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Beta-blockers in COPD: time for reappraisal

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"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.

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

impact on pulmonary function, and 5) attempted to draw conclusions about the current clinical use of beta-blockers in COPD.

COPD and the heart (Figure 1 and Box 1)

The main accepted clinical indications for the use of beta-blockers in COPD are for patients post myocardial infarction and for patients with heart failure. However, the presence of untreated or unrecognized (i.e. silent) cardiovascular disease may contribute to mortality in COPD and may also be an underlying causative factor in exacerbations which can be difficult to separate from respiratory etiologies.[6] [7] It is also possible, if not likely, that the burden of cardiovascular disease may be under-rated by pulmonologists when treating COPD patients because symptoms are presumed to be primarily driven by airflow obstruction, especially during exacerbations.

The prevalence of left ventricular systolic dysfunction ranges between 10-46% in patients with COPD and though the occurrence of heart failure with preserved left ventricular ejection fraction is less clear, estimates in patients with severe COPD are as high as 90%.[7] The benefits of beta-blockers in patients with heart failure due to left ventricular systolic dysfunction are well established from pivotal trials as well as meta-analysis.[21-24] The challenge in COPD may be more with respect to diagnosis of heart failure with echocardiography where image acquisition is difficult due to lung hyperinflation.[25]

Beta-blockers only have proven benefits in patients post myocardial infarction but not in stable coronary arterial disease.[11, 12] Nevertheless, the presence of coronary calcium on chest CT scans is associated with mortality in COPD,[13] and known coronary arterial disease is also associated with longer exacerbations, more

dyspnoea, lower health status and exercise capacity in stable patients with COPD.[14] There is also an acute increase in arterial stiffness particularly during infective exacerbations of COPD, along with increases in cardiac enzymes especially in patients with coronary arterial disease;[15] one study found that one in twelve patients admitted to hospital with an exacerbation of COPD met the criteria for a myocardial infarction.[16] The presence of coronary heart disease in COPD along with the adverse effects of hypoxaemia [17] may be compounded by the positive chronotropic effects of concomitant inhaled beta-agonist therapy,[18, 19] further compromising cardiac reserve. It has been shown that even a low dose of a beta-1 selective antagonist such as atenolol might protect against chronotropic, inotropic and electrocardiographic effects of inhaled beta-agonists which are mediated by cardiac $beta_2$ receptor stimulation.[20]

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

a fall in the ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) was associated with reduced left atrial size and cardiac output.[32] Left ventricular end diastolic and end systolic wall stress measured by magnetic resonance imaging (MRI) is associated with increasing severity of airflow obstruction in patients with COPD and coexistent heart failure.[33] Impaired left ventricular filling is clinically important because it can eventually produce left atrial enlargement which is a key risk factor for atrial fibrillation and associated mortality during exacerbations of COPD.[34] Furthermore, the presence of impaired diastolic filling in patients with COPD is also related to impaired walking distance.[35] Thus, the absence of benefits of beta-blockers in diastolic dysfunction may not apply in COPD and deserved re-evaluation in this patient group.

Effects of beta-blockers on mortality and exacerbations

Due to the high cardiovascular comorbidity in COPD from smoking along with increased sympathetic drive due to hypoxaemia,[36] beta-blockers have been proposed as a cogent therapeutic intervention for their known cardio-protective effects in addition to reducing heart rate and improving systolic and diastolic dysfunction. One of the fundamental issues with regards to more widespread use of beta-blockers in COPD is the concern regarding $beta_2$ receptor antagonism and associated airway smooth muscle constriction which may even occur with cardio-selective agents which exhibit preferential $beta_1$ blockade, especially in more susceptible severe patients with impaired respiratory reserve. The risk-benefit equation in COPD becomes more favorable for patients who already have overt cardiac disease such as heart failure or post myocardial infarction, where beta-blockers have proven protective effects.[11, 21] There are, however, no data as to

the putative beneficial effects of beta-blockers in those COPD patients who may have concomitant silent coronary arterial disease or heart failure.

Retrospective observational data have shown beneficial effects of beta-blockers in a cohort of 5977 patients with COPD who were followed over a mean of 4.35 years [37] where their use was associated with an overall 22% (95% confidence interval 8-33) reduction in mortality. In a study b of 825 patients admitted to hospital for an exacerbation of COPD, beta-blocker use among 142 patients was associated with a 61% (1-86) reduction in mortality.[38] Rutten et al showed 32% (17-44) and 29% (17-40) reductions in mortality and exacerbations, respectively, conferred by taking beta-blockers among 2230 patients with COPD followed up for a mean of 7.2 years.[39] In a cohort study from Sweden of 4858 patients with COPD, those who were discharged on a beta-blocker (84%) post myocardial infarction had 13% (2-22) lower mortality.[40] In a retrospective report of 256 patients with COPD with either coronary heart disease or heart failure, 58% were taking beta-blockers where there was a 73% (50-85) reduction in the likelihood of being admitted to a hospital emergency room.[41] In contrast, in an observational study using time dependent analysis of 2249 severe oxygen dependent COPD patients there was a 19% increase in mortality associated with taking beta-blockers.[42] However, in a prospectively followed cohort of 3464 patients Bhatt et al found a 27% (10-40) reduction in total exacerbations, while in GOLD 3/4 patients on home oxygen there was a 67% reduction (42-81).[43]

In a 2012 meta-analysis of 9 retrospective cohort studies, the pooled estimate for mortality reduction with beta-blockers was reported to be 31% (22-38).[8] In a subsequent 2014 meta-analysis of 15 retrospective studies of 21,596 patients with COPD, the pooled estimate for reduction in overall mortality conferred by beta-

blockers was 28% (17-37) and for exacerbations was 38% (18-58).[9] The reduction in mortality was 36% (24-46) among the subgroup of patients (5 studies: 39% weighting) with known coronary heart disease and 26% (7-42) in the subgroup with known heart failure (3 studies: 18% weighting).

The beneficial effects of beta-blockers on exacerbations may involve other potential non-cardiac mechanisms whereby beta-blockers could reduce COPD exacerbations. In heart failure, use of cardioselective beta-blockers reduces systemic inflammatory cytokine release such as IL-6 and alters leukocyte distribution which may also impact inflammation during respiratory infections.[44] Beta-blockers have also been reported to inhibit neutrophil chemotaxis and oxygen free radical production,[45] while in human endothelial cells they have been reported to reduce the release of endothelin-1, a bronchoconstrictor peptide implicated in the pathogenesis of COPD exacerbations.[46, 47]

It is not possible to eliminate the possibility of residual confounding in the observational studies suggesting beta-blockers may reduce exacerbations and mortality in COPD and thus definitive randomized trials are needed. There is now a planned placebo controlled trial powered for a reduction in exacerbations using metoprolol over 1 year via the US COPD Clinical Research Network and funded by the Department of Defense (Clinicaltrials.gov Identifier:NCT02587351).

This study will only exclude those patients with an absolute indication for beta-blockers including an MI or revascularization procedure within three years or with an ejection fraction <40%. However, it remains possible that this and similar studies may run the risk of only including patients where beta-blockers are less efficacious.

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 mycocardial 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

diabetes, peripheral vascular disease and renal impairment, who are more prone to postural hypotension.

Choice of beta-blocker and effects on pulmonary function (Box 2)

The mechanism of beta-blocker induced bronchoconstriction is thought to be due to the effects of pre and post-junctional beta$_2$ receptor antagonism uncovering the prevailing cholinergic tone via post-junctional smooth muscle muscarinic type 3 receptors, resulting in airway smooth muscle constriction.[57]

In a subgroup analysis of 2712 patients from the Tayside cohort who had serial spirometry measures over 4 years, there was no deleterious effect of long term beta-blocker use (88% were cardioselective) on either FEV_1 or FVC, even among the more severe patients taking triple inhaled therapy, who had the greatest reductions in exacerbations and mortality.[37] In a meta-analysis of randomized controlled trials with cardio-selective beta-blockers there was no significant change in FEV_1 compared to placebo, when given either as single -2.1% (-6.1-2.0) or chronic dosing -2.6% (-5.9-0.8), and also no significantly effect on the FEV_1 response to beta$_2$-agonists[10]. In a randomized controlled trial of 27 patients with heart failure who also had coexistent moderate to severe COPD, after 4 months of treatment there was a 190ml significant fall FEV_1 between bisoprolol and placebo, while salbutamol reversibility, symptoms and quality of life were unchanged.[60] In a comparison of bisoprolol and placebo in patients with moderate to severe COPD, there was a significantly worsening of dynamic hyperinflation during cycle endurance while exercise duration was unaltered.[61] In a study comparing 24 COPD patients on beta-blockers matched to patients not taking beta-blockers there was no difference

in exercise capacity or gas exchange despite lower heart rate and blood pressure, in turn suggesting great oxygen delivery per heart beat.[62]

The beta-blockers currently licensed for heart failure are the $beta_1$ selective bisoprolol, nebivolol, metoprolol and the non-selective carvedilol. As has already been shown in heart failure [63] and asthma [49] it is important to slowly titrate up the dose of beta-blocker to improve cardiovascular and pulmonary tolerability. Bisoprolol has a licensed indication for use in heart failure and coronary artery disease and has a $beta_{1/2}$ receptor selectivity ratio of 14:1, which is higher than either atenolol (5:1) or metoprolol (2:1).[64] In a cross-over study of 51 patients with COPD and heart failure, directly comparing 6 weeks of bisoprolol, metoprolol and carvedilol,[65] FEV_1 was lowest with carvedilol and highest with bisoprolol with metoprolol in between. In a randomized controlled trial comparing bisoprolol (mean dose 6.4mg) and carvedilol (mean dose 47mg) in patients with heart failure and COPD, FEV_1 significantly improved by 137ml with bisoprolol but not with carvedilol (30ml improvement).[66] In 15 mild to moderate COPD patients there was a significant worsening in airway hyper-reactivity to methacholine challenge with metoprolol and propranolol but not celiprolol compared to placebo, while the acute bronchodilator response to fenoterol was only blunted by propranolol.[67]

Nebivolol has been shown to exhibit greater in vitro $beta_{1/2}$ receptor selectivity than bisoprolol in human myocardium.[68] In healthy volunteers attenuation of $beta_2$ receptor mediated terbutaline induced hypokalaemia was significantly greater with bisoprolol 10mg or atenolol 50mg/100mg verses nebivolol 5mg, which in turn was not different from placebo.[69] Nebivolol produced significant blunting of terbutaline induced glucose and insulin responses compared to placebo in keeping with $beta_2$ receptor antagonism at the 5mg dose. However the relative $beta_{1/2}$ selectivity cannot

be inferred since this would require comparison of beta-blocker doses which exhibit the same degree of $beta_1$ antagonism as assessed by exercise heart rate reduction,[70] which was not measured.

In a post hoc analysis of 2670 patients from the organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF), there were no differences between selective and non-selective beta-blockers in terms of lower mortality or re-hospitalization in patients with and without COPD.[72] Carvedilol blocks both cardiac $beta_1$ and $beta_2$ receptors as well as exhibiting peripheral vasodilatation due to alpha receptor blockade, which in addition to its anti-oxidant activity [73] may explain its superiority verses metoprolol in heart failure in one particular study, which may not have compared comparable doses.[63] Until there is more convincing evidence to support the superiority of carvedilol in heart failure, it would be prudent to choose a selective agent such as bisoprolol, nebivolol or metoprolol due to their superior safety profile in COPD.

Long acting muscarinic antagonists such as tiotropium have been shown to obviate bronchoconstriction even when using non-selective beta-blockade with propranolol in asthmatic patients.[58] It is the more severe COPD patients who would in theory be most at risk of beta-blocker induced bronchoconstriction. These patients would usually already be taking concomitant LAMA and hence be protected from bronchospasm. The relatively small degree of dose related $beta_2$ receptor antagonism conferred for example by bisoprolol [59] would not be expected to result in worsening of pulmonary function. It is also important to consider the potential impact of $beta_2$ receptor genotype on the risk-benefit equation with beta-blockers in COPD. It has been shown that asthmatic patients who possess one or two copies of the arginine-16 $beta_2$ receptor polymorphism are more prone to propranolol induced

bronchoconstriction in terms of FEV_1 and airway resistance.[75] While the arginine-16 polymorphism conferred a worse outcome on survival in patients receiving metoprolol after an acute coronary syndrome,[76] it was not associated with survival in HF patients treated with metoprolol or carvedilol.[77]

Conclusions and the ways forward (Box 3)

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

There is currently not sufficient evidence to advocate treatment with beta-blockers for the prevention of exacerbations or exacerbation-related mortality. Long term placebo controlled multicenter trials in COPD are indicated to confirm the benefits of beta-blockers already seen on mortality and exacerbations in observational studies. The key question to answer is whether the potential benefits of beta-blockers are confined to those patients with known cardiovascular disease or are present in the wider population who may have silent cardiovascular disease. Likewise, beta-blockers are not currently indicated in COPD patients with diastolic dysfunction alone where controlled trials are also warranted.

Beta-blockers are likely to be part of a more complex therapeutic jigsaw in addressing the composite risk from different cardiovascular abnormalities in COPD, and as has already been shown with heart failure there may be additive effects from drugs acting on other neuro-hormonal pathways. This includes drugs which block the renin-angiotensin system that may be particularly effective at regressing left ventricular hypertrophy.[78] Dual angiotensin/neprolysin inhibition [79] may also confer benefits by augmenting BNP levels and ameliorate the adverse effects of hypoxic pulmonary vasoconstriction.[80, 81] Anti-platelet drugs might also be beneficial for treating silent coronary artery disease in more severe COPD patients who are oxygen dependent.[42] Pulmonologists have tended to focus on drugs which act on the lung rather than the heart, because of the evidence supporting the former. Perhaps now is time to look at the lungs' next door neighbour in the chest 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)

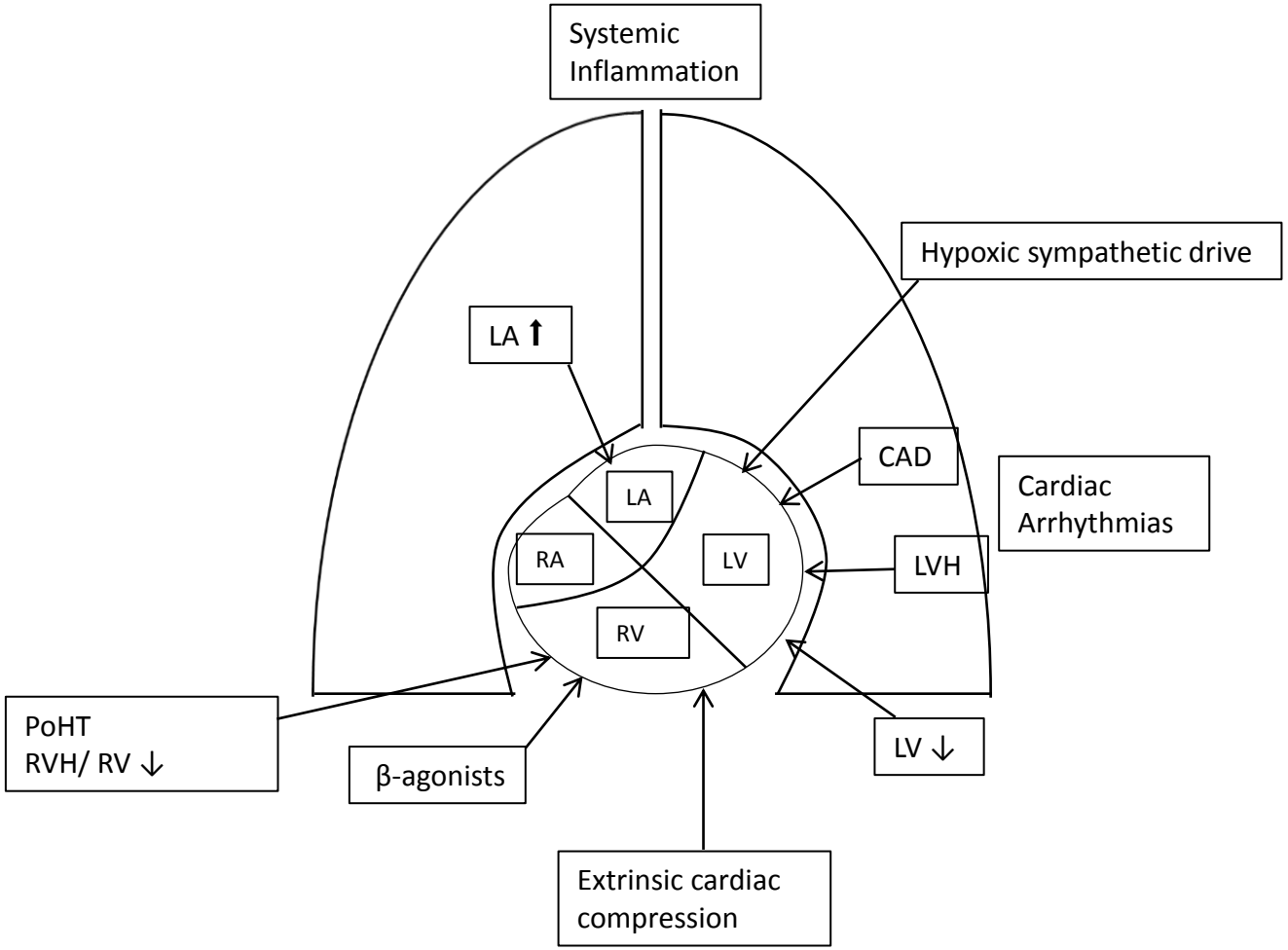
- Beta-1 selective antagonists including metoprolol, bisoprolol and nebivolol exhibit dose related beta-2 receptor blockade
- Carvedilol is a non-selective beta-antagonist which is more likely to cause bronchoconstriction than beta-1 selective antagonists
- Slowly titrate the dose of beta-blockers at 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.

- 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.

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