



**University of Dundee**

## **Beta-blockers in COPD**

Lipworth, Brian; Wedzicha, Jadwiga; Devereux, Graham; Vestbo, Jørgen; Dransfield, Mark T.

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## Beta-blockers in COPD: time for reappraisal

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**Beta-blockers in COPD: time for reappraisal**

**Authors:** Dr Brian Lipworth<sup>1</sup>, Prof Jadwiga Wedzicha<sup>2</sup>, Prof Graham Devereux<sup>3</sup>,  
Professor Jørgen Vestbo<sup>4</sup>, Dr Mark T. Dransfield<sup>5</sup>

**Affiliations:** <sup>1</sup>Scottish Centre for Respiratory Research, Ninewells Hospital and  
Medical School, University of Dundee, Scotland, UK, <sup>2</sup>Airways Disease  
Section, National Heart & Lung Institute, Imperial College London, London, UK,  
<sup>3</sup>Applied Health Sciences, University of Aberdeen, Aberdeen, UK, <sup>4</sup>Centre for  
Respiratory Medicine and Allergy, University Hospital South Manchester NHS  
Foundation Trust, University of Manchester, UK, <sup>5</sup>Lung Health Center, Division of  
Pulmonary, Allergy and Critical Care Medicine, University of Alabama at  
Birmingham, Alabama, USA; Birmingham VA Medical Center, Alabama, USA

**Correspondence:** Dr Brian Lipworth, Scottish Centre for Respiratory Research,  
Ninewells Hospital & Medical School, University of Dundee, Dundee, DD1 9SY  
[b.j.lipworth@dundee.ac.uk](mailto:b.j.lipworth@dundee.ac.uk)

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presentation of the manuscript, and approval of the final version.

**“Take Home” message:**

Beta-blockers (BB) are used for heart failure and after myocardial infarction but remain underused in COPD despite recommendations in guidelines.

**Abstract**

The combined effects on the heart of smoking and hypoxaemia may contribute to an increased cardiovascular burden in COPD. The use of beta-blockers in COPD has been proposed because of their known cardio-protective effects as well as reducing heart rate and improving systolic function. Despite the proven cardiac benefits of beta-blockers post myocardial infarction and in heart failure they remain underused due to concerns regarding potential bronchoconstriction even with cardio-selective drugs. Initiating treatment with beta-blockers requires dose titration and monitoring over a period of weeks, and beta-blockers may be less well tolerated in older patients with COPD who have other comorbidities. Medium term prospective placebo controlled safety studies in COPD are warranted to reassure prescribers regarding the pulmonary and cardiac tolerability of beta-blockers as well as evaluating their potential interaction with concomitant inhaled long acting bronchodilator therapy. Several retrospective observational studies have shown impressive reductions in mortality and exacerbations conferred by beta-blockers in COPD. However, this requires confirmation from long term prospective placebo controlled randomized controlled trials. The real challenge is to establish whether beta-blockers confer benefits on mortality and exacerbations in all patients with COPD including those with silent cardiovascular disease where the situation is less clear.

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**Key words:** COPD, beta-blocker, coronary artery disease, heart failure, exacerbations

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## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the world's leading causes of morbidity and is now the third leading cause of mortality amounting to 3 million deaths in 2010.[1, 2] Exacerbations in particular account for up to three quarters of the total costs due to COPD,[3] with attributable costs exceeding 30 billion USD.[4] A recent COPD taskforce statement [5] identified an unmet need in terms of finding drugs to treat common co-morbidities specifically mentioning the putative effects of beta-blockers on the cardiovascular burden and its associated impact on mortality. Cardiovascular comorbidity is common in patients with COPD due to smoking in addition to other shared risks including genetic susceptibility, systemic inflammation and ageing.[6] The prevalence of COPD in patients with heart failure ranges from 11-52% in North American patients and 9-41% in European patients.[7] The purpose of this article is to critically reappraise the current knowledge regarding beta-blockers in COPD looking at the current evidence for their therapeutic index and how this relates to management guidelines.

We have not attempted a systematic review or meta-analysis as described elsewhere,[8-10] but rather highlighted the key areas of clinical relevance for physicians who treat patients with COPD. In this article we have 1) considered the putative link between COPD and the heart in terms of potential targets for beta-blockers, 2) reviewed retrospective data linking use of beta-blockers to reduced exacerbations and mortality, 3) examined the unmet need for use of beta-blockers in patients with COPD and both known, and potentially unknown cardiovascular disease, 4) evaluated which beta-blocker to use based on their pharmacology and

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3 impact on pulmonary function, and 5) attempted to draw conclusions about the  
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5 current clinical use of beta-blockers in COPD.  
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### 10 **COPD and the heart (Figure 1 and Box 1)**

11  
12 The main accepted clinical indications for the use of beta-blockers in COPD are for  
13  
14 patients post myocardial infarction and for patients with heart failure. However, the  
15  
16 presence of untreated or unrecognized (i.e. silent) cardiovascular disease may  
17  
18 contribute to mortality in COPD and may also be an underlying causative factor in  
19  
20 exacerbations which can be difficult to separate from respiratory etiologies.[6] [7] It is  
21  
22 also possible, if not likely, that the burden of cardiovascular disease may be under-  
23  
24 rated by pulmonologists when treating COPD patients because symptoms are  
25  
26 presumed to be primarily driven by airflow obstruction, especially during  
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28 exacerbations.  
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32  
33 The prevalence of left ventricular systolic dysfunction ranges between 10-46% in  
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35 patients with COPD and though the occurrence of heart failure with preserved left  
36  
37 ventricular ejection fraction is less clear, estimates in patients with severe COPD are  
38  
39 as high as 90%.[7] The benefits of beta-blockers in patients with heart failure due to  
40  
41 left ventricular systolic dysfunction are well established from pivotal trials as well as  
42  
43 meta-analysis.[21-24] The challenge in COPD may be more with respect to  
44  
45 diagnosis of heart failure with echocardiography where image acquisition is difficult  
46  
47 due to lung hyperinflation.[25]  
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50  
51 Beta-blockers only have proven benefits in patients post myocardial infarction but not  
52  
53 in stable coronary arterial disease.[11, 12] Nevertheless, the presence of coronary  
54  
55 calcium on chest CT scans is associated with mortality in COPD,[13] and known  
56  
57 coronary arterial disease is also associated with longer exacerbations, more  
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3 dyspnoea, lower health status and exercise capacity in stable patients with  
4 COPD.[14] There is also an acute increase in arterial stiffness particularly during  
5 infective exacerbations of COPD, along with increases in cardiac enzymes especially  
6 in patients with coronary arterial disease;[15] one study found that one in twelve  
7 patients admitted to hospital with an exacerbation of COPD met the criteria for a  
8 myocardial infarction.[16] The presence of coronary heart disease in COPD along  
9 with the adverse effects of hypoxaemia [17] may be compounded by the positive  
10 chronotropic effects of concomitant inhaled beta-agonist therapy,[18, 19] further  
11 compromising cardiac reserve. It has been shown that even a low dose of a beta-1  
12 selective antagonist such as atenolol might protect against chronotropic, inotropic  
13 and electrocardiographic effects of inhaled beta-agonists which are mediated by  
14 cardiac beta<sub>2</sub> receptor stimulation.[20]

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Another potential target is diastolic dysfunction though a meta-analysis suggests that the beneficial effects of beta-blockers in such patients are less clear cut.[26] Several factors may contribute to the occurrence of impaired diastolic function in COPD.

Firstly, patients with COPD also appear to have a higher left ventricular mass (hypertrophy) even in the absence of left ventricular dilatation. Secondly, lung hyperinflation in COPD may cause cardiac compression reducing both left ventricular and atrial filling even in the absence of raised pulmonary arterial pressure.[28-30]

These factors, may also be compounded by the negative effects of hypoxaemia on diastolic filling.[31] [17]

In addition to these COPD related risks, patients with the disease commonly have other co-morbidities such as coronary artery disease, hypertension and diabetes, which can all adversely affect diastolic function. This was addressed in a recent prospective longitudinal study of healthy young adults followed over 25 years, where



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3 a fall in the ratio of forced expiratory volume in one second to forced vital capacity  
4 (FEV<sub>1</sub>/FVC) was associated with reduced left atrial size and cardiac output.[32] Left  
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7 ventricular end diastolic and end systolic wall stress measured by magnetic  
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10 resonance imaging (MRI) is associated with increasing severity of airflow obstruction  
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12 in patients with COPD and coexistent heart failure.[33] Impaired left ventricular filling  
13  
14 is clinically important because it can eventually produce left atrial enlargement which  
15  
16 is a key risk factor for atrial fibrillation and associated mortality during exacerbations  
17  
18 of COPD.[34] Furthermore, the presence of impaired diastolic filling in patients with  
19  
20 COPD is also related to impaired walking distance.[35] Thus, the absence of  
21  
22 benefits of beta-blockers in diastolic dysfunction may not apply in COPD and  
23  
24 deserved re-evaluation in this patient group.  
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### 29 **Effects of beta-blockers on mortality and exacerbations**

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32 Due to the high cardiovascular comorbidity in COPD from smoking along with  
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34 increased sympathetic drive due to hypoxaemia,[36] beta-blockers have been  
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36 proposed as a cogent therapeutic intervention for their known cardio-protective  
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38 effects in addition to reducing heart rate and improving systolic and diastolic  
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40 dysfunction. One of the fundamental issues with regards to more widespread use of  
41  
42 beta-blockers in COPD is the concern regarding beta<sub>2</sub> receptor antagonism and  
43  
44 associated airway smooth muscle constriction which may even occur with cardio-  
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46 selective agents which exhibit preferential beta<sub>1</sub> blockade, especially in more  
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48 susceptible severe patients with impaired respiratory reserve. The risk-benefit  
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50 equation in COPD becomes more favorable for patients who already have overt  
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52 cardiac disease such as heart failure or post myocardial infarction, where beta-  
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54 blockers have proven protective effects.[11, 21] There are, however, no data as to  
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3 the putative beneficial effects of beta-blockers in those COPD patients who may  
4 have concomitant silent coronary arterial disease or heart failure.  
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8 Retrospective observational data have shown beneficial effects of beta-blockers in a  
9 cohort of 5977 patients with COPD who were followed over a mean of 4.35 years  
10 [37] where their use was associated with an overall 22% (95% confidence interval 8-  
11 33) reduction in mortality. In a study b of 825 patients admitted to hospital for an  
12 exacerbation of COPD, beta-blocker use among 142 patients was associated with a  
13 61% (1-86) reduction in mortality.[38] Rutten et al showed 32% (17-44) and 29% (17-  
14 40) reductions in mortality and exacerbations, respectively, conferred by taking beta-  
15 blockers among 2230 patients with COPD followed up for a mean of 7.2 years.[39] In  
16 a cohort study from Sweden of 4858 patients with COPD, those who were  
17 discharged on a beta-blocker (84%) post myocardial infarction had 13% (2-22) lower  
18 mortality.[40] In a retrospective report of 256 patients with COPD with either  
19 coronary heart disease or heart failure, 58% were taking beta-blockers where there  
20 was a 73% (50-85) reduction in the likelihood of being admitted to a hospital  
21 emergency room.[41] In contrast, in an observational study using time dependent  
22 analysis of 2249 severe oxygen dependent COPD patients there was a 19%  
23 increase in mortality associated with taking beta-blockers.[42] However, in a  
24 prospectively followed cohort of 3464 patients Bhatt et al found a 27% (10-40)  
25 reduction in total exacerbations, while in GOLD 3/4 patients on home oxygen there  
26 was a 67% reduction (42-81).[43]  
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49 In a 2012 meta-analysis of 9 retrospective cohort studies, the pooled estimate for  
50 mortality reduction with beta-blockers was reported to be 31% (22-38).[8] In a  
51 subsequent 2014 meta-analysis of 15 retrospective studies of 21,596 patients with  
52 COPD, the pooled estimate for reduction in overall mortality conferred by beta-  
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3 blockers was 28% (17-37) and for exacerbations was 38% (18-58).[9] The reduction  
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5 in mortality was 36% (24-46) among the subgroup of patients (5 studies: 39%  
6  
7 weighting) with known coronary heart disease and 26% (7-42) in the subgroup with  
8  
9 known heart failure (3 studies: 18% weighting).  
10

11 The beneficial effects of beta-blockers on exacerbations may involve other potential  
12  
13 non-cardiac mechanisms whereby beta-blockers could reduce COPD exacerbations.  
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15 In heart failure, use of cardioselective beta-blockers reduces systemic inflammatory  
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17 cytokine release such as IL-6 and alters leukocyte distribution which may also impact  
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19 inflammation during respiratory infections.[44] Beta-blockers have also been  
20  
21 reported to inhibit neutrophil chemotaxis and oxygen free radical production,[45]  
22  
23 while in human endothelial cells they have been reported to reduce the release of  
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25 endothelin-1, a bronchoconstrictor peptide implicated in the pathogenesis of COPD  
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27 exacerbations.[46, 47]  
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31 It is not possible to eliminate the possibility of residual confounding in the  
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33 observational studies suggesting beta-blockers may reduce exacerbations and  
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35 mortality in COPD and thus definitive randomized trials are needed. There is now a  
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37 planned placebo controlled trial powered for a reduction in exacerbations using  
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39 metoprolol over 1 year via the US COPD Clinical Research Network and funded by  
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41 the Department of Defense (Clinicaltrials.gov Identifier:NCT02587351).  
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47 This study will only exclude those patients with an absolute indication for beta-  
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49 blockers including an MI or revascularization procedure within three years or with an  
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51 ejection fraction <40%. However, it remains possible that this and similar studies  
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53 may run the risk of only including patients where beta-blockers are less efficacious.  
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### The unmet cardiac need in COPD

Beta-blockers have an established position in the management of coronary artery disease while heart failure guidelines reinforce their use in patients with concomitant COPD.[51] Similarly, COPD management strategies also state that the benefits of selective beta-1 blocker treatment in heart failure clearly outweigh any potential risk associated with treatment even in patients with severe COPD.[52] Despite this guidance there is a reluctance to prescribe even cardio-selective beta-blockers in COPD, even in the presence of known cardiac disease because of persistent concerns regarding potential bronchoconstriction, especially in more severe patients. In a cohort from Scotland we found that only 14% of patients with COPD were taking beta-blockers for cardiovascular comorbidity.[37] Further evidence of a reluctance to prescribe beta-blockers in COPD was documented by Quint et al where 55% of patients who had a myocardial infarction were not prescribed a beta-blocker, with only 22% being prescribed on admission.[53] In the UK 64% of patients without COPD and acute coronary syndrome were prescribed beta-blockers as compared to 16% of similar patients with COPD who were prescribed beta-blockers.[54] Furthermore COPD was documented as a reason for withholding beta-blockers in 33% of patients who did not receive a beta-blocker, while non-cardiologists were 40% less likely to prescribe beta-blockers. In the United States, Chen et al found that elderly patients after an acute myocardial infarction were 62% less likely to be given beta-blockers in the presence of a history of treated COPD or asthma.[55] Initiating treatment with beta-blockers is not simple as it requires dose titration over a period of weeks along with monitoring of heart rate, blood pressure and perhaps spirometry, all of which take time, incurring extra healthcare costs. Moreover beta-blockers may be less well tolerated in older patients with co-existing comorbidities such as

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3 diabetes, peripheral vascular disease and renal impairment, who are more prone to  
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5 postural hypotension.  
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### 9 **Choice of beta-blocker and effects on pulmonary function (Box 2)**

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11 The mechanism of beta-blocker induced bronchoconstriction is thought to be due to  
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13 the effects of pre and post-junctional beta<sub>2</sub> receptor antagonism uncovering the  
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15 prevailing cholinergic tone via post-junctional smooth muscle muscarinic type 3  
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17 receptors, resulting in airway smooth muscle constriction.[57]  
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21 In a subgroup analysis of 2712 patients from the Tayside cohort who had serial  
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23 spirometry measures over 4 years, there was no deleterious effect of long term beta-  
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25 blocker use (88% were cardioselective) on either FEV<sub>1</sub> or FVC, even among the  
26  
27 more severe patients taking triple inhaled therapy, who had the greatest reductions  
28  
29 in exacerbations and mortality.[37] In a meta-analysis of randomized controlled trials  
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31 with cardio-selective beta-blockers there was no significant change in FEV<sub>1</sub>  
32  
33 compared to placebo, when given either as single -2.1% (-6.1-2.0) or chronic dosing  
34  
35 -2.6% (-5.9-0.8), and also no significantly effect on the FEV<sub>1</sub> response to beta<sub>2</sub>-  
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37 agonists[10]. In a randomized controlled trial of 27 patients with heart failure who  
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39 also had coexistent moderate to severe COPD, after 4 months of treatment there  
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41 was a 190ml significant fall FEV<sub>1</sub> between bisoprolol and placebo, while salbutamol  
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43 reversibility, symptoms and quality of life were unchanged.[60] In a comparison of  
44  
45 bisoprolol and placebo in patients with moderate to severe COPD, there was a  
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47 significantly worsening of dynamic hyperinflation during cycle endurance while  
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49 exercise duration was unaltered.[61] In a study comparing 24 COPD patients on  
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51 beta-blockers matched to patients not taking beta-blockers there was no difference  
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3 in exercise capacity or gas exchange despite lower heart rate and blood pressure, in  
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5 turn suggesting great oxygen delivery per heart beat.[62]  
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8 The beta-blockers currently licensed for heart failure are the beta<sub>1</sub> selective  
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10 bisoprolol, nebivolol, metoprolol and the non-selective carvedilol. As has already  
11  
12 been shown in heart failure [63] and asthma [49] it is important to slowly titrate up the  
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14 dose of beta-blocker to improve cardiovascular and pulmonary tolerability. Bisoprolol  
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16 has a licensed indication for use in heart failure and coronary artery disease and has  
17  
18 a beta<sub>1/2</sub> receptor selectivity ratio of 14:1, which is higher than either atenolol (5:1) or  
19  
20 metoprolol (2:1).[64] In a cross-over study of 51 patients with COPD and heart  
21  
22 failure, directly comparing 6 weeks of bisoprolol, metoprolol and carvedilol,[65] FEV<sub>1</sub>  
23  
24 was lowest with carvedilol and highest with bisoprolol with metoprolol in between. In  
25  
26 a randomized controlled trial comparing bisoprolol (mean dose 6.4mg) and carvedilol  
27  
28 (mean dose 47mg) in patients with heart failure and COPD, FEV<sub>1</sub> significantly  
29  
30 improved by 137ml with bisoprolol but not with carvedilol (30ml improvement).[66] In  
31  
32 15 mild to moderate COPD patients there was a significant worsening in airway  
33  
34 hyper-reactivity to methacholine challenge with metoprolol and propranolol but not  
35  
36 celiprolol compared to placebo, while the acute bronchodilator response to fenoterol  
37  
38 was only blunted by propranolol.[67]  
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44 Nebivolol has been shown to exhibit greater in vitro beta<sub>1/2</sub> receptor selectivity than  
45  
46 bisoprolol in human myocardium.[68] In healthy volunteers attenuation of beta<sub>2</sub>  
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48 receptor mediated terbutaline induced hypokalaemia was significantly greater with  
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50 bisoprolol 10mg or atenolol 50mg/100mg verses nebivolol 5mg, which in turn was  
51  
52 not different from placebo.[69] Nebivolol produced significant blunting of terbutaline  
53  
54 induced glucose and insulin responses compared to placebo in keeping with beta<sub>2</sub>  
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56 receptor antagonism at the 5mg dose. However the relative beta<sub>1/2</sub> selectivity cannot  
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3 be inferred since this would require comparison of beta-blocker doses which exhibit  
4 the same degree of beta<sub>1</sub> antagonism as assessed by exercise heart rate  
5 reduction,[70] which was not measured.  
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9 In a post hoc analysis of 2670 patients from the organized program to initiate  
10 lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF), there  
11 were no differences between selective and non-selective beta-blockers in terms of  
12 lower mortality or re-hospitalization in patients with and without COPD.[72]  
13 Carvedilol blocks both cardiac beta<sub>1</sub> and beta<sub>2</sub> receptors as well as exhibiting  
14 peripheral vasodilatation due to alpha receptor blockade, which in addition to its anti-  
15 oxidant activity [73] may explain its superiority verses metoprolol in heart failure in  
16 one particular study, which may not have compared comparable doses.[63] Until  
17 there is more convincing evidence to support the superiority of carvedilol in heart  
18 failure, it would be prudent to choose a selective agent such as bisoprolol, nebivolol  
19 or metoprolol due to their superior safety profile in COPD.  
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34 Long acting muscarinic antagonists such as tiotropium have been shown to obviate  
35 bronchoconstriction even when using non-selective beta-blockade with propranolol in  
36 asthmatic patients.[58] It is the more severe COPD patients who would in theory be  
37 most at risk of beta-blocker induced bronchoconstriction. These patients would  
38 usually already be taking concomitant LAMA and hence be protected from  
39 bronchospasm. The relatively small degree of dose related beta<sub>2</sub> receptor  
40 antagonism conferred for example by bisoprolol [59] would not be expected to result  
41 in worsening of pulmonary function. It is also important to consider the potential  
42 impact of beta<sub>2</sub> receptor genotype on the risk-benefit equation with beta-blockers in  
43 COPD. It has been shown that asthmatic patients who possess one or two copies of  
44 the arginine-16 beta<sub>2</sub> receptor polymorphism are more prone to propranolol induced  
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3 bronchoconstriction in terms of FEV<sub>1</sub> and airway resistance.[75] While the arginine-  
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5 16 polymorphism conferred a worse outcome on survival in patients receiving  
6  
7 metoprolol after an acute coronary syndrome,[76] it was not associated with survival  
8  
9 in HF patients treated with metoprolol or carvedilol.[77]  
10

### 11 12 13 14 **Conclusions and the ways forward (Box 3)**

15  
16 There are compelling reasons to use cardio-selective beta-blockers in patients with  
17  
18 COPD who have coexistent heart failure or are post myocardial infarction. Current  
19  
20 evidence would suggest that there remains a reticence to prescribe beta-blockers in  
21  
22 such patients because of a fear of adverse events, particularly worsened lung  
23  
24 function. Further prospective medium term safety studies are therefore required to  
25  
26 carefully follow effects of cardio-selective drugs on pulmonary function in patients  
27  
28 with more severe COPD by employing slow initial dose titration as well as evaluating  
29  
30 their interaction with long acting bronchodilators (ClinicalTrials.gov  
31  
32 Identifier:NCT01656005).  
33  
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35

36 There is currently not sufficient evidence to advocate treatment with beta-blockers  
37  
38 for the prevention of exacerbations or exacerbation-related mortality. Long term  
39  
40 placebo controlled multicenter trials in COPD are indicated to confirm the benefits of  
41  
42 beta-blockers already seen on mortality and exacerbations in observational studies.  
43  
44 The key question to answer is whether the potential benefits of beta-blockers are  
45  
46 confined to those patients with known cardiovascular disease or are present in the  
47  
48 wider population who may have silent cardiovascular disease. Likewise, beta-  
49  
50 blockers are not currently indicated in COPD patients with diastolic dysfunction alone  
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52 where controlled trials are also warranted.  
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3 Beta-blockers are likely to be part of a more complex therapeutic jigsaw in  
4  
5 addressing the composite risk from different cardiovascular abnormalities in COPD,  
6  
7 and as has already been shown with heart failure there may be additive effects from  
8  
9 drugs acting on other neuro-hormonal pathways. This includes drugs which block the  
10  
11 renin-angiotensin system that may be particularly effective at regressing left  
12  
13 ventricular hypertrophy.[78] Dual angiotensin/neprolysin inhibition [79] may also  
14  
15 confer benefits by augmenting BNP levels and ameliorate the adverse effects of  
16  
17 hypoxic pulmonary vasoconstriction.[80, 81] Anti-platelet drugs might also be  
18  
19 beneficial for treating silent coronary artery disease in more severe COPD patients  
20  
21 who are oxygen dependent.[42] Pulmonologists have tended to focus on drugs  
22  
23 which act on the lung rather than the heart, because of the evidence supporting the  
24  
25 former. Perhaps now is time to look at the lungs' next door neighbour in the chest  
26  
27 and begin to address the unmet need of cardiac disease in COPD.  
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### Potential cardiac targets for beta-blockers in COPD (Box 1)

- Improved left ventricular systolic and diastolic function
- Reduced left ventricular dilatation
- Protection against myocardial ischemia
- Reduced left ventricular mass
- Reduced heart rate
- Anti-arrhythmic effects
- Inhibition of myocyte apoptosis
- Protection against hypoxic sympathetic drive
- Protection against adverse effects of beta-agonists

### Potential non-cardiac targets for beta-blockers in COPD

- Inhibition of endothelin-1 release
- Reduction in circulating pro-inflammatory cytokines
- Inhibition of neutrophil chemotaxis and respiratory burst
- Reduction in Goblet cell number and mucus release



**Prescribing of beta-blockers in COPD for cardiovascular disease (Box 2)**

- Beta-1 selective antagonists including metoprolol, bisoprolol and nebivolol exhibit dose related beta-2 receptor blockade
- Carvedilol is a non-selective beta-antagonist which is more likely to cause bronchoconstriction than beta-1 selective antagonists
- Slowly titrate the dose of beta-blockers at 1-2 weekly intervals up to the usual maintenance dose
- Monitor supine and erect blood pressure, heart rate and spirometry during dose titration
- Concomitant long-acting muscarinic antagonists may obviate potential bronchoconstriction
- Symptomatic bradycardia may occur if beta-blockers are used with other rate limiting drugs such as calcium blockers (e.g. verapamil, diltiazem), ivabradine or anti-arrhythmic agents (e.g. digoxin, amiodarone, flecainide)
- Symptomatic hypotension may occur when beta-blockers are used with other vasodilator drugs (e.g. angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, alpha receptor blockers)

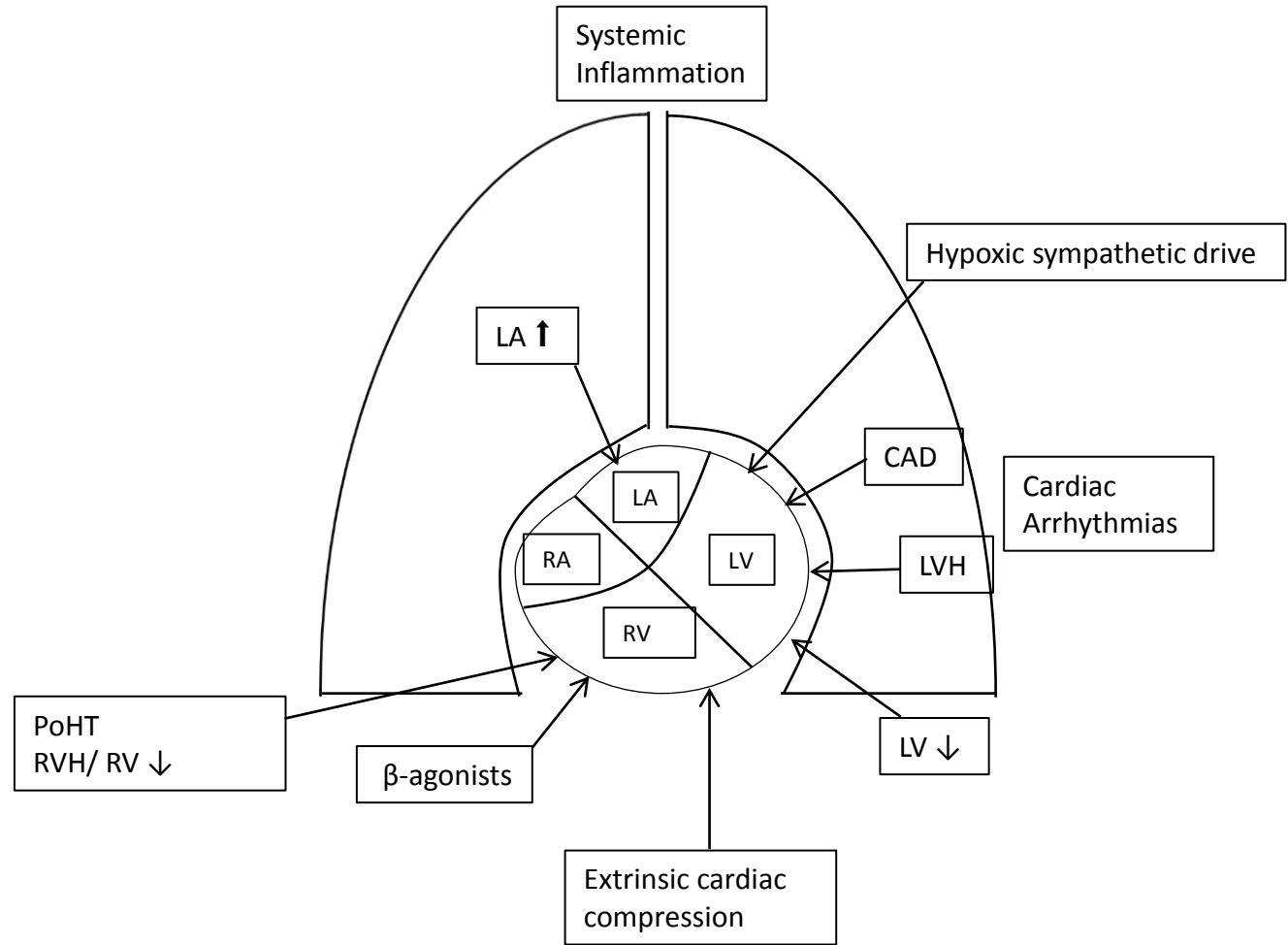
**Key messages (Box 3)**

- Cardiovascular comorbidity, including coronary artery disease and heart failure, commonly coexists in COPD due to the effects of smoking, systemic inflammation, hypoxaemia and other shared risks.
- COPD may also be associated with impaired diastolic filling due to lung hyperinflation, which may be compounded by the negative lusitropic effects of hypoxaemia and left ventricular hypertrophy.
- The main indications for beta blockers in patients with COPD are post myocardial infarction and heart failure with reduced ejection fraction. Despite clear evidence beta-blockers improve outcomes in these COPD patients they remain significantly underused due to concerns about adverse respiratory effects, even with beta-1 selective antagonists.
- Meta-analyses of retrospective studies with beta-blockers in COPD have shown pooled estimates for reductions in mortality of 28% and exacerbations of 38%.
- Initiating treatment with beta-blockers requires careful dose titration and monitoring. This may be particularly relevant for patients with COPD who are often older and have other comorbidities that increase the risk of intolerance.
- Beta-1 selective antagonists such as bisoprolol, nebivolol and metoprolol are preferred to the non-selective carvedilol as they are less likely to produce bronchoconstriction in COPD.

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- Long acting muscarinic antagonists, which are commonly used in COPD protect against the potential for bronchoconstriction due to dose related beta-2 receptor antagonism.
- The key unanswered question is whether beta-blockers may confer benefits on mortality and exacerbations in all patients with COPD including those with silent cardiovascular disease.

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Cardio-pulmonary interactions in COPD



LA ↑ left atrial dilatation , LV ↓ : reduced LV filling LVH: left ventricular hypertrophy  
CAD: coronary artery disease, PoHT: pulmonary hypertension , RV ↓:reduced right ventricular filling  
RVH: right ventricular hypertrophy

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