 0.26–3.15) 3) MI (relative risk 0.74, 95% CI 0.26–2.07)</td>
<td>Relative risk of tachycardia with tiotropium versus placebo: 1.68 (95% CI 0.69–4.11)</td>
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<td><strong>Travers</strong> [2007] [75]</td>
<td>Randomised, double blind, placebo controlled, crossover (n=18)</td>
<td>7–10 day treatment period + 35 day washout period</td>
<td>COPD (FEV1 ≤65% pred; FRC ≥120% pred; modified baseline dyspnoea index score ≤6)</td>
<td>Tiotropium 18 µg once daily versus placebo</td>
<td>Effect of tiotropium on CV response to exercise</td>
<td>Tiotropium improved cardiac function during exercise versus placebo: 1) Significantly reduced heart rate (105 bpm versus 112 bpm, p&lt;0.05) 2) Higher O2 pulse (10.9 mL·beat⁻¹ versus 10.1 mL·beat⁻¹, p&lt;0.05) 3) Lower SBP (148 mmHg versus 156 mmHg, p&lt;0.05)</td>
<td>Tiotropium significantly improved measures of dynamic hyperinflation during exercise: IRV was significantly greater with tiotropium versus placebo (0.60 L versus 0.44 L, p&lt;0.05)</td>
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<td><strong>Singh</strong> [2008] [76]</td>
<td>Systematic review and meta-analysis (17 RCTs; 12 on tiotropium, 5 on ipratropium) (n=14 783)</td>
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<td>Tiotropium or ipratropium versus control [placebo/active control] (n=7311)</td>
<td>Composite of non-fatal MI, non-fatal stroke and CV death</td>
<td>Tiotropium or ipratropium significantly increased risk of CV death, MI or stroke versus control (1.8% versus 1.2%; relative risk 1.58 (95% CI 1.21–2.06), p&lt;0.001)</td>
<td>Tiotropium or ipratropium did not significantly increase risk of all-cause mortality versus control (2.0% versus 1.6%; relative risk 1.26 (95% CI 0.99–1.61), p=0.06)</td>
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<tr>
<td><strong>Rodrigo</strong> [2009] [77]</td>
<td>Systematic review and meta-analysis (19 RCTs) (n=18111)</td>
<td>7 trials (28–48 months) 12 trials (8 weeks–6 months)</td>
<td>Patients with COPD (average baseline FEV1: 41% pred normal) Mean age 64.8 years</td>
<td>Tiotropium versus placebo [n=15³], SFC [n=2⁴], salmeterol [n=1⁴], salmeterol/ placebo [n=1⁴]</td>
<td>Composite of MACE, CV mortality and non-fatal MI or stroke</td>
<td>No difference in incidence of MACE versus control groups [relative risk 0.96, 95% CI 0.82–1.12]</td>
<td>Compared with control groups, tiotropium did not significantly increase risk of: 1) CV death [relative risk 0.93, 95% CI 0.73–1.20] 2) Non-fatal MI [relative risk 0.84, 95% CI 0.64–1.09] 3) Non-fatal stroke [relative risk 1.04, 95% CI 0.78–1.39]</td>
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<td>Celii (2009, UPLIFT)</td>
<td>Multicentre, randomised, double blind, placebo-controlled, parallel group (n=5993)</td>
<td>4 years</td>
<td>Patients aged &gt;40 years with COPD (post-bronchodilator FEV1 &lt;70% pred normal; FEV1/FVC ≤70%)</td>
<td>Tiotropium (n=2987) Placebo (n=3006)</td>
<td>Effect of tiotropium on survival</td>
<td>Reduced risk of cardiac mortality with tiotropium versus placebo (HR 0.85, 95% CI 0.75–0.99)</td>
<td>Reduced risk of all-cause mortality for tiotropium versus placebo (HR 0.84 [95% CI 0.73–0.97], p=0.016)</td>
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<td>Ojiri (2012)</td>
<td>Single-centre, prospective, pilot (n=21)</td>
<td>12 weeks</td>
<td>Patients with COPD (FEV1/FVC &lt;0.70) and prior ≥1 year pulmonary resection for lung cancer ECOG status 1 &gt;20 pack-year smoking history</td>
<td>Tiotropium 18 µg once daily</td>
<td>Pulmonary function and left-ventricular diastolic dysfunction (E/e′ ratio)</td>
<td>Significant improvements before/after tiotropium (versus before tiotropium) in: 1) FEV1 [1.84 L versus 1.60 L, p&lt;0.001] 2) E/e′ ratio (7.59 versus 8.97, p&lt;0.001)</td>
<td>Significant improvement in PASP versus before tiotropium [33.0 mmHg versus 38.5 mmHg, p&lt;0.01]</td>
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<td>Pepin (2014)</td>
<td>Multicentre, randomised, double dummy, parallel group, blinded (n=257)</td>
<td>12 weeks</td>
<td>COPD patients aged ≥40 years Smoking history ≥10 pack-years Post-bronchodilator FEV1 ≤70% pred normal FEV1/FVC ≤0.70 aPWV ≥11 m·s⁻¹</td>
<td>Tiotropium 18 µg once daily</td>
<td>Change from baseline in arterial stiffness (aPWV) at 12 weeks</td>
<td>At 12 weeks there was a comparable reduction from baseline in aPWV with tiotropium (1.118 m·s⁻¹) and fluticasone furoate/vilanterol combination (−0.859 m·s⁻¹, p=NS)</td>
<td>No significant differences between tiotropium and fluticasone furoate/vilanterol combination for change from baseline in trough FEV1 [0.080 L versus 0.117 L] or IC (0.019 L versus 0.089 L)</td>
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<td>Suissa (2017)</td>
<td>UK observational, population-based prior ICS-matched cohort analysis [primary care, CPRD] (n=115397, base cohort (new users of a long-acting bronchodilator); n=70 550, sub-cohort [linked to HES database])</td>
<td>1 year</td>
<td>New users of long-acting bronchodilators [LABA or tiotropium] for COPD Aged ≥55 years ≥2 years medical history First LABA/tiotropium prescription on/after September 25, 2003</td>
<td>Full cohort [matched by propensity score]: tiotropium (n=26442), LABA (n=26442) HES sub-cohort: tiotropium (n=15427), LABA (n=15427)</td>
<td>Incidence of acute MI, stroke, HF (full cohort) and incidence of arrhythmia and pneumonia [HES sub-cohort] following 1 year of treatment with tiotropium versus LABA</td>
<td>No difference between incidence of acute MI versus LABA in CV events, as follows: 1) Acute MI: HR 1.10 [95% CI 0.88–1.38] 2) Stroke: HR 1.02 [95% CI 0.78–1.34] 3) Heart failure: HR 0.90 [95% CI 0.79–1.02] 4) Arrhythmia: HR 0.81 [95% CI 0.60–1.09]</td>
<td>Risk of pneumonia significantly reduced with tiotropium versus LABA (HR 0.81, 95% CI 0.72–0.92)</td>
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**β₂-agonists and muscarinic antagonists**

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<tr>
<td>Berton (2010)</td>
<td>Double-blind, placebo-controlled, crossover (n=12)</td>
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<td>Moderate-to-severe COPD (FEV1/FVC &lt;0.7; post-bronchodilator FEV1 &lt;60% pred) Resting P0₂ &gt;60 mmHg</td>
<td>Salbutamol 120 µg + ipratropium 20 µg/actuation versus placebo</td>
<td>Key determinants of O₂ delivery and uptake during high-intensity, constant work rate cycling exercise</td>
<td>Compared with placebo, bronchodilators accelerated central haemodynamic response at exercise onset, as follows: 1) t½QT: 75.9±10.3 s versus 58.9±18.9 s (p=0.02)</td>
<td>Bronchodilators led to lung deflation and increased exercise tolerance versus placebo (454±131 s versus 321±140 s, p&lt;0.05)</td>
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<td>Wilchesky (2012–part 1) [82]</td>
<td>Retrospective, cohort (healthcare databases, Province of Saskatchewan, Canada) (n= 6018)</td>
<td>COPD patients aged ≥55 years Newly treated COPD (three or more prescriptions for a bronchodilator, on two different dates, within any 1-year period)</td>
<td>LABA SABA Methylxanthines Ipratropium bromide</td>
<td>Rate of cardiac arrhythmias</td>
<td>Rate of arrhythmia increased with new use of: 1) ipratropium (relative risk 2.4, 95% CI 1.4–4.0) 2) LABA (relative risk 4.5, 95% CI 1.4–14.4)</td>
<td>Rate of arrhythmia was not increased with new use of: 1) SABA (relative risk 0.9, 95% CI 0.5–1.6) 2) Methylxanthines (relative risk 1.6, 95% CI 0.7–3.7)</td>
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<td>Wilchesky (2012–part 2) [83]</td>
<td>Retrospective, cohort (healthcare databases, Quebec, Canada) (n=76661)</td>
<td>COPD patients aged ≥67 years Newly treated COPD (three or more prescriptions for a bronchodilator, on two different dates between January 01, 1990 and December 31, 2002)</td>
<td>LABA SABA Methylxanthines Ipratropium bromide</td>
<td>Rate of cardiac arrhythmias</td>
<td>Rate of arrhythmia increased with new use of: 1) SABA (relative risk 1.27, 95% CI 1.03–1.57) 2) LABA (relative risk 1.47, 95% CI 1.01–2.15)</td>
<td>Rate of arrhythmia slightly (not significantly) increased with new use of: 1) ipratropium bromide (relative risk 1.23, 95% CI 0.95–1.57) 2) Methylxanthines (relative risk 1.28, 95% CI 0.93–1.77)</td>
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<td>Gershon (2013) [84]</td>
<td>Population-based, nested case-control analysis of a retrospective study (n=191005)</td>
<td>COPD patients aged ≥66 years Receiving treatment (September 2003–March 2009) 53532 had a CV event 26628 matched to control</td>
<td>LABA LAMA</td>
<td>Hospitalisation or ED visit for a CV event</td>
<td>New users of LABAs and LAMAs more likely versus non-users to have a CV-related hospitalisation/ED visit LABAs: OR 1.31 (95% CI 1.12–1.52), p&lt;0.001 LAMAs: OR 1.14 (95% CI 1.01–1.28), p=0.03</td>
<td>No significant difference in CV events between LABAs and LAMAs [OR 1.15 (95% CI 0.95–1.38), p=0.16]</td>
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<tr>
<td>Wang (2018) [123]</td>
<td>Nested case-control study (healthcare database, Taiwan) (n=284 229)</td>
<td></td>
<td>COPD patients aged ⩾40 years LABA-LAMA naïve 37 719 had a CV event Matched with 146 139 randomly selected controls</td>
<td>LABA, LAMA</td>
<td>Inpatient or ED visit for CAD, HF, ischaemic stroke or arrhythmia</td>
<td>New LABA and LAMA use were associated with an increased risk of a CV event within 30 days (OR 1.50 [95% CI 1.35–1.67], p&lt;0.001 and OR 1.52 [95% CI 1.28–1.80], p&lt;0.001, respectively). The risk was absent, or even reduced, with prevalent use</td>
<td>No difference in risk was observed between individual LABA agents, LAMA dosage forms, or concomitant COPD regimens</td>
</tr>
<tr>
<td>Suissa (2017) [66]</td>
<td>UK observational, population-based cohort analysis (primary care, CPRD) (n=463 899, base cohort) 31 174 patients on combined bronchodilator therapy matched to 31 174 patients on bronchodilator monotherapy</td>
<td>1 year</td>
<td>New users of long-acting bronchodilators (LABA or tiotropium) for COPD Aged &gt;55 years ≥2 years medical history First LABA/tiotropium prescription on/after September 25, 2002</td>
<td>LABA/tiotropium initiation + second long-acting bronchodilator (n=31 174) Bronchodilator monotherapy (n=31 174)</td>
<td>Incidence of acute MI, stroke, HF and arrhythmia following 1 year of treatment</td>
<td>Combination of two long-acting bronchodilators was not associated with increased risk of: 1) Acute MI (HR 1.12, 95% CI 0.92–1.37) 2) Stroke (HR 0.87, 95% CI 0.69–1.10) 3) Arrhythmia (HR 1.05, 95% CI 0.81–1.36)</td>
<td>Two long-acting bronchodilators in combination were associated with increased risk of HF [HR 1.16, 95% CI 1.03–1.30]</td>
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<tr>
<td>Samp (2017) [85]</td>
<td>Retrospective, observational cohort (using health insurance claims data) (n=19 078 matched patients)</td>
<td></td>
<td>Patients with COPD initiating LABA/LAMA or ICS/LABA</td>
<td>LABA/LAMA (n=38 646) ICS/LABA (n=15 234)</td>
<td>CCV outcomes: hospitalisations for ACS, HF, cardiac dysrhythmia, stroke, or TIA Change in LVEDV measured with MRI on day 14</td>
<td>LABA/LAMA treatment was associated with fewer CV events versus ICS/LABA treatment [HR 0.794, 95% CI 0.623–0.997] Compared with placebo, indacaterol/glycopyrronium resulted in a significant increase in LVEDV (10.27 mL, p&lt;0.0001) and QT (0.337 L·min⁻¹, p=0.0032)</td>
<td>No difference between treatments in cerebrovascular events [HR 1.166, 95% CI 0.653–1.959] Compared with placebo, indacaterol/glycopyrronium was associated with: 1) Improved lung function (peak FEV1 increased by 0.42 L, p&lt;0.0001) 2) Reduced lung hyperinflation (RV −0.75 L, p&lt;0.0001)</td>
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<td>Hohlfeld (2017) [86]</td>
<td>Randomised, double-blind, single centre, placebo-controlled, two period, crossover (n=62)</td>
<td></td>
<td>Patients with COPD and increased RV (&gt;135% predicted) without CVD</td>
<td>Indacaterol/glycopyrronium 110 µg/50 µg once daily Placebo</td>
<td></td>
<td>Compared with placebo, indacaterol/glycopyrronium resulted in a significant increase in LVEDV (10.27 mL, p&lt;0.0001) and QT (0.337 L·min⁻¹, p=0.0032)</td>
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<tr>
<td>Huart (2005) [87]</td>
<td>Nested case–control analysis (health services databases, Saskatchewan, Canada) (n=5 648)</td>
<td>Follow-up until first MI</td>
<td>Patients ⩾55 years with new-onset COPD who had not received any bronchodilator, anti-asthma drug or ICS</td>
<td>ICS</td>
<td>First fatal or non-fatal acute MI Results based on 371 cases with first acute MI matched to 1864 controls Low-dose ICS (50–200 µg·day⁻¹)</td>
<td>Overall, current use of ICS was not associated with a significant decrease in risk of acute MI [rate ratio 0.82, 95% CI 0.57–1.16]</td>
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</table>

**LABA/LAMA combinations**

**ICS and ICS/LABA combinations**
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<tr>
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<td>Loke [2010]</td>
<td>Systematic review of 23 RCTs (n=23396) and 12 observational studies</td>
<td>RCTs ≥24 weeks</td>
<td>Patients with COPD of any severity</td>
<td>ICS versus placebo or ICS/LABA versus LABA</td>
<td>Risk of fatal and non-fatal MI and CV death</td>
<td>Findings from RCTs indicated that ICS were not associated with significantly reduced risk of MI (relative risk 0.95, 95% CI 0.73–1.23), CV death (relative risk 1.02, 95% CI 0.81–1.27) or mortality (relative risk 0.89, 95% CI 0.86–1.07)</td>
<td>Findings from observational studies indicated that ICS use was associated with a significant reduction in CV death (two studies: relative risk 0.79 [95% CI 0.72–0.86], p&lt;0.0001) and mortality (11 studies: relative risk 0.78 [95% CI 0.75–0.80], p&lt;0.0001)</td>
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<tr>
<td>Calverley [2010, TORCH] [89]</td>
<td>Multicentre, randomised, double-blind, placebo-controlled, parallel group (post hoc analysis) (n=6184)</td>
<td>3 years</td>
<td>Patients [current/former smokers] with COPD (pre-bronchodilator FEV1 &lt;60% pred and FEV1/FVC ≤0.70) Aged 40–80 years</td>
<td>Salmeterol/fluticasone propionate combination 50 µg/500 µg (n=1546) Salmeterol 50 µg (n=1542) Fluticasone propionate 500 µg (n=1552) Placebo (n=1544) (all twice daily)</td>
<td>CV AEs and SAEs</td>
<td>The probability of patients having a CV AE by 3 years was lowest for salmeterol/fluticasone propionate combination (20.8%) versus placebo (24.2%), salmeterol (22.7%) and fluticasone propionate (24.3%)</td>
<td>Treatment with salmeterol/fluticasone propionate combination was associated with a significant reduction versus placebo in probability of a CV AE by 3 years in patients receiving CV therapy at baseline (27.9% versus 33.5%, respectively; p&lt;0.05)</td>
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<tr>
<td>Dransfield [2011] [90]</td>
<td>Multicentre, randomised, double-blind, placebo-controlled (n=249)</td>
<td>12 weeks</td>
<td>Patients with COPD (post-bronchodilator FEV1 &lt;80% pred and FEV1/FVC ratio ≤0.70) Aged ≥50 years Smoking history of ≥10 pack-years</td>
<td>Salmeterol/fluticasone propionate combination 50 µg/250 µg twice daily (n=123) Placebo (n=126) (Both arms received open label tiotropium 18 µg once daily for 4 weeks after a 12 week treatment period)</td>
<td>aPWV change from baseline at 12 weeks</td>
<td>For patients that remained on treatment for 12 weeks (n=96 in each group), salmeterol/fluticasone propionate combination was associated with a significant reduction in aPWV versus placebo (−0.49 m·s⁻¹, p&lt;0.045)</td>
<td>No significant changes in aPWV for salmeterol/fluticasone propionate combination + tiotropium versus tiotropium from 12–16 weeks [mean change 0.18 m·s⁻¹]</td>
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<td>Stone [2016] [91]</td>
<td>Single-centre, randomised, double-blind, placebo-controlled, crossover (n=45)</td>
<td>Two 7-day treatment periods separated by a 7±2-day washout period</td>
<td>COPD (FEV₁ &lt;70% pred)</td>
<td>Fluticasone furoate/ vilanterol combination 100 µg/25 µg once daily</td>
<td>Change in RVEDVI from baseline versus placebo after 7 days treatment (maximum 14 days)</td>
<td>Mean increase in change from baseline in RVEDVI of 5.8 mL·m⁻² (95% CI 2.74–8.91), p&lt;0.001 versus placebo</td>
<td>Improved lung hyperinflation and airflow limitation from baseline with fluticasone furoate/ vilanterol combination relative to placebo, as follows: 1) RV: 429 mL reduction (p&lt;0.001) 2) Increased IC, IC/TLC, FEV₁ and FVC (261 mL, 4.6%, 220 mL and 350 mL, respectively; all p&lt;0.001)</td>
</tr>
<tr>
<td>Vestbo [2016, SUMMIT] [92]</td>
<td>Multicentre, randomised, double-blind, placebo-controlled, parallel group, event-driven (n=16485)</td>
<td>Maximum follow-up was 4 years</td>
<td>COPD (post-bronchodilator FEV₁ 50–70% pred and FEV₁/FVC ≤0.70)</td>
<td>Fluticasone furoate/ vilanterol combination 100 µg/25 µg once daily</td>
<td>All-cause mortality</td>
<td>All-cause mortality did not differ significantly between fluticasone furoate/vilanterol combination and placebo (HR 0.88 (95% CI 0.74–1.04); 12% relative reduction, p=0.137) or components</td>
<td>Fluticasone furoate/ vilanterol combination had no effect on composite CV events (CV death, MI, stroke, unstable angina, TIA) compared with placebo (HR 0.93, 95% CI 0.75–1.14)</td>
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<tr>
<td>Bhatt [2017] [93]</td>
<td>Multicentre, randomised, double-blind, parallel group, placebo-controlled [stratified by COPD exacerbation history] (n=430)</td>
<td>24 weeks</td>
<td>Patients aged ≥40 years with a history of COPD ≥10 pack-year smoking history FEV₁/FVC ≤0.70 Post-bronchodilator FEV₁ ≤70% pred aPWV ≥11 m·s⁻¹</td>
<td>Fluticasone furoate/ vilanterol combination 100 µg/25 µg once daily</td>
<td>Change from baseline in aPWV after 24 weeks with fluticasone furoate/ vilanterol combination versus placebo</td>
<td>No significant difference in mean change from baseline in aPWV at 24 weeks with fluticasone furoate/ vilanterol combination (−1.75 m·s⁻¹) versus placebo (−1.97 m·s⁻¹)</td>
<td>Post-hoc analysis indicated a greater proportion of responders in the fluticasone furoate/ vilanterol combination versus placebo groups when withdrawn patients were classified as non-responders (50% versus 36%, respectively)</td>
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### TABLE 1 Continued

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| **Other COPD pharmacological treatments**

**SUSSA**
(1996) [94]
Population-based cohort from Saskatchewan, Canada (n=12,301)

Patients with asthma aged 5–54 years

Theophylline and β-agonists versus control

Identified 30 CV deaths in which acute asthma did not appear to be a contributing factor

Rate of CV death was greater with theophylline [rate ratio 2.7, 95% CI 1.2–6.1] and β-agonists administered orally or by nebuliser [rate ratio 2.4, 95% CI 1.0–5.4]

Rate of CV death was not greater with β-agonists administered by MDI [rate ratio 1.2, 95% CI 0.5–2.7]

**HUERTA**
(2005) [95]
Nested case-control (population-based cohort, UK General Practice Research Database after January 01, 1994) (n=5710)

Patients aged 10–79 years with asthma or COPD (710 cases and 5000 controls)

Theophylline (and other therapies: β-agonists, oral steroids, ICS)

Rhythm disorders

Short-term theophylline use was weakly associated with:

1) Arrhythmia (relative risk 1.8, 95% CI 1.0–3.3)
2) AF (relative risk 1.8, 95% CI 0.9–3.7)

Short-term theophylline use was associated with supraventricular tachycardia (relative risk 4.0, 95% CI 0.9–18.1)

**WHITE**
(2013) [96]
Pooled analysis of 14 intermediate and long-term trials (n=12,054)

Range: 12–52 weeks

Patients with moderate-to-very-severe COPD

Roflumilast

Placebo

MACE (CV death, non-fatal MI and stroke)

MACE composite rate was significantly lower with roflumilast versus placebo (HR 0.65 (95% CI 0.45–0.93), p=0.019)

MACE experienced by 14.3/1000 patient-years (roflumilast) and by 22.3/1000 patient-years (placebo)

ACS: acute coronary syndrome; AE: adverse event; AF: atrial fibrillation; aPWV: aortic pulse wave velocity; BP: blood pressure; CAD: coronary artery disease; CCV: cardiovascular and cerebrovascular; CPRD: Clinical Practice Research Datalink; CVD: cardiovascular disease; DT-TR: tricuspid E-wave deceleration time; ECOG: Eastern Cooperative Oncology Group; ED: emergency department; E/e′: ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular movement velocity; FEV1: forced expiratory volume in 1 s; FRC: functional residual capacity; FVC: forced vital capacity; HES: hospital episode statistics; HF: heart failure; HR: hazard ratio; IC: inspiratory capacity; ICS: inhaled corticosteroid; IRV: inspiratory reserve volume; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; LVEDV: left-ventricular end-diastolic volume; LVEF: left-ventricular ejection fraction; MACE: major adverse cardiovascular event; MDI: metered dose inhaler; MI: myocardial infarction; mMRC: modified Medical Research Council; MRI: magnetic resonance imaging; NS: not significant; OR: odds ratio; PaO2: arterial oxygen tension; PASP: pulmonary arterial systolic pressure; QT: cardiac output; RCT: randomised controlled trial; RV: residual volume; SAB/A: short-acting β2-agonist; SAE: serious adverse event; SFC: salmeterol/fluticasone combination; SBP: systolic blood pressure; sPAP: systolic pulmonary arterial pressure; SV: stroke volume; TAPSE: tricuspid annular plane systolic excursion; TIA: transient ischaemic attack; TLC: total lung capacity; VC: vital capacity. #: number of studies; ¶: increases with elevation of left-ventricular filling pressure that occurs due to impaired left-ventricular diastolic function; §: marker of CV risk; †: for each case, one control was randomly selected, matched for age (±1 year), sex, duration of COPD, HF and history of hospitalisation for ACS, HF, ischaemic stroke, cardiac arrhythmia and acute respiratory disease [acute exacerbation of COPD, pneumonia, influenza, or acute bronchitis]; ‡: patients with aPWV reduction from baseline of ≥1 m·s⁻¹ on day 168.
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<td><strong>β-blockers</strong></td>
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<td>DRANSFIELD (2008) [97]</td>
<td>Retrospective, cohort (University of Alabama Hospital) (n=825)</td>
<td>Discharge or death summaries indicated primary diagnosis of AECOPD or primary diagnosis of ARF and secondary diagnosis of AECOPD</td>
<td>Users of β-blockers (n=142) Non-users (n=683)</td>
<td>In-hospital mortality</td>
<td>β-blocker use was associated with a reduction in mortality (OR 0.39, 95% CI 0.14–0.99)</td>
<td>SABA use was also associated with a reduction in mortality (OR 0.39, 95% CI 0.14–0.99)</td>
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<tr>
<td>RUTTEN (2010; Utrecht GP Network Database) [98]</td>
<td>Observational, cohort (n=2230)</td>
<td>Individuals aged ≥45 years with an incident or prevalent diagnosis of COPD</td>
<td>β-blockers</td>
<td>All-cause mortality First COPD exacerbation</td>
<td>β-blocker use was associated with: 1) A reduction in mortality (HR 0.68, 95% CI 0.56–0.83) 2) A reduction in exacerbations (HR 0.71, 95% CI 0.60–0.83)</td>
<td>Subgroup analyses revealed that patients with COPD but without overt CVD had similar results</td>
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<td>SHORT (2011) [99]</td>
<td>Retrospective, cohort (NHS Tayside Respiratory Disease Information System) (n=5977)</td>
<td>Diagnosis of COPD [GOLD guidelines]</td>
<td>Respiratory and CV drugs</td>
<td>Mortality COPD-related hospital admissions</td>
<td>β-blocker use was associated with: 1) A 22% reduction in all-cause mortality versus no β-blocker use 2) Reduction in mortality from MI (HR 0.67, 95% CI 0.41–1.10) and COPD (HR 0.88, 95% CI 0.32–2.38) 3) Reduced risk of respiratory-related hospital admissions (HR 0.31, 95% CI 0.22–0.44)</td>
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<td>STEFAN (2012) [100]</td>
<td>Retrospective, cohort (Perspective Inpatient Administrative Database [Premier Inc, Charlotte, NC, USA], 404 hospitals) (n=35 082)</td>
<td>Individuals aged ≥40 years with a principal diagnosis of AECOPD, or a principal diagnosis of respiratory failure and a secondary diagnosis of AECOPD or emphysema, and with a secondary diagnosis of IHD or HF</td>
<td>β-blockers Treatment with inhaled β₂-agonists and systemic corticosteroids on the first or second day of the hospitalisation</td>
<td>In-hospital mortality</td>
<td>No association between β-blocker therapy and: 1) In-hospital mortality (OR 0.88, 95% CI 0.71–1.09) 2) 30-day readmission (OR 0.96, 95% CI 0.89–1.03) 3) Late mechanical ventilation (OR 0.98, 95% CI 0.77–1.24)</td>
<td>25% increased odds of 30-day readmission (OR 1.25, 95% CI 1.08–1.44) with nonselective β-blocker versus β₁-selective β-blocker</td>
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<td>Du (2014)</td>
<td>Meta-analysis [15 observational, cohort studies] (n=121,956)</td>
<td>1–7.2 years</td>
<td>Individuals with COPD</td>
<td>β-blockers</td>
<td>Mortality</td>
<td>β-blocker use was associated with: 1) A reduction in COPD exacerbations (rate ratio 0.63, 95% CI 0.57–0.71) 2) A reduction in the risk of overall mortality (rate ratio 0.72, 95% CI 0.63–0.83)</td>
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<td>Puente-Maestu (2014)</td>
<td>Analytical, cross-sectional (n=256)</td>
<td></td>
<td>Individuals with previous COPD diagnosis and CHF/CAD diagnosis ≥1 year prior to baseline who meet the criteria for β-blocker treatment with no contraindications</td>
<td>β-blocker</td>
<td>Lung function, ECG, LVEF, Haemoglobin concentrations, Heart rate, Exacerbations, Hospital admissions, CAT, Comorbidities</td>
<td>β-blocker use was associated with: 1) Fewer COPD patients experiencing exacerbations requiring ER visits (36.9% versus 58.8% among patients without β-blockers, p&lt;0.000) 2) Fewer COPD patients experiencing ≥2 exacerbations or ER visits (38.8% versus 58.8% among patients without β-blockers, p&lt;0.000)</td>
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<td>Bhatt (2016; follow-up of the COPDGene cohort)</td>
<td>Prospective, follow-up (n=3464)</td>
<td>2.1 years median follow-up</td>
<td>Individuals diagnosed with GOLD stage 2 to 4 COPD</td>
<td>β-blocker CCB, ACEI/ARB</td>
<td>Exacerbation rate (total and severe)</td>
<td>β-blocker use was associated with a reduction in the rate of total exacerbations (IRR 0.73 (95% CI 0.60–0.90), p=0.003) and severe exacerbations (IRR 0.67 (95% CI 0.48–0.93), p=0.016) In individuals with GOLD stage 3 and 4, β-blocker use was associated with a reduction in the rate of total exacerbations (IRR 0.33 (95% CI 0.19–0.58), p&lt;0.001) and severe exacerbations (IRR 0.35 (95% CI 0.16–0.76), p=0.008)</td>
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<td>Key (2017)</td>
<td>Cohort, cross-over (n=48)</td>
<td></td>
<td>Individuals were aged ≥18 years and able to perform a cardiopulmonary exercise test</td>
<td>β-blocker</td>
<td>Lung function</td>
<td>β-blocker use led to a small reduction in FEV1 compared with non-use</td>
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<td><strong>RAAS blockers (ACEIs, ARBs)</strong></td>
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<td>KANAZAWA (2003) [105]</td>
<td>Randomised, double-blind, placebo-controlled, crossover, pilot (n=36)</td>
<td>4 months</td>
<td>Males with COPD [ACE genotypes II (n=13), ID (n=11), DD (n=12)]</td>
<td>Captopril 25 mg·day$^{-1}$ Placebo</td>
<td>Pulmonary haemodynamics (mean PAP, PVR, lactate concentration and $P_{V\text{O}_2}$)</td>
<td>Mean PAP, PVR and lactate concentration after exercise were lower for captopril than placebo in patients with the genotypes II or ID</td>
<td>$P_{V\text{O}_2}$ after exercise was higher with captopril versus placebo in patients with genotype II</td>
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<td>ANDREAS (2006) [106]</td>
<td>Randomised, double-blind, placebo-controlled (n=60)</td>
<td>4 months</td>
<td>Patients with COPD (FEV$_1$ &lt;50% pred)</td>
<td>Irbesartan 150 mg·day$^{-1}$ (increased to 300 mg·day$^{-1}$ after 4 weeks) (n=30) Placebo (n=30)</td>
<td>Lung function ($P_{\text{Imax}}$)</td>
<td>Irbesartan did not affect $P_{\text{Imax}}$ (baseline: 4.8 kPa; 4 months: 4.5 kPa)</td>
<td>Irbesartan reduced: 1) TLC (baseline: 119.7% pred; 4 months: 113.7% pred; p=0.01) 2) Haematocrit (from 46.4% to 43.9%, p=0.0001 versus placebo)</td>
</tr>
<tr>
<td>PARIKH (2017) [124]</td>
<td>Population-based cohort study (as part of the Multi-Ethnic Study of Atherosclerosis) (n=4472)</td>
<td>9.3 years median follow-up</td>
<td>Participants aged 45–84 years from the general population (3% had emphysema at baseline)</td>
<td>ACEIs ARBs</td>
<td>Percent emphysema (percentage of lung regions less than −950 Hounsfield units on CT scans)</td>
<td>Higher doses of ACE or ARB were independently associated with a slower change in percent emphysema (p=0.03). Over 10 years, the predicted mean increase in participants who used maximum doses of ARBs or ACEIs was 0.06 percentage points versus 0.66 percentage points in those who did not take ARBs or ACEIs (p=0.01)</td>
<td>The findings were of greatest magnitude among former smokers (p=0.001)</td>
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<tr>
<td>LAI (2018) [122]</td>
<td>Population-based cohort (Taiwan National Health Insurance Database) (n=12 452)</td>
<td>6–11 year follow-up</td>
<td>Patients with COPD aged ≥40 years who received prescriptions for an ACEI or ARB for &gt;90 days between 2000 and 2005 Allocated to ACEI (n=6226) and ARB (n=6226) cohorts</td>
<td>ACEIs ARBs</td>
<td>Pneumonia Severe exacerbations (COPD-related hospitalisation or ER visit) Mortality</td>
<td>Patients treated with ACEIs had significantly higher rates of severe COPD exacerbations [adjusted rate ratio 1.22, 95% CI 1.15–1.29] and a higher risk of pneumonia [adjusted HR 1.22, 95% CI 1.15–1.29] than those in the ARB group</td>
<td>ARBs were also associated with a lower risk of pneumonia requiring mechanical ventilation (adjusted HR 1.35, 95% CI 1.24–1.47) and of mortality (adjusted HR 1.33, 95% CI 1.26–1.42)</td>
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<td><strong>Statins</strong>&lt;br&gt;Manini (2006) [107]&lt;br&gt;Retrospective, time-matched nested case-control (Quebec Linked Databases) [n=19 720]&lt;br&gt;Two cohorts (aged ≥65 years) as follows:&lt;br&gt;1) Revascularised patients with high CV risk [n=946 cases; n=18774 controls]&lt;br&gt;2) General population of NSAID users without previous MI [n=4907 cases; n=98 097 controls]</td>
<td>Statins&lt;br&gt;ACEIs&lt;br&gt;ARBs&lt;br&gt;COPD hospitalisation&lt;br&gt;Mortality</td>
<td>Statin use was associated with reduced risk for COPD hospitalisation (p=0.0091) and with the combined use of statins and ACEIs or ARBs (p=0.0012). Risk ratios for MI were reduced by all three drug classes, particularly by the combination of statins with ACEIs or ARBs (p&lt;0.0001). Death risk ratios were reduced by ARBs (p=0.0010), statins (p&lt;0.0001) and statins with ACEIs or ARBs (p&lt;0.0001).</td>
<td>Similar benefits were observed when steroid users were included in the analysis.</td>
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<td>Alexeeff (2007; Veterans Administration normative study) [108]&lt;br&gt;10 year follow-up&lt;br&gt;Elderly men with no prior known medical conditions</td>
<td>Statins&lt;br&gt;[FEV1, FVC]</td>
<td>Estimated decline in FEV1 was lower in patients using statins than those not using statins (10.9 mL·year⁻¹ versus 23.9 mL·year⁻¹, respectively). Estimated decline in FVC was lower in patients using statins than those not using statins (14 mL·year⁻¹ versus 36.2 mL·year⁻¹, respectively).</td>
<td>There was a significant three-way association between time since first visit, statin use and smoking status (p&lt;0.001).</td>
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<td>Lee (2009) [109]&lt;br&gt;Randomised, double-blind, parallel group [n=53]&lt;br&gt;Patients with COPD and PH aged 40–80 years&lt;br&gt;FEV1 &lt;80% pred&lt;br&gt;FEV1/FVC &lt;70%</td>
<td>Pravastatin&lt;br&gt;40 mg·day⁻¹ [n=27]&lt;br&gt;Placebo [n=26]</td>
<td>Exercise time significantly increased from baseline with pravastatin (52% at 6 months, from 660 s to 1006 s; p&lt;0.0001).</td>
<td>Pravastatin was associated with less dyspnoea after exercise versus placebo (Borg dyspnoea score decreased from 6.7 at baseline to 3.86 at 6 months with pravastatin versus 6.9 to 6.8 with placebo; p=0.05).</td>
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<td>Mortensen (2009) [110]</td>
<td>Retrospective national cohort [VA administrative data] (n=11 212)</td>
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<td>Patients [98% male] aged &gt;65 years hospitalised with COPD exacerbation and received one or more respiratory medications within 90 days of presentation</td>
<td>Users of statins or ACEIs/ARBs (n=6711) Non-users (n=6501)</td>
<td>90-day mortality</td>
<td>Statin use associated with significantly reduced 90-day mortality [OR 0.51, 95% CI 0.40–0.64]</td>
<td>ACEI/ARB use associated with significantly reduced 90-day mortality [OR 0.55, 95% CI 0.46–0.66]</td>
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<td>Bartziokas (2011) [111]</td>
<td>Prospective follow-up (n=245)</td>
<td>12 months</td>
<td>Patients with COPD admitted to hospital for COPD exacerbations</td>
<td>Statins</td>
<td>30-day or 1-year mortality</td>
<td>Statins had no effect on 30-day or 1-year mortality</td>
<td>Statins were associated with a lower risk for COPD exacerbations [HR 0.656, 95% CI 0.454–0.946] and severe exacerbations [HR 0.608, 95% CI 0.381–0.972]</td>
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<td>Huang (2011) [112]</td>
<td>Population-based cohort [Taiwan National Health Insurance Database] (n=18 721)</td>
<td>4.58 year mean follow-up</td>
<td>Patients newly diagnosed with COPD [median age 64 years] receiving statins for hyperlipidaemia</td>
<td>Statins (n=6252) Control (n=12 469; matched for age, sex and COPD treatment [non-statin users])</td>
<td>Hospitalisation for COPD</td>
<td>Fewer patients in the statin group (n=508, 8.1%) were hospitalised for COPD exacerbation versus the control group (n=1324, 10.6%; p&lt;0.001)</td>
<td>Statin use was associated with decreased risk of COPD hospitalisation [HR 0.66 (95% CI 0.60–0.74), p&lt;0.001]</td>
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<td>Bando (2012; Japan) [113]</td>
<td>Observational, cross-sectional (n=853)</td>
<td></td>
<td>Outpatients &gt;40 years who regularly visited a primary healthcare facility</td>
<td>Statins</td>
<td>Lung function</td>
<td>The prevalence of airflow limitation was lower among patients with a history of statin use than those who had not used statins [2.3% versus 10.5%, respectively]</td>
<td>Airflow limitation was not observed in patients with a history of smoking who had used statins</td>
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<td>Wang (2013) [114]</td>
<td>Retrospective nested case-control [nationwide health insurance claims database, Taiwan] (n=14 316)</td>
<td></td>
<td>Patients with COPD hospitalised for COPD exacerbations (n=1584) matched to 5950 controls</td>
<td>Statins</td>
<td>COPD exacerbation</td>
<td>Current use of statins associated with a 40% decreased risk of COPD exacerbation [OR 0.60, 95% CI 0.44–0.81]</td>
<td>Statins reduced risk of COPD exacerbations in a dose-dependent manner (medium average daily dose: OR 0.60, 95% CI 0.41–0.89; high daily dose: OR 0.33, 95% CI 0.14–0.73)</td>
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<td><strong>LAHOUSSE</strong> (2013; Rotterdam Study) [115]**</td>
<td>Nested case–control (n=7983)</td>
<td>363 patients with COPD who died during follow-up versus 2345 age-/sex-matched COPD controls</td>
<td>Statins</td>
<td>Mortality</td>
<td>Long-term statin use (&gt;2 years) was associated with a 39% decreased risk of death</td>
<td>Long-term statin use was associated with 78% reduced mortality with hsCRP &gt;3 mg·L⁻¹ (versus 21% reduction for hsCRP ≤3 mg·L⁻¹)</td>
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<td><strong>CRINER</strong> (2014; STATCOPE) [116]**</td>
<td>Multicentre, randomised, parallel group, placebo-controlled (n=885)</td>
<td>Up to 36 months (mean follow-up ~21 months)</td>
<td>Patients 40–80 years old with moderate-to-severe COPD (post-bronchodilator FEV₁/FVC &lt;70% and FEV₁ &lt;80% pred) and smoking history &gt;10 pack-years COPD exacerbation in the previous year**</td>
<td>Simvastatin 40 mg once daily (n=433) Placebo (n=452)</td>
<td>Exacerbation rate (number of exacerbations per person-year)</td>
<td>No significant difference in mean exacerbation rate between simvastatin and placebo (1.36 versus 1.39 exacerbations per person-year, respectively)</td>
<td>Median days to first exacerbation was similar for simvastatin (223 days) and placebo (231 days)</td>
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<td><strong>INGEBRIGTSEN</strong> (2015; Copenhagen General Population Study) [117]**</td>
<td>Nested case–control (n=5794)</td>
<td>3 year follow-up</td>
<td>Individuals with COPD and CRP measurement matched for age, sex, smoking, COPD severity and comorbidity</td>
<td>Statins</td>
<td>COPD exacerbations</td>
<td>Statins associated with reduced risk of COPD exacerbations (crude analysis: OR 0.68 [95% CI 0.51–0.91], p=0.01; multivariate analysis: OR 0.67 [95% CI 0.48–0.92], p=0.01)</td>
<td>In a subgroup of patients with the most severe COPD and no CV comorbidity, statins did not reduce risk of COPD exacerbations (OR 1.1, 95% CI 0.5–2.1)</td>
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<td><strong>ROSSI</strong> (2017; GISSI-HF) [118]**</td>
<td>Randomised, double-blind, placebo-controlled (n=1060)</td>
<td>Rosuvastatin 10 mg (n=538) Placebo (n=522)</td>
<td>All-cause mortality</td>
<td>There was no significant difference in all-cause mortality between rosuvastatin and placebo (p=0.30)</td>
<td>There were no significant differences in CV death (p=0.88), non-CV death (p=0.09) and all-cause hospitalisation (p=0.82) between rosuvastatin and placebo</td>
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<td>EKSTRÖM (2013; national Swevedox register) [119]</td>
<td>Prospective, national, multicentre (n=2249)</td>
<td>4 years prior to baseline</td>
<td>Individuals aged ≥ 45 years with physician-diagnosed COPD treated with LTOT</td>
<td>All dispensed prescriptions in outpatient care in Sweden after July 01, 2005</td>
<td>Comorbidity and in-hospital time</td>
<td>Patients treated with antiplatelet drugs had higher BMI and more CVD, diabetes mellitus and renal failure than patients not on antiplatelets. The use of antiplatelet drugs was associated with decreased mortality (HR 0.86 (95% CI 0.75-0.99), p=0.030)</td>
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<td>HARRISON (2014; EXODUS cohort) [120]</td>
<td>Observational, cohort, 1 year multicentre (n=1343)</td>
<td>Individuals &gt;40 years old with spirometry-confirmed COPD admitted to hospital between 2009 and 2011 with AECOPD</td>
<td>All COPD and CV medications</td>
<td>1-year all-cause mortality</td>
<td>Antiplatelet therapy was correlated with a reduction in 1-year mortality (OR 0.63 (95% CI 0.47-0.85), p=0.003)</td>
<td>Antiplatelet therapy was not correlated with a reduction in hospital mortality [p=0.124], CV hospitalisation [p=0.097] or CV death [p=0.311]</td>
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<td>Herrin (2013) [121]</td>
<td>Observational, cohort (n=7104)</td>
<td>Receiving care between January 2001 and December 2006 Follow-up April 2009</td>
<td>Individuals with COPD and hypertension prescribed with two antihypertensive medications</td>
<td>Thiazide diuretic plus β-blocker Thiazide diuretic plus ACEI/ARB Thiazide diuretic plus CCB β-blocker plus ACEI/ARB</td>
<td>CHF (time to first event requiring hospitalisation)</td>
<td>Choice of antihypertensive medications in combination with a thiazide diuretic had no significant effect on the risk of COPD exacerbations</td>
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ACE: angiotensin-converting enzyme; ACEI: ACE inhibitor; AECOPD: acute exacerbation of COPD; ARB: angiotensin receptor blocker; ARF: acute respiratory failure; BMI: body mass index; CAD: coronary artery disease; CAT: COPD Assessment Test; CCB: calcium channel blocker; CHF: congestive heart failure; CRP: C-reactive protein; CT: computed tomography; CVD: cardiovascular disease; ER: emergency room; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HF: heart failure; HR: hazard ratio; hsCRP: high-sensitivity C-reactive protein; IHD: ischaemic heart disease; IRR: incidence risk ratio; LTOT: long-term oxygen therapy; LVEF: left-ventricular ejection fraction; MI: myocardial infarction; NHS: National Health Service; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; PAP: pulmonary arterial pressure; Pmax: maximal inspiratory pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; P50: mixed venous oxygen tension; RAAS: renin–angiotensin–aldosterone system; SABA: short-acting β2-agonist; TLC: total lung capacity; VA: Veterans Affairs. |
There are also data to suggest that LABAs may also have direct beneficial effects on pulmonary haemodynamics (indacaterol were associated with improvements in indices of right-ventricular compliance [73]. Inhaled microvascular oxygen delivery have also been observed [81], while improvements in dyspnoea with indacaterol were associated with improvements in indices of right-ventricular compliance [73]. Inhaled LABAs may also have direct beneficial effects on pulmonary haemodynamics (e.g. pulmonary arterial pressure (PAP)) [27] and reduce the rate of COPD exacerbations [70, 131, 132], which are associated with an increased CV risk and mortality [12].

Muscarinic antagonists
Similar to LABAs, LAMAs have been associated with both positive and negative CV effects. Anti-muscarinic agents may suppress parasympathetic control of heart rate, which could increase the risk of tachyarrhythmias [133]. However, there are various potential mechanisms whereby muscarinic antagonists could lower CV risk, such as by reducing lung hyperinflation [134, 135].

The LAMA tiotropium was shown to reduce lung hyperinflation and improve CV responses to exercise (such as reducing heart rate and blood pressure (BP)) [75]. The reduction in heart rate correlated with an increase in inspiratory reserve volume (IRV) [75], consistent with an observed improvement in CV effects due to mechanical unloading of ventilator muscles. Tiotropium also reduces arterial stiffness [80]. Other potential CV benefits of LAMAs include reduction in exacerbations and an improvement in left-ventricular diastolic function, although not left-ventricular ejection fraction (LVEF) [79].

There are inconsistent results regarding the effects of muscarinic antagonists on CV risk and mortality in COPD. Meta-analyses and cohort analyses reported that muscarinic antagonists, and tiotropium specifically, are not associated with an increase in CV events, risks, or deaths [65, 77]. In contrast, an analysis of Canadian healthcare databases indicated that new ipratropium use was associated with an elevated rate of cardiac arrhythmia in patients with COPD [82, 83] and another meta-analysis reported that ipratropium and tiotropium increased the risk of the composite endpoint of CV mortality, MI, and stroke compared with control therapy [76]. However, it has been suggested that the latter meta-analysis had methodological flaws [136], such as the inclusion of many patients from one study and that many CV deaths occurred in patients who were non-compliant with ipratropium. Tiotropium may also have pro-ischaeamic and pro-arrhythmic effects [133]. Further data from Taiwan found that new LAMA use (as well as new LABA use) was associated with a 1.52-fold increase in the risk of a severe CV event within 30 days of therapy initiation compared with non-use of a LABA or a LAMA (p<0.001). It was hypothesised that this effect, observed for both LAMAs and LABAs, may be related to sympathetic over-activation or an increase in inflammatory cytokine levels [123]. However, in the same study, there was no risk associated with long-term use [123] and tiotropium has been associated with a trend towards reduced risk for all-cause, CV and respiratory mortality in RCTs [74, 78, 137].

LABA/LAMA combinations
The CV risk associated with combining long-acting bronchodilators is largely uncertain. A combination of the short-acting bronchodilators salbutamol and ipratropium reduced lung hyperinflation and provided faster QT kinetics as well as larger improvements in microvascular oxygen delivery versus placebo [81]. Furthermore, in the CLAIM study [86], the LABA/LAMA combination indacaterol/glycopyrronium significantly improved left-ventricular and right-ventricular end diastolic volumes, QT and peak forced expiratory volume in 1 s (FEVs1), and induced lung deflation compared with placebo.

Large RCTs have not identified additional CV-associated safety concerns with combining long-acting bronchodilators versus monotherapy alone, although studies were not designed to investigate this outcome [64, 138]. Real-world, primary care data indicated that the addition of a second long-acting bronchodilator to existing LABA or tiotropium treatment was not associated with an increased risk of acute MI, stroke or arrhythmia after 1 year compared with monotherapy, but the risk of developing HF was significantly elevated [66]. Furthermore, HF risk increased by 21% when patients with prior HF were removed from the

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mortality with multiple CV risk factors [92]. Fluticasone furoate/vilanterol did not significantly reduce the risk of CV events in certain subgroups of patients, such as those receiving CV medications at baseline or those with metabolic diseases [94]. While this latter analysis was not specific to patients with COPD, the balance of available data suggests that theophylline should be used with caution in patients with COPD and CVD. High doses of theophylline have been linked to changes in cardiac electrophysiology [149]. Weak associations of theophylline and arrhythmias, AF and supraventricular tachycardias have been suggested by a UK case-control study [95], and a cohort study of 12301 subjects from Canada indicated that the rate of CV death was greater in users of theophylline (with most deaths occurring in individuals with pre-existing COPD as part of integrated patient management [1]). Phosphodiesterase inhibitors have anti-inflammatory effects, can reduce the risk of exacerbations [145] and may therefore have beneficial effects on CV mortality, RCTs have not shown any significant effect on CV death [88]. To date, no studies have been designed to investigate the effect of ICS/LABA/LAMA combination therapies on CV events; however, RCTs comparing ICS/LABA/LAMA with LAMA/LAMA or ICS/LABA combinations have provided no evidence of an excess CV risk with triple therapy [143, 144].

ICS, ICS/LABA and ICS/LABA/LAMA combinations

The effects of ICS on systemic inflammation [41, 139, 140] and cardioprotection [87, 88] are unclear. Systemic corticosteroids appear to promote progression of atherogenesis, but may also improve recovery from occlusive vascular events and intravascular injury [141, 142]. Lung deflation with fluticasone furoate/vilanterol improved cardiac function (right-ventricular, left-ventricular and left atrial volumes) versus placebo [91]. Treatment with ICS/LABA also reduced arterial stiffness to a similar extent as tiotropium in a study of 257 patients with COPD, suggesting that the long-acting bronchodilator component of the combination drives this effect [80]. However, no reduction in aortic pulse wave velocity (aPWV) was observed compared with placebo [90, 93].

A hypothesis-generating post hoc analysis of TORCH (Towards a Revolution in COPD Health) indicated that the ICS/LABA combination salmeterol/fluticasone propionate might have beneficial effects on reducing CV events in certain subgroups of patients, such as those receiving CV medications at baseline or with moderate COPD [89]. The SUMMIT study investigated this hypothesis by comparing fluticasone furoate/vilanterol, respective monotherapies, and placebo in patients with moderate COPD and CVD or multiple CV risk factors [92]. Fluticasone furoate/vilanterol did not significantly reduce the risk of mortality versus placebo and there were no significant differences when data were analysed by age, sex, baseline therapy or presence of CVD [92]. In addition, there was no effect on the composite CV endpoint [92]. Why SUMMIT did not reproduce the results of the TORCH post hoc analysis is unclear. This could reflect differences in the efficiency of the treatments used, or other methodological considerations related to RCTs [68], as discussed above.

Data on the CV risks or benefits of ICS or ICS/LABA combinations in observational studies are also mixed, with reports that low-dose ICS (50–200 µg·day$^{-1}$) may be associated with a reduction in the risk of acute MI in patients with COPD [87]. Although observational studies have indicated that ICS have benefits on CV mortality, RCTs have not shown any significant effect on CV death [88]. To date, no studies have been designed to investigate the effect of ICS/LABA/LAMA combination therapies on CV events; however, RCTs comparing ICS/LABA/LAMA with LAMA/LAMA or ICS/LABA combinations have provided no evidence of an excess CV risk with triple therapy [143, 144].

Other COPD treatments

Phosphodiesterase-4 inhibitors, such as roflumilast, are recommended as an additional therapy on top of triple therapy (a combination of ICS, LABA and LAMA) in inadequately controlled patients in Global Initiative for Chronic Obstructive Lung Disease (GOLD) Group D [1]. Phosphodiesterase inhibitors have anti-inflammatory effects, can reduce the risk of exacerbations [145] and may therefore have beneficial effects on CV events in patients with COPD and increased CV risk. Available data are limited, however, a lower rate of major CV adverse events (AEs) with roflumilast versus placebo has been reported [96]. A more recent meta-analysis did not identify any particular CV safety signal with roflumilast, but it did report an increased incidence of some (non-CV) AEs, which led the authors to conclude that further, long-term safety studies were needed [146].

Theophylline, a further possible treatment for COPD, [1] has anti-inflammatory effects [147] and intravenous theophylline reduces pulmonary vascular resistance (PVR) and improves ventricular function [148]. However, high doses of theophylline have been linked to changes in cardiac electrophysiology [149]. Weak associations of theophylline and arrhythmias, AF and supraventricular tachycardias have been suggested by a UK case-control study [95], and a cohort study of 12301 subjects from Canada indicated that the rate of CV death was greater in users of theophylline (with most deaths occurring in individuals with pre-existing conditions) [94]. While this latter analysis was not specific to patients with COPD, the balance of available data suggests that theophylline should be used with caution in patients with COPD and CVD.

Aside from pharmacological strategies, pulmonary rehabilitation (PR) is recommended for patients with COPD as part of integrated patient management [1]. For those with CVD, it is important to consider both diseases when creating PR programmes [150]. Retrospective analyses and prospective studies provide conflicting insight into the effect of CVD on PR efficacy, with the former suggesting a reduction in the ability to achieve a clinically-important difference in 6-minute walking distance and health status in patients with metabolic diseases versus those without [151]. However, when studied prospectively, this effect was not observed [152]. Furthermore, the effect of PR on CVD risk is largely unknown. A systematic review of studies investigating arterial stiffness in response to PR or an exercise-training programme in
COPD patients only found three eligible studies, with conflicting results [153]; however, there may be subpopulations of patients who benefit from PR with regards to CV risk [153].

Finally, as an intervention, smoking cessation has the greatest potential to influence the natural history of COPD [1]. A network meta-analysis of pharmacological and behavioural smoking cessation interventions in CVD patients indicated that varenicline and bupropion were associated with greater abstinence than placebo, with increased efficacy also noted with telephone therapy and individual counselling versus usual care [154]. However, a further network meta-analysis found no association between cessation medications and major CV events, although nicotine replacement therapy was associated with an increase in CV events overall (driven predominantly by less serious events) compared with smoking cessation advice alone [155, 156].

In summary, the clinical data suggests that inhaled therapies used in the treatment of COPD are not associated with significant CV risk while smoking cessation remains a core strategy for both COPD and CVD, reducing the overall risk of premature mortality from smoking-related diseases. However, more data are required to establish the long-term safety of COPD pharamcotherapies, particularly among patients at high risk of CV events who are often excluded from COPD clinical trials. Observational studies suggest that new users of LABAs and LAMAs with COPD are at higher risk of CV events compared with non-use of LABAs and LAMAs, which indicates the need to monitor patients with CV comorbidities, particularly when bronchodilator therapies are initiated.

Effects of CV treatments on COPD

β-blockers

The European Society of Cardiology (ESC) advocates the use of β-blockers in HF patients irrespective of the presence of COPD [52], but advises caution in patients with stable coronary artery disease (CAD) and concurrent COPD [157]. The use of β-blockers in patients with COPD and concurrent CVD has historically been avoided because of concerns about potential adverse pulmonary effects. Bronchial smooth muscle contains adrenergic receptors, primarily of the β2-subtype, and activation of these receptors by agonists causes bronchodilation [158]. Consequently β-blockers are contraindicated in patients with COPD due to concerns about the potential for acute bronchospasm [159]. Indeed, the non-selective blockade of β-receptors by agents such as propranolol has been shown to inhibit the bronchodilator response to β2-agonists in patients with COPD [160]. However, concerns over the safety of β-blocker therapy in patients with COPD have resulted in sub-optimal therapy in patients with CVD and comorbid COPD [161, 162].

Data which address these safety concerns are increasing. Selective β1-blockers (e.g. atenolol, bisoprolol and metoprolol) have a 20-fold greater affinity for β1-receptors versus β2-receptors; thus, this subclass of agents are significantly less likely to induce bronchoconstriction. Clinical trials and large meta-analyses have shown that single-dose and long-term use of selective β1-blockers does not have a significant effect on FEV1, β-agonist response, respiratory symptoms, or overall patient condition compared with patients with COPD not receiving β1-blockers [163–165]. Indeed, selective β1-blockers and β2-agonists may have complementary effects, as the use of β1-blockers in patients with COPD can sensitize β2-receptors to β2-agonists [166]. Clinical resistance to administer selective β1-blockers when respiratory conditions are present is reflected in review articles and practice guidelines; however, a Cochrane review found that β1-blockers in mild-to-moderate reversible airway disease or COPD did not produce adverse respiratory effects [163]. Furthermore, selective β1-blockers do not increase the risk for moderate or severe exacerbations in patients with asthma [167]. This finding is particularly noteworthy given that airflow obstruction reversibility (following β2-agonist inhalation) is characteristically greater in asthma than in COPD. Thus, one might expect that patients with asthma would be more vulnerable to the adverse effects of β-blockade than patients with COPD; however, with selective β1-blockade this appears not to be the case.

Evidence from observational studies suggests that β-blockers are associated with various benefits in patients with COPD with or without CVD, such as reductions in mortality, hospital admissions, emergency room (ER) visits and COPD exacerbations [97–99, 101–103], although these studies may have been affected by biases from immortal and immeasurable time [168–170].

Furthermore, the continued use of β-blockers in COPD patients hospitalised for exacerbation did not result in an increase in in-hospital mortality, 30-day readmission or late mechanical ventilation [100]. However, the use of β-blockers may have little effect on lung function and dynamic hyperinflation [104]. Such data must be interpreted cautiously in the absence of RCT data, particularly given the recent discrepancy between observational and RCT data in CV therapy for COPD discussed below in relation to statins.

Renin–angiotensin–aldosterone system inhibitors ACEIs and ARBs

The renin–angiotensin–aldosterone system (RAAS) has been implicated in various processes in the lungs that may be important in the pathogenesis of COPD, including the induction of pro-inflammatory
modulators, the generation of reactive oxygen species and the development of pulmonary fibrosis [171]. Data on the effects of RAAS inhibitors in patients with COPD are limited, although a couple of small studies have indicated a potential benefit on pulmonary function and haemodynamics [105, 106]. More recently, an analysis of the Multi Ethnic Study of Atherosclerosis (MESA), including individuals in the general population aged 45–84 years who had no clinical evidence of CV disease, found that baseline use of an ACEI or ARB protected against the progression of emphysema, especially when prescribed at high doses [124]. The authors attributed the effects of such RAAS inhibitors to inhibition of transforming growth factor-β signalling in the lung, thereby reducing the progression of airspace enlargement.

Unfortunately, the most common side effect of therapy with ACEIs is cough, which develops in 5–20% of patients and may be problematic for patients with COPD. Although uncommon, worsening airflow obstruction has been associated with ACEI treatment, leading to suggestions that these agents be used with caution or as a second-line in patients with COPD [158]. No such safety concerns have been reported with ARBs [158]; indeed, data from an observational cohort study among patients with COPD who used ACEIs or ARBs found that ARBs were associated with fewer COPD complications, including severe exacerbations, pneumonia and mortality, than ACEIs [122]. Although these findings require further confirmation, this may suggest that ARBs are a better choice for patients with COPD requiring treatment with a RAAS inhibitor compared with ACEIs [122].

**Statins**

Given the high prevalence of CVD and CV risk factors in COPD [3], many patients with COPD receive statin therapy for the primary or secondary prevention of CVD. The lipid-lowering effects of statins are well documented; however, anti-inflammatory effects have also been observed in the airways and CV tissue [172–176] and therefore these agents could have beneficial effects in COPD. Indeed, statin therapy has been shown to improve Borg dyspnoea scores versus placebo in patients with COPD and PH [109] and data from retrospective analyses and prospective observational studies support a role for statins in patients with COPD in terms of reductions in exacerbations, hospitalisations and mortality after an exacerbation [107, 110–112, 114, 117, 177, 178]. However, many of these studies may have been affected by biases from immortal and immeasurable time [179].

In the Rotterdam study, long-term statin use had a beneficial effect on mortality in patients with COPD compared with never use [115]. Observational studies suggest that statins may also be associated with a reduced prevalence of airflow limitation [113] and a reduction in FEV1 decline [108]. However, an analysis of patients with chronic HF and history of COPD found no favourable effect between statins and all-cause mortality, CV death, non-CV death or all-cause hospitalisation [118]. Indeed, in the STATCOPE study (a randomised placebo-controlled trial of simvastatin in the prevention of COPD exacerbations), statin therapy did not decrease exacerbation rates [116]. However, patients with diabetes and coronary heart disease were not included in this study and therefore a benefit of statin therapy on patients at CV risk cannot be excluded.

**Anticoagulants**

Anticoagulants (e.g. warfarin and newer agents such as apixaban, dabigatran, edoxaban and rivaroxaban) are often used to prevent future thrombotic events in patients with CVD. It is well known that smoking increases the risk of venous thromboembolism (VTE) [180], but patients with severe COPD are also at increased risk of secondary VTE and mortality is higher in patients who have COPD and VTE versus COPD alone [181]. Furthermore, a recent meta-analysis revealed that pulmonary embolism was present in approximately one-sixth of patients who had an acute COPD exacerbation of unknown cause and that these emboli were often in regions indicated for anticoagulant therapy [182]. Thus, use of anticoagulants in at-risk COPD patients may help to reduce future thrombotic-related morbidity and mortality.

**Antiplatelet therapy**

Thrombocytosis has been reported in an observational cohort of 1343 patients hospitalised for an acute exacerbation of COPD and antiplatelet therapy correlated with lower 1-year mortality in this study [120]. A national prospective multicentre study also suggests a positive effect of antiplatelet therapy on mortality in patients with COPD [119].

**Other CV medications**

Data are limited for the effects of other CV medications in patients with COPD. There are no safety concerns or contraindications regarding the use of calcium channel blockers (CCBs) or aldosterone receptor blockers, such as spironolactone, in patients with COPD [158]. In patients with COPD and hypertension, the use of a thiazide diuretic in combination therapy did not affect the risk of COPD exacerbations [121]. However, respiratory acidosis, a common condition in patients with COPD, may be
further complicated by the effects of diuretics on electrolyte levels and acid–base balance, leading to development of mixed acid–base disorders [183]. For example, treating patients with COPD and HF with high-dose diuretics can result in metabolic acidosis and metabolic alkalosis, in addition to pre-existing respiratory acidosis [183]. Patients with HF with reduced ejection fraction may also be treated with sacubitril/valsartan, a first-in-class angiotensin receptor–neprilysin inhibitor (ARNI) [184]. However, the potential impact of ARNIs on COPD outcomes has not been studied.

Overall, the evidence to support the use of CV therapies in patients with COPD is reassuring. Indeed, there are some data to suggest that RAAS inhibitors and statins have a protective effect on the progression of COPD although outcomes studies specifically designed to assess the effect of therapy on patients with COPD and CV would be welcome. Furthermore, historic concerns about the safety of β-blockers are not borne out by the data, which indicates that this class is beneficial in patients with COPD.

Recognising and managing comorbid COPD and CVD
Comorbidity in COPD is common and can be fatal. Therefore, in order to treat patients appropriately, physicians should proactively search for prevalent and clinically important comorbidities such as CVD. The three most commonly occurring cardiac comorbidities of COPD are AF, HF and IHD [185]. However, non-specific symptoms such as dyspnoea and fatigue are common to all four diseases and acute exacerbations of each of these conditions can result in exacerbation of respiratory symptoms. Indeed, acute respiratory symptoms invariably have mixed pulmonary and cardiac origin [185]. Diagnosing and managing comorbid COPD and CVD and their exacerbations thus remain challenging [186].

Recognition
Given the impact of CVD in COPD, it is important to recognise and treat CVD and CV risk factors (such as smoking, cholesterol and BP) as early as possible, but practical guidance is limited. Numerous guidelines have been published to assist in the differential diagnosis of COPD and CVD in isolation, but few exist in the setting of comorbidity or multimorbidity. However, ROVERSE et al. [185] have made important progress in this regard, publishing a set of diagnostic and screening procedures to help differentiate COPD from AF, HF and IHD.

When used in addition to lung function tests, CV risk scores significantly improve the prediction of CV events and mortality in patients with COPD [187]. Over and above guidelines-recommended diagnostic procedures for CVD, further subclinical markers and biomarkers may also assist the assessment and diagnosis of patients in clinical practice. For example, arterial stiffness (as measured by aPWV) has been shown to be predictive of CV events independent of classic CV factors and has been proposed as a surrogate marker of severity [38]. In addition, a prospective cohort study indicated that angiopoietin-like protein 4 was independently associated with CV function in patients with COPD [188].

There is also potential for pulmonologists to learn from other specialities that recognise the importance of identifying and managing key comorbidities. For example, diabetes guidelines from the American Diabetes Association recognise the need to look beyond blood glucose, highlighting the importance of effectively managing high BP in patients with diabetes [189].

Management
Key international, regional and local guidelines provide limited recommendations on how to manage patients with COPD and CVD [1, 190–192]. The GOLD strategy document states that the presence of comorbidities should not, in general, alter COPD treatment and that comorbidities should be treated as per usual standards, irrespective of the presence of COPD [1].

In approaching the treatment of COPD in HF patients, the ESC advocate the use of β-blockers without contraindication for COPD [52]. Unfortunately, despite no consistent evidence contraindicating concurrent β-blocker and LABA administration, some patients with COPD and CVD are not receiving guideline-based therapies due to historical concerns [63, 193] and patients with HF are less likely to receive β-blockers if they also have COPD [63, 193].

In 2016, the National Institute for Health and Care Excellence published a set of clinical guidelines for the assessment, prioritisation and management of patients with commonly occurring multimorbidities [7]. However, more extensive, integrated recommendations specifically concerning CV risk assessment and management in patients with COPD are necessary to optimise management of comorbid COPD and CVD. Indeed, in order to ascertain the most appropriate treatment in patients with further exacerbations despite treatment with a LABA/LAMA, recent proposals for alternative treatment algorithms advocate the assessment of comorbidities [186]. Adoption of strategies aimed at improving outcomes in these
“cardiopulmonary” patients (e.g. via joint management by respiratory and cardiac health professionals in a cardiopulmonary outpatient clinic) is to be encouraged [185].

Our recommendations

CV diseases are often underdiagnosed and under-treated in patients with COPD [18]. Furthermore, treatment with therapies targeted to treat comorbidities such as HF, IHD, AF and hypertension have the potential to modify the natural history of patients with COPD [115, 124]. We therefore support the active detection and management of comorbidities in COPD and suggest using relevant treatment guidelines for patients without COPD in the absence of more specific information. Our recommendations for clinicians regarding management of patients with both COPD and CVD in clinical practice are as follows: 1) multimorbidity is often overlooked during the diagnosis of an initial (i.e. index) chronic disease; however, all patients who have COPD, CVD or another index chronic disease should be evaluated thoroughly to rule out the presence of additional chronic diseases. This is especially important for index diseases such as COPD, in which treatment is purely symptomatic and does not address underlying pathophysiological causes; 2) consider and measure CV risk in every patient with COPD using a validated score (e.g. QRISK3 [194]). Where this gives intermediate results, consider an individualised assessment of risk, such as coronary calcium score or pulse wave velocity. Assess diffusion capacity for the differential diagnosis of dyspnoea in COPD; 3) in patients with COPD, manage comorbid CVD and CV risks according to guidelines. Prescribe β-blockers only in accordance with approved indications, use cardioselective β₁-blockers (e.g. atenolol, bisoprolol and metoprolol), initiate treatment at the lowest dose and up-titrate slowly. Engage/interact with other medical disciplines to address treating patients with multimorbidity; 4) in patients with COPD, monitor lung hyperinflation routinely via IC assessments; 5) reassess risk and control in response to changes in intervention.

Conclusion

COPD and CVD are complex disorders that frequently co-exist and are associated with worse outcomes than either condition alone. Potential mechanisms have been discussed whereby COPD and CVD may interact and treatments for COPD may help to reduce the risk of CVD. These include mechanical offloading of the CV system through reductions in lung hyperinflation, anti-inflammatory effects and the prevention of exacerbations. Current guidelines offer only limited recommendations for the management of CVD in patients with COPD and there is an urgent need for more extensive and specific recommendations to guide physicians in clinical practice.

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