

# Beta-blockers use in patients with chronic obstructive pulmonary disease and concomitant cardiovascular conditions

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**Abstract:** The mortality and incidence of chronic obstructive pulmonary disease (COPD) and coronary heart disease increase with age. Despite the clear evidence of beta blockers (BBs) effectiveness, there is a general reluctance to use them in patients with COPD due to a perceived contraindication and fear of inducing adverse reactions and bronchospasm. BBs are well tolerated in patients with cardiac disease and concomitant COPD with no evidence of worsening of respiratory symptoms or FEV<sub>1</sub>, and the safety of BBs in patients with COPD has been demonstrated, but their use in this group of patients remains low. The cumulative evidence from trials and meta-analysis indicates that cardioselective BBs should not be withheld in patients with reactive airway disease or COPD.

Patients with COPD have a high incidence of cardiac events necessitating careful consideration of prophylactic treatment. The benefits of beta blockade in this group appear to outweigh any potential risk of side effects according to the available evidence.

In this article, we will discuss the use of BBs in patients with COPD and review the evidence for their use and safety in this group of patients.

## Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death and is estimated to rise to be the third most common cause of death worldwide by 2020 (Rielly et al 2005). Many patients with COPD have concomitant conditions, mostly coronary artery disease (CAD), that require the use of beta-blockers (BBs). However, despite the clear evidence of BBs effectiveness, there is a general reluctance to use them in patients with COPD due to a perceived contraindication and fear of inducing adverse reactions and bronchospasm (Kennedy and Rosenson 1995; Viskin and Barron 1996; Gottlieb et al 1998; Chafin et al 1999). It is a common practice of physicians to consider COPD as contraindication to the use of BBs, based mainly on anecdotal evidence and case reports citing acute bronchospasm following the administration of BBs (Tattersfield 1986, 1990; Belli and Topol 1995; Craig et al 1996; Kendall 1997).

The most common comorbid conditions associated with withholding BBs in elderly patients after myocardial infarction (MI) are COPD and asthma (Heller et al 2000), while peripheral arterial and bronchial problems are reported to be the leading side effects (Frishman et al 1979; Frishman 1998). On the other hand, many patients are diagnosed and treated for COPD with no objective evidence, such as pulmonary function tests or specialist assessment, to confirm the diagnosis, as recommended by most thoracic societies. This may indicate that a significant number of patient are deprived the prognostic benefits of using BBs (Chen et al 2001).

BBs are well tolerated in patients with cardiac disease and concomitant COPD with no evidence of worsening of respiratory symptoms or FEV<sub>1</sub> (Formgren 1976; George

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et al 1983; Quan et al 1983; Krauss et al 1984; Falliers et al 1985; Dorrow, Bethge et al 1986; Mooss et al 1994) and the safety of BBs in patients with COPD has been demonstrated, but their use in this group of patients remains low (Salpeter et al 2001, 2002a, 2002b, 2003). The cumulative evidence from trials and meta-analysis indicates that cardioselective BBs should not be withheld in patients with reactive airway disease or COPD (Salpeter et al 2001, 2002a, 2002b, 2003). Patients with COPD have a high incidence of cardiac events necessitating careful consideration of prophylactic treatment. The benefits of beta blockade in this group appear to outweigh any potential risk of side effects according to the available evidence. For instance, BBs are well tolerated by the large majority of patients with heart failure, even in those with comorbid conditions such as diabetes mellitus, COPD, and peripheral vascular disease (HFSA 2006).

In this article, we will discuss the use of BBs in patients with COPD and review the evidence for their use and safety in this group of patients.

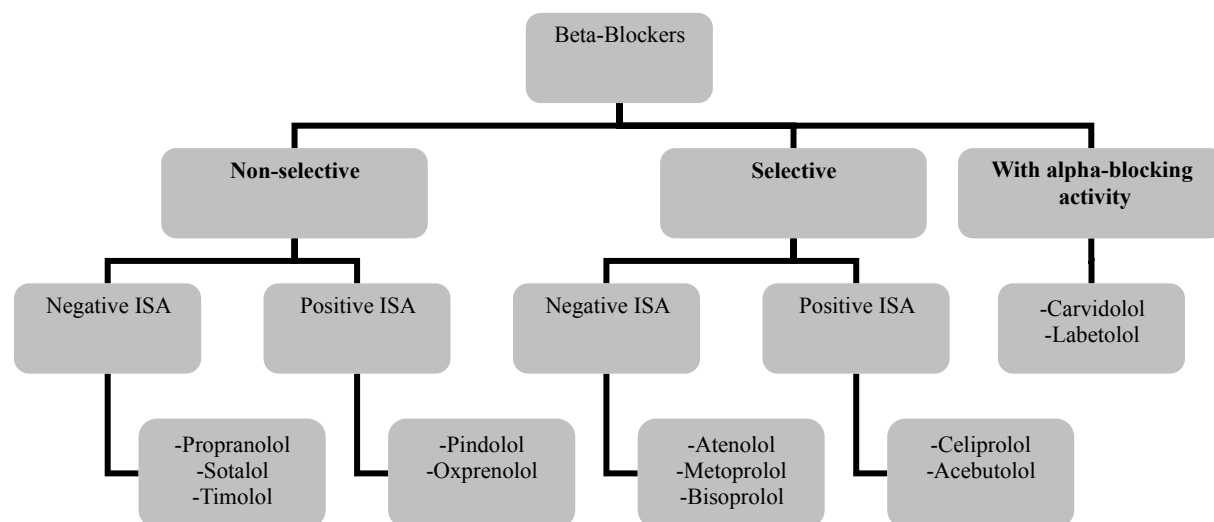
## Beta-blockers

Beta-blockers were originally designed by the Nobel Prize winner Sir James Black to counteract the adverse effects of adrenergic stimulation. He demonstrated that, by blocking the cardiac  $\beta$ -receptors, these agents could cause inhibitory effects on the sinus node (chronotropic effect), atrioventricular node (dromotropic effect), and on myocardial contractility (inotropic effect).

There are 3 types of  $\beta$  receptors.  $\beta$ 1-Adrenoceptors are situated in the cardiac sarcolemma. If activated, they lead to an increase in the rate and force of myocardial contraction

(positive inotropic effect) by opening the calcium channels. On the other hand,  $\beta$ 2-Adrenoceptors are found mainly in bronchial and vascular smooth muscles. If activated, they cause broncho- and vaso-dilatation. There are, however, sizable populations of  $\beta$ 2-Adrenoceptors in the myocardium, of about 20%–25%, which leads to the cardiac effects of any  $\beta$ 2-Adrenoceptors stimulation. There is a relative up-regulation of these receptors to about 50% in heart failure. The role of  $\beta$ 3-Adrenoceptors in the heart is not yet fully identified and accepted (Kalinowski et al 2003).

Beta-blockers are classified into three generations (Figure 1). The first generation agents (such as Propranolol, Sotalol, Timolol, and Nadolol), are nonselective and block  $\beta$ 1 and  $\beta$ 2 receptors. Blocking  $\beta$ 1-receptors affects the heart rate, conduction and contractility, while blocking  $\beta$ 2-receptors, tends to cause smooth muscle contraction, therefore, bronchospasm in predisposed individuals. The second-generation agents or the cardioselective agents (such as Atenolol, Bisoprolol, Celiprolol, and Metoprolol) block  $\beta$ 1-receptors in low doses but are capable of blocking  $\beta$ 2-receptors in higher doses. This selective mode of action makes the use of these agents more suitable in patients with chronic lung disease (Wellstien et al 1987) or those with insulin-requiring diabetes mellitus. Cardioselectivity varies between agents with the Bisoprolol among the most selective. The third generation agents have vasodilatory properties. Their action is either selective (Nebivolol) or nonselective (Carvidolol and Labetolol). The vasodilatory properties are mediated either by nitric oxide release as for Nebivolol or Carvidolol (Kalinowski et al 2003) or by added  $\alpha$ -adrenergic blockade as in Labetolol and Carvidolol. A third



**Figure 1** Beta blockers classification.

**Abbreviations:** ISA, intrinsic sympathomimetic activity.

vasodilatory mechanism, as in Pindolol and Acebutolol, acts via  $\beta_2$ -intrinsic sympathomimetic activity (ISA). These beta-blockers therefore have the capacity to stimulate as well as to block adrenergic receptors and tend to cause less bradycardia than the other beta-blockers and may cause less coldness of the extremities.

Beta-blockers are used extensively and have a proven morbidity and mortality benefits in the management of patients with cardiac disease (Frishman 1984; The IPPPSH Collaborative Group 1985; Wadworth et al 1991; Stienbeck et al 1992; Mangano et al 1996; Doughty et al 1997; JNC VI 1997; Lechat et al 1998; Freemantle et al 1999; Heidenreich et al 1999; Poldermans et al 1999). They are a standard therapy for hypertension, angina, unstable angina, post myocardial infarction, tachyarrhythmias, and congestive heart failure (The MERIT-HF Study Group 2000; Packer et al 2001). BBs also reduce mortality in the perioperative period. Despite the evidence, their use remains low in patients with COPD.

## Beta-blockers use in COPD

Many patients with COPD have concomitant conditions such as CAD (coexists in up to 27% of COPD patients (Karoli and Rebrov 2005)) that require the use of BBs. BBs are often avoided in these patients (Kennedy and Rosenson 1995; Viskin and Barron 1996; Gottlieb et al 1998; Chafin et al 1999) because of fear of bronchospasm and possible adverse reactions, despite the known cardiovascular mortality and morbidity benefit (Frishman et al 1984; The IPPPSH Collaborative Group 1985; Wadworth et al 1991; Stienbeck et al 1992; Mangano et al 1996; Doughty et al 1997; JNC VI 1997; Lechat et al 1998; Freemantle et al 1999; Heidenreich et al 1999; Polderman et al 1999). This is mainly based on anecdotal evidence and case reports citing acute bronchospasm following the administration of beta-blocker (Tattersfield 1986, 1990; O'Malley et al 1991; Belli and Topol 1995; Craig et al 1996; Kendall 1997).

COPD patients are at greater risk of ischaemic heart disease than asthmatics, so would benefit from the use of BBs. On the other hand, they also have more severe airway obstruction, so may be more sensitive to small changes in FEV<sub>1</sub> due to beta-blockade.

## The trial evidence

The use and effectiveness of BBs therapy after MI for elderly patients with COPD or asthma was evaluated (Chen et al 2001). The study was rationalised by the fact that patients with COPD and asthma have largely been excluded from clinical

trials of BBs therapy for AMI. The authors used the data from the Cooperative Cardiovascular Project (Marciniak et al 1998) to examine the relationship between discharge use of BBs and one-year mortality in patients with COPD or asthma who were divided into three groups: those who are not using beta-agonists, those who are using beta-agonists, and those with severe disease (on prednisone or previous hospitalization) in comparison with patients free from COPD or asthma. Of 54,962 patients without contraindications to beta-blockers, patients with COPD or asthma (20%) were significantly less likely to be prescribed beta-blockers at discharge after AMI. Patients with COPD or asthma who were not on beta-agonist had lower one-year mortality if they were on BBs. This mortality benefit was not found among patients using beta-agonists or those with severe COPD or asthma.

Large meta-analyses were published by Salpeter et al (2001, 2002a, 2002b) where randomized, blinded, placebo-controlled trials that studied the effects of cardioselective BBs on FEV<sub>1</sub>, symptoms, and the use of inhaled  $\beta_2$ -agonists in patients with reactive airway disease were selected, of which, there were 19 single dose treatment studies and 10 continued treatment studies. The outcomes measures were the change in FEV<sub>1</sub> from baseline, the number of patients with respiratory symptoms, and the use of inhaled  $\beta_2$ -agonists with active treatment compared with placebo. The results were that no significant treatment effect in terms of FEV<sub>1</sub> was found in patients with concomitant COPD, whether single doses (change in FEV<sub>1</sub>, -5.28% [CI, -10.03% to -0.54%]) or continued treatment (change in FEV<sub>1</sub>, 1.07% [CI, -3.3% to 5.44%]) was used. The conclusion was that cardioselective BBs do not produce clinically significant adverse respiratory effects in patients with mild to moderate reactive airway disease, and that they should not be withheld from these patients. The studies were not designed to make recommendations about people with significant chronic airway obstruction.

A similar review on a similar cohort of patients 11 single dose treatment studies (Schanning and Vilsvik 1976; Beil and Ulmer 1977; McGavin and Williams 1978; Perks et al 1978; Sinclair 1979; Anderson et al 1980; Sorbini et al 1982; Von Wichert 1982; Adam et al 1984; Dorow, Bethge et al 1986; Macquin-Mavier et al 1988) and 8 continued treatment studies (Tivenius 1976; Wunderlich et al 1980; Ranchod et al 1982; Buttand et al 1983; Fenster et al 1983; Lammers et al 1985; Dorow, Clauzel et al 1986; Fogari et al 1990) was also published by the previous group (Salpeter et al 2003). This demonstrated that cardioselective BBs produced no significant change in FEV<sub>1</sub> or respiratory symptoms compared to placebo and did not significantly affect the FEV<sub>1</sub> treatment response to

$\beta_2$ -agonists. Subgroup analysis revealed no significant change in results for those participants with severe COPD or for those with a reversible obstructive component. The conclusion was again that cardioselective BBs given to COPD patients do not produce a significant reduction in airway function or an increase in the incidence of COPD exacerbations.

A retrospective study (Egred et al 2005) assessed the use of BBs in patients with COPD admitted with acute coronary syndrome (ACS). Only 54% were discharged on BBs. A diagnosis of "COPD" was the most common cause for withholding BBs and only 62% of patients with COPD have been reviewed by a chest physician or had a previous pulmonary function test. Of these COPD patients, only 16% were prescribed BBs and many patients with a diagnosis of COPD have no objective evidence to support this diagnosis. The conclusion was that, these patients are being denied the prognostic benefits of BBs when presenting with ACS, and the recommendation was that before withholding BBs, COPD and reversibility should be ascertained by pulmonary function testing and that the overall use of BBs was sub-optimal in this setting.

The use of BBs in congestive heart failure patients with COPD and/or asthma was also assessed in a retrospective analysis (Peters et al 2004). One thousand sixty seven patients with CHF were included and reviewed over 18 months period. Medications, non-routine office visits, emergency room visits, and hospitalizations for respiratory events were assessed. Of the 1067 patients, 19.6% had obstructive pulmonary disease (OLD): 5.9% asthma, 11.2% COPD and 2.5% asthma/COPD. Only 35.9% of the patients with OLD were on BBs half of which were cardioselective. The use of BBs did not result in any increased respiratory events, respiratory encounters, emergency room visits, or hospitalizations. The result showed that the long-term use of BBs did not increase the risk of respiratory complications and there was no difference in outcomes with the use of cardioselective or noncardioselective BBs and the conclusion was that cardioselective BBs without intrinsic sympathomimetic activity are preferred until future studies resolve this issue.

Most of the evidence presented is meta-analysis; therefore, it has many limitations like any other meta-analysis (Ionnidis and Lau 1999). It only reports on published literature and is therefore subject to publication bias. A few studies did not have placebo controls, and many did not provide standard deviations for FEV<sub>1</sub> treatment effects. In addition, most of the studies were of short duration. It is possible that a longer study period may be required in order to detect clinically important side effects of BBs.

In the recent publication of the Heart Failure Society of America (HFSA) on heart failure practice guidelines (HFSA 2006), BBs therapy is recommended in the great majority of patients with LV systolic dysfunction, even in the presence of concomitant COPD. They recommend that BBs are initiated at a low dose and uptitrated gradually in two weeks intervals. The guidelines also recommend that patients with difficulties in initiating, uptitrating, or maintaining BBs therapy to be referred to a physician with expertise in the management of these patients. This is to ensure that no patient is denied the benefits of BBs (HFSA 2006).

In this article, we presented a review of the data supporting the use of cardioselective BBs in patients with mild to moderate COPD. The evidence suggests that cardio-selective BBs are not only safe but also beneficial in patients with co-existing airways and coronary disease and can significantly improve prognosis. Due to the proven mortality benefit of BBs in numerous cardiac conditions, many of the other relative or absolute contraindications traditionally listed for BBs have been questioned, including impaired left ventricular function, peripheral vascular disease, and diabetes mellitus (Kjekshus et al 1990; Wichkmayr et al 1990; Radack and Deck 1991; Rosenson 1993; Jonas et al 1996; Gottlieb et al 1998; Lechat et al 1998).

Finally, although we believe physicians should feel more comfortable prescribing cardioselective BBs to COPD patients, we can not make a generalised recommendation that BBs can be used in all COPD patients. This is due to the fact that almost all of the evidence is from retrospective analysis of data available and more prospective studies are needed. Physicians should use their clinical judgment and use BBs where they think the benefits outweigh the risks.

We suggest that patients who are admitted with any cardiac condition requiring BBs and who have concomitant COPD should be tried on BBs. A safe approach is to initiate cardio-selective BBs at a low dose and titrate them up as tolerated during the hospital admission. Metoprolol is cardioselective BBs with short half-life and has been shown to be safe and effective in patients with COPD (Camsari et al 2003) and may be the BBs of choice to initiating therapy. This will allow close observation and assessment of tolerance of these medications and will ensure that these patients are not denied the prognostic benefits of a well-tolerated and effective treatment. It may be necessary to discontinue the drug in few patients due to bronchospasm, but the potential benefit appears large enough to warrant this small risk.

Further randomised studies may be required to assess the use of the new BBs (Nebivolol) with its nitric oxide (NO)



releasing property in patient with COPD. This will allow the assessment of whether it is safe and similarly will help define whether NO has any role to play in reducing the effect of BBs on bronchospasm.

A drug called Pimobendan which is a phosphodiesterase (PDE) III-inhibitor, with vasodilatory and bronchodilatory effects, has been used in two patients with heart failure who were unable to tolerate BBs. The use of Pimobendan allowed the start and maintenance of BBs without worsening COPD or heart failure with evidence of progressive decline in brain natriuretic peptide (BNP) (Shiga et al 2002). This may present an interesting way of dealing with BBs intolerant patients, where the bronchodilatory effects of Pimobendan would allow the initiation of BBs. This is only two case reports and the safety and efficacy of this drug has not been tested in a controlled manner.

## Conclusion

BBs reduce mortality in patients with COPD and coexisting CAD and should be used whenever possible. Cardioselective BBs are safe in patients with COPD who have an indication for their use. Nonselective BBs are better avoided in general, except in patients with heart failure who may benefit from the use of Carvedilol. A short acting cardioselective BBs (such as metoprolol) should be started at a low dose and uptitrated slowly. Once Metoprolol is established, it can be changed to a once daily longer acting product such as Bisoprolol or Atenolol. In case of uncertainty or difficulty, specialist opinion should be sought to insure that these patients are not denied the prognostic benefit of BBs therapy.

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