β -Blockers, heart disease and COPD: current controversies and uncertainties

Jillian G Baker,¹ Robert G Wilcox²

¹Respiratory Medicine, Cell Signalling, School of Life Sciences, University of Nottingham, Nottingham, UK
²Department of Clinical Neurosciences, Queen's Medical Centre, University of Nottingham, Nottingham, UK

Correspondence to
 Professor Jillian G Baker,
 Respiratory Medicine, Cell Signalling, School of Life Sciences, C Floor Medical School, Queen's Medical Centre, University of Nottingham, Nottingham NG11 2UH, UK;
 jillian.baker@nottingham.ac.uk

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ABSTRACT

Treating people with cardiovascular disease and COPD causes significant clinician anxiety. β -Blockers save lives in people with heart disease, specifically postinfarction and heart failure. COPD and heart disease frequently coexist and people with both disorders have particularly high cardiovascular mortality. There are concerns about giving β -blockers to people with concomitant COPD that include reduced basal lung function, diminished effectiveness of emergency β -agonist treatments, reduced benefit of long-acting β -agonist treatment and difficulty in discriminating between asthma and COPD. β -Blockers appear to reduce lung function in both the general population and those with COPD because they are poorly selective for cardiac β_1 -adrenoceptors over respiratory β_2 -adrenoceptors, and studies have shown that higher β -agonist doses are required to overcome the β -blockade. COPD and cardiovascular disease share similar environmental risks and both disease states have high adrenergic and inflammatory activation. β -Blockers may therefore be particularly helpful in reducing cardiovascular events in this high-risk group. They may reduce the background inflammatory state, and inhibit the tachycardia and hypertension associated with both the endogenous adrenaline and high-dose β -agonist treatment associated with acute exacerbations of COPD. Some studies have suggested no increased and, at times, reduced mortality in patients with COPD taking β -blockers for heart disease. However, these are all observational studies and there are no randomised controlled trials. Potential ways to improve this dilemma include the development of highly β_1 -selective β -blockers or the use of non- β -blocking heart rate reducing agents, such as ivabradine, if these are proven to be beneficial in randomised controlled trials.

β -Blockers save lives in people with cardiovascular disease. They reduce mortality in patients with heart failure and postmyocardial infarction (MI). β -Blockers are also first-line therapy for several atrial arrhythmias, are important in managing symptoms in patients with angina and in the treatment of hypertension, thyrotoxicosis, portal hypertension, migraine, glaucoma and anxiety. However, there is significant theoretical and clinical concern about giving β -blockers to patients with cardiovascular disease who also have obstructive lung disease. This review focuses on the dilemma of using β -blockers in people with COPD and heart disease, but it is important to remember this dilemma extends to those with peripheral vascular disease (in whom β -blockade can worsen limb ischaemia) and those with asthma (in whom

β -blockade can be life-threatening). This review does not address the issue of β -blockers in people with asthma, in whom β -blockers remain contraindicated (section 7.11.7¹).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In England, the Department of Health estimates that 3.2 million people have COPD and 40% of these patients also have heart disease,² especially heart failure.^{3–4} People with COPD and heart disease have a particularly high risk of death from heart disease and stroke (2–5 times higher than those with heart disease alone^{5–6}). As β -blockade is highly desirable in this high-risk group, it is therefore very important to sort out the thorny issue of whether any, some or all of these patients can be given a β -blocker and how this can be safely achieved in everyday clinical practice and not just within a carefully monitored study population.

The definition of COPD includes 'airflow limitation that is not fully reversible'.⁷ Theoretically, patients with COPD have significant fixed, irreversible airways obstruction and therefore little reversibility and so β -blockade should pose no risk. Global initiative for chronic obstructive lung disease (GOLD)⁷ recommend that ideally the obstruction should be measured postbronchodilator (in order to truly assess the degree of 'fixed' obstruction), although for practical reasons this is not always followed in the real world. The problem is that possibly half of patients with a diagnosis of COPD have some significant reversibility and up to 50% of patients change from being 'irreversible' to 'reversible' between visits, making it difficult for the clinician to be certain of a real 'fixed' component.^{8–10}

Traditionally reversibility has been defined as >12% improvement, or 200 mL increase, in FEV₁. However, the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force concluded that for COPD, a 100 mL change in FEV₁ was clinically significant and a 5%–10% change from baseline clinically important.¹¹ Furthermore, β_2 -agonists are the mainstay of treatment in COPD and have been proven to improve lung function, breathlessness and quality of life, and to reduce the exacerbation rate (many studies including^{12–14}).

β -BLOCKERS

β -Blockers were developed by Sir James Black in the 1960s for the treatment of hypertension and angina¹⁵ and there are now many different β -blockers available for use in patients. β -Blockers primarily have their beneficial effects by blocking the β_1 -adrenoceptors in the heart¹⁴ and thus preventing the action of endogenous catecholamines adrenaline and noradrenaline. Therefore, β -blockade

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results in a reduction in both the rate and force of contraction and thus a reduction in myocardial demand and, beyond doubt, reduce mortality in heart disease (table 1).^{16–20}

In patients with heart failure, randomised placebo-controlled trials have demonstrated a 34%–35% reduction in mortality (metoprolol,²¹ bisoprolol,²² carvedilol²³). A further β -blocker, nebivolol, was found useful in elderly patients.²⁴ However, β -blockers are not a single entity and differ, among other properties, in their receptor selectivity (between β 1-adrenoceptors and β 2-adrenoceptors) and in the extent of intrinsic sympathomimetic activity (ISA, or partial agonism). In heart failure, the two studies that examined β -blockers with ISA, were found to be not beneficial (bucindolol²⁵) or actually increased mortality (xamoterol²⁶). In ischaemic heart disease, a variety of β -blockers without ISA reduced mortality during the acute MI period (usually taken as 2 years), for example, timolol by 39%,²⁷ propranolol by 26%²⁸ and metoprolol by 36%,²⁹ whereas trials with β -blockers with ISA (eg, oxprenolol and pindolol) did not show beneficial effects.^{30–33}

Although β 1-adrenoceptors predominate, the human heart also has a small proportion of β 2-adrenoceptors.^{34–35} Animal studies have suggested that long-term activation of β 1-adrenoceptors has more marked deleterious effects than activation of β 2-adrenoceptors,³⁶ and the beneficial effects of β -blockers are therefore attributed to β 1-blockade.¹⁶

The β -adrenoceptor present in the lungs is the β 2-adrenoceptor. Stimulation of these β 2-adrenoceptors results in bronchodilation and this has been the mainstay of treatment for both short-term rescue and long-term maintenance in patients with asthma and COPD for decades.³⁷ Current β -blockers are poorly selective for the cardiac β 1-receptors over the respiratory β 2-receptors.^{38–41} Even those considered ‘cardio-selective’ are actually poorly β 1-selective, with a β 1-selectivity of only 13-fold to 19-fold (eg, bisoprolol^{38–40}). To put this in context, the β 2-agonist salmeterol has a β 2-selectivity of

1000–3000 over the β 1-adrenoceptor, and commonly used laboratory antagonists are about 500-fold selective for their respective β 1-adrenoceptor or β 2-adrenoceptor subtypes. Thus, current β -blockers available for clinical use, even those considered to be the most cardioselective, can cause the β 2-mediated respiratory side effects of bronchospasm or a fall in FEV₁ in susceptible individuals.⁴²

THEORETICAL AND CLINICAL STUDY CONCERNS OF β -BLOCKERS IN COPD

There are several theoretical concerns over giving β -blockers to patients with COPD. First, a β -blocker may reduce the patient’s basal (stable) FEV₁, and in severe disease, even a small decrease in lung function could have a major impact on symptoms. Second, a β -blocker would diminish the response to rescue β 2-agonist therapy. Thus, during an acute exacerbation a β -blocked patient may have a lack or diminished response to important and potential life-saving β 2-agonist rescue therapy. This would occur even if the β -blocker is well tolerated while the patient was stable. Third, there is concern that the long-term co-administration of a β -blocker would block or reduce the long-term beneficial effects reported with long-acting β 2-agonist therapy (table 2).

Several clinical studies have shown that β -blockers do reduce FEV₁. In a recent large general population study, non-selective β -blockers reduced FEV₁ by 198 mL and ‘cardioselective’ β -blockers by 118 mL,⁴³ that is, above the ATS/ERS Task Force ceiling of 100 mL change in FEV₁ being clinically significant in COPD. This population included people with asthma and COPD. If these people (ie, those at high risk of bronchospasm) were excluded, the reduction in FEV₁ was still over 100 mL, even with ‘cardioselective’ β -blockers. Furthermore in the general population, FEV₁ increased in those who stopped taking β -blockers during the study. Other studies in patients with COPD report a fall in lung function and wheeze with

Table 1 Overview of effects of β -agonists and β -blockers on organs relevant to cardiovascular and respiratory disease

	Effect of adrenaline/noradrenaline or β -agonists: ‘fight or flight response’	Effect of β -blockers
<div>Heart</div> <div>β1</div>	Increase in heart rate Increase in force of contraction Increase cardiac output	Reduction in heart rate Reduction in force of contraction Reduction in cardiac output Beneficial in heart disease (eg, heart failure, ischaemic heart disease, arrhythmia)
<div>Lungs</div> <div>β2</div>	Bronchodilatation	Risk of bronchoconstriction in susceptible individuals (eg, those with asthma, COPD)
<div>Leg blood vessels</div> <div>β2</div>	Vasodilatation	Risk of vasoconstriction or worsening of ischaemia in susceptible individuals (eg, those with peripheral vascular disease)

Images from Clipart.

Table 2 Theoretical risks and benefits for those with heart disease and COPD treated with β -blockers (over and above the known cardiovascular benefits)

Theoretical risks of β -blockers	Theoretical benefits of β -blockers
Reduction in basal lung function	Inhibition of cardiac stimulation by increased endogenous catecholamines during exacerbation
Reduction in efficacy of emergency rescue β -agonists	Inhibition of cardiac stimulation of β -agonists given during exacerbation
Reduction in efficacy of long-acting β -agonist	Potential reduction in systemic inflammation
Concern over distinguishing COPD from asthma	

propranolol and metoprolol.^{44 45} A study directly examining β -blocker tolerability in patients with concomitant heart disease and carefully documented airways disease, found that β -blockers were tolerated by 84% of the COPD patients (but only 50% with asthma).⁴⁶

A complication of examining historical β -blocker studies for safety in obstructive airways disease is that many of the older studies used β -blockers that are no longer recommended. For example, β -blockers with ISA (ie, partial agonists^{41 47 48}) were thought to be beneficial because they would block the potentially harmful effect of high levels of catecholamines while providing a background increased sympathetic activation to maintain cardiac output and prevent bronchospasm.⁴⁹ Clinical studies have since shown that β -blockers with agonist activity are not beneficial, and even detrimental, in cardiovascular therapy and so are no longer recommended. A Cochrane review concluded that β -blockers were safe in patients with COPD.⁵⁰ However, 11 of the original 20 studies cited were one day, single-dose studies in patients with stable COPD. The remainder were of short duration (2 days to 12 weeks), and many studies used β -blockers with ISA that are not now recommended. Furthermore, the limitations listed by the authors included small sample size studies, 80% were male patients, randomisation was not always clear, some studies were only single blinded and some had no placebo controls.

To assess the safety of β -blockers in people with COPD, and particularly to assess their safety during exacerbations, long-term clinical studies are needed. Dorow *et al*⁵¹ studied the effects of bisoprolol and atenolol in 40 patients with COPD and angina in a double-blind cross-over study. They reported a 460 mL/min reduction in peak expiratory flow rate (PEFR) following 6 months bisoprolol and a 270 mL reduction in PEFR with atenolol. They also showed that the decrease in FEV₁ improved during the washout period after the β -blocker was stopped, suggesting the decline was treatment related rather than disease progression. Hawkins *et al*⁵² studied bisoprolol in patients with heart failure and COPD and found a 70 mL reduction in FEV₁ with bisoprolol (14 patients), while a 120 mL increase in FEV₁ with placebo (13 patients). They also assessed symptoms and concluded that 'despite the fall in FEV₁, symptoms and quality of life were not impaired'. Another cross-over study looking at lung function in heart failure patients taking carvedilol, metoprolol and bisoprolol noted that the biggest reduction in lung function was in those taking the least β 1-selective β -blocker carvedilol.⁵³

Thus, β -blockers are associated with a reduction of lung function (FEV₁) in the general population and in those with COPD, and the β 1-selectivity versus β 2-selectivity of the β -blocker used appears to play a part.

A recent study examined the effect of β -blockers on mortality in patients with severe, oxygen-dependent COPD.⁵⁴ In this prospective study, which attempted to account for the immortal time bias⁵⁵ and immeasurable time bias⁵⁶ suggested to be present in many other COPD and β -blocker studies,⁵⁷ Ekström *et al* reported an increased mortality in patients with severe COPD taking β -blockers.

THEORETICAL AND CLINICAL STUDY BENEFITS OF β -BLOCKERS IN COPD

There are several theoretical reasons why β -blockers could be protective in the COPD population (table 2). COPD and heart disease share environmental risk factors (smoking and pollution) and both share pathophysiological factors—high adrenergic activation and increased systemic inflammation.^{20 58 59} A deterioration or exacerbation of either disease will increase both the adrenergic and inflammatory state, which could potentially worsen the other condition. Furthermore, β -adrenergic activation and immunomodulation are linked.^{60–62} β -blockers have been shown to reduce cytokines in patients with heart failure⁶³ and improve outcomes in sepsis.⁶⁴ So, first, β -blockers may reduce the background risk of exacerbation of both COPD and heart disease by lowering both the background adrenergic and inflammatory states (which may include both systemic inflammation and organ-specific inflammation).

Second, during an exacerbation of COPD, there are yet higher circulating catecholamines. This increases the risk of myocardial ischaemia, tachycardias, deterioration in heart failure and hypertension (and therefore stroke risk). β -Blockers could counteract all of these endogenous exacerbation-associated cardiovascular risks.

Third, during an exacerbation of COPD, patients are treated with β -agonists (often nebulised salbutamol), which in themselves cause significant tachycardia. Salbutamol (especially when nebulised) is significantly systemically absorbed but this compound is also a poorly selective ligand⁴¹ and will cause activation of cardiac β 1-adrenoceptors. Treatment with β 2-agonists has been shown to precipitate MI and increase adverse cardiovascular events.^{65–68} β -Blockade might also prevent this drug-induced cardiovascular risk.

There are several observational studies suggesting that β -blockers are effective in heart disease in people with COPD, the benefit outweighing the risk in terms of improved overall survival. Following an MI, Gottlieb *et al*⁶⁹ noted a 40% reduction in mortality with β -blockers (in keeping with the later randomised controlled trials), for those with and those without COPD. Lower all-cause mortality was also observed in COPD patients post-MI by Quint *et al*⁷⁰ (average follow-up 2.9 years) and Andell *et al*⁷¹ (average follow-up 2.8 years). Quint *et al* used data from the Myocardial Ischaemia National Audit Project and highlighted the ongoing uncertainty of prescribing β -blockers to patients with COPD, for only 38% were taking one of seven β -blockers on discharge, despite a very high uptake of other drugs for secondary prophylaxis. In another study in people with heart failure and COPD, patients taking β -blockers had less exacerbations and emergency room visits (although exacerbation here was taken as any change from the stable state, be that cardiovascular, respiratory or anything else).⁷²

With regard to the general COPD population, observational studies have reported lower exacerbation rates and improved survival in patients with COPD and cardiovascular disease treated with β -blockers.^{73 74} Others also reported a decrease in COPD exacerbations, including in people with severe COPD and those on home oxygen (in contrast to the study by Ekström

*et al*⁵⁴), and that this benefit was only seen with β -blockers, not with ACE inhibitors or calcium channel blockers, suggesting there is something special about β -blockers that reduced exacerbations.⁷⁵ This issue is to be further investigated in a placebo-controlled trial with metoprolol,⁷⁶ which has a β 1-selectivity versus β 2-selectivity of twofold to sixfold.^{38–40}

Giving β -blockers during exacerbations has also been reported as safe. Dransfield *et al*⁷⁷ observed a lower mortality in inpatients with an acute exacerbation of COPD taking β -blockers than those not. Rutten *et al*⁷⁸ noted an improved mortality in patients with 'acute bronchitis' (taken as a surrogate for COPD) taking 'cardioselective' β -blockers and calcium antagonists (but not for non-cardioselective β -blockers, ACE inhibitors or angiotension receptor blockers). In a study involving 35 000 patients, Stefan *et al*⁷⁹ observed no difference in mortality in those taking β -blockers admitted for an exacerbation of COPD (ie, β -blockers did not kill patients during the exacerbation), but neither did they observe the reduced mortality reported by Dransfield *et al*⁷⁷ nor Rutten *et al*,⁷⁸ and non-selective β -blocker use was associated with an increase in readmissions.

However, before recommending prescribing β -blockers to all with a diagnosis of COPD and heart disease, it is important to remember that the above are all observational studies and therefore open to significant bias.⁵⁷ The severity of, or specific diagnostic criteria for COPD, is not always known, β -blockers used are not always specified, prior or new events of angina and MI and specific causes of death are not always reported. There are no long-term randomised studies assessing cardiovascular prophylaxis with β -blockers in patients with a history of either angina or MI and COPD, which is where a large potential benefit lies. Thus, although there is plenty of observational evidence of a potential benefit in people with COPD and cardiovascular disease, conclusive evidence is lacking. Despite this crucial deficit, some argue that it would be unethical to withhold β -blockers, for example, after an MI, a view seemingly endorsed by the National Institute for Health and Care Excellence.^{70 80 81} However, we believe it is time to move on with randomised controlled trials to generate definite answers, and to define which groups benefit from which treatments and how long the treatment should be continued (particularly in the post-MI COPD cohort).

CURRENT RECOMMENDATIONS AND MOVING FORWARD

There are an estimated >1.2 million people in England alone with COPD and heart disease.² Furthermore, given the smoking rates in Asia (eg, two-thirds of men in China smoke⁸²), this is a growing global problem that needs to be addressed. Even if a small decrease in FEV₁ does not impair quality of life, clinician anxiety and the need to ensure that absolutely no harm is caused (including the need for effective β 2-agonist rescue therapy during and acute exacerbation) is paramount in achieving better β -blockade for those who have COPD and concomitant heart disease. Furthermore, the difficulty in separating 'pure' COPD patients from those with asthma/COPD is not always easy and it is now recognised that there is significant overlap.⁸³

GOLD⁸⁴ recommends treating those with heart failure or ischaemic heart disease and COPD with β -blockers. Clearly, however, it is crucial to observe patients for worsening breathlessness and deterioration of spirometry despite this guidance, and review the patient and stop β -blocker treatment if needed. The current recommendation is therefore to use the most 'cardioselective' β -blockers currently available (eg, bisoprolol), starting at a low dose, whenever possible in patients with COPD in a

'try it and see' approach.^{20 85} The Scottish guidelines (SIGN 147, also published this year) makes similar recommendations for those with 'COPD without significant reversible airways obstruction,' where there is 'no suitable alternative', and also recommends close monitoring for adverse effects (see Annex 4 of SIGN 147).⁸⁶ Likewise, limiting systemic exposure to β -agonists (eg, using 2.5 mg nebulised salbutamol instead of 5 mg, and stopping nebulisers as soon as possible after the acute phase of an exacerbation) in those with COPD and heart disease would reduce the cardiovascular risk as much as possible.⁸⁵ These recommendations, however, are not founded on well-conducted prospective randomised trials and does not extrapolate to patients with asthma, where β -blockers remain contraindicated.

Moving forward, to understand whether our current β -blockers are safe or indeed beneficial, we need large randomised placebo-controlled trials to truly explore whether the benefit for cardiovascular mortality and morbidity (and potential improvement in COPD morbidity) does indeed outweigh the potential mortality and morbidity from bronchospasm or reduction in benefit of both long-acting and short-acting β -agonists in COPD.

An alternative may be the further development and assessment of a truly β 1-selective β -blocker, one that has such poor affinity for the β 2-adrenoceptor that it could not cause any β 2-mediated bronchospasm. Such molecules have recently been synthesised (with β 1-selectivity vs β 2-selectivity of 500-fold to 5000-fold⁸⁷) and have been proven to be orally bioavailable and highly β 1-selective in animals. Such a drug would circumnavigate the entire bronchospasm issue, yet still provide the well-proven cardiovascular β -blocker benefit. In addition to providing a safe way forward for those with COPD and heart disease, peripheral vascular disease or other conditions mentioned above, it would potentially extend the safe use of β -blockers to those who have heart disease and asthma.

Another alternative is to avoid β 1-adrenoceptor antagonists altogether. If their beneficial prophylactic effect is predominantly due to a reduction in heart rate,^{88 89} then other drugs with this effect might fulfil this role. Ivabradine is such a contender. This recently licensed drug reduces heart rate by blocking I_f sodium-potassium channels, expressed particularly in the sinoatrial node, without reducing the power of myocardial contractility, unlike β -blockers. In a large randomised controlled trial in patients with stable coronary artery disease and left ventricular systolic dysfunction <40%, ivabradine (in addition to standard therapy, ie, for many patients in addition to β -blockers) failed to reduce the primary end point of cardiovascular death, admission for new or worsening heart failure or MI, but it did establish its tolerability and a suggested benefit in those with an entry heart rate above 70 bpm.⁹⁰ The SHIFT trial, in patients with stable systolic heart failure (left ventricular ejection fraction $\leq$ 35%) and basal sinus rhythm >70 bpm, suggested an improvement in heart failure (due to a reduction in heart rate) in those taking ivabradine in addition to standard therapy.⁹¹ Unfortunately, this benefit was not confirmed in a subsequent trial of patients with stable coronary artery disease without heart failure, in whom the addition of ivabradine reduced heart rate but not improve clinical outcomes.⁹²

In the COPD arena, ivabradine has been demonstrated to lower heart rate without impairing lung function,⁹³ and to reduce tachycardia after salbutamol inhalation.⁹⁴ In a substudy of patients with COPD in the SHIFT (heart failure) trial, those randomised to ivabradine (in addition to routine β -blockers) derived similar relative reductions in cardiovascular events to

patients with no COPD, albeit without statistical confirmation.⁹⁵ So the role of ivabridine in safe and effective cardiovascular prophylaxis in patients with COPD is, like β -blockers, not yet established either alone or in combination.

CONCLUSION

Treating people with cardiovascular disease and COPD is a difficult everyday problem and the balance of doing good while doing no harm is one that causes significant clinician anxiety. β -Blockers save lives in people with heart disease, specifically postinfarction and with heart failure, but are associated with a reduction in lung function. Observational studies suggest that many patients with COPD appear to tolerate this. However, the final answers as to whether β -blockers can be safely given to patients with COPD *en masse* on a long-term basis, how much of a fall in FEV₁ is significant, whether long-term β -blockade negates the beneficial effect of long-acting β -agonist and the balance between β -blockade and β -agonist rescue during exacerbations is uncertain. Randomised controlled trials in β -blocker-naïve patients are the only way to answer this question, and therefore give confidence to clinicians to prescribe β -blockers to those with COPD. Maybe, the potential of novel highly β 1-selective antagonists might provide the impetus to study this important clinical problem.

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