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Use of β blockers in patients with COPD

David H Au

Chronic obstructive pulmonary disease (COPD) is the leading cause of respiratory-related deaths in the USA.[1] This simple and dramatic statistic, however, does not present the full story. In developed countries, smoking tobacco is the principal cause of COPD and also represents a major risk factor for other conditions such as cardiovascular disease and lung cancer.[2] One question that remains largely unanswered is how the presence of COPD modifies the treatment of coexisting illnesses such as cardiovascular disease. This question is important because most patients with COPD do not die of COPD but, as demonstrated by randomised trials and observational studies, the principal causes of death are most often listed as cardiovascular-related or lung cancer-related.[3–5] Tension in treatment decisions often occurs when clinicians must decide about providing patients with treatments that are known to improve outcomes for selected patients while potentially causing harm in others. A paradigm for this dilemma is the use of β blockers in patients with COPD.

Beta blockers are first-line therapy for patients with cardiovascular disease and have been shown in randomised clinical trials to reduce mortality.[6–8] The strongest evidence for the mortality benefit of β blockers is in myocardial infarction,[6–8] ischaemia[8] and left ventricular systolic dysfunction,[9 10] but there are a number of other settings including hypertension,[11–13] tachyarrhythmia,[14] perioperative risk modification[15 16] and thyrotoxicosis.[17–19] Although there are many potential explanations for the reduction in mortality, the benefit is clear. Beta blockers, by their effect on the β adrenoceptor, decrease myocardial contractility, chronotropic response and myocardial oxygen demand.[20] In the setting of myocardial ischaemia, these effects reduce overall myocardial injury.[21–23] In addition, β blockers reduce cardiovascular mortality based on anti-arrhythmic properties and the prevention of malignant arrhythmias.[24 25] Although it may seem reasonable to apply the results of clinical trials to all individuals with the proper indication, the results of clinical trials are generalisable only to those individuals who would have qualified to participate. For most clinical trials of cardiovascular diseases and β blockers, participants with obstructive pulmonary diseases were excluded.[26] This has led to a major gap in our ability to use randomised evidence to support the use of these medications in patients with COPD.

Although last updated some time ago, the most current American College of Chest Physicians guidelines for the treatment of systemic hypertension recommend that β blockers are relatively contraindicated in patients with COPD. This opinion is consistent with a more recent review which suggested that these agents should not be used without careful examination of the risk and benefits.[27] Others, however, suggest that the evidence from short-term randomised studies and observational studies for the safety of at least cardioselective β blockers is growing. Meta-analyses of randomised studies suggest that cardioselective β blockers are not associated with decrements in symptoms or in forced expiratory volume in 1 s (FEV_1).[28] Moreover, there are now several observational studies that suggest that β blockers may, in fact, reduce mortality among patients with COPD.[29–32] Given the conflicting recommendations, how do clinicians decide what is the correct course of action? A fair interpretation is that both groups are neither right nor wrong. There is simply a paucity of data to address this question. As a result, clinicians may in fact use β blockers in patients with COPD who have appropriate indications, but they do so significantly less often than in patients without COPD.

In this issue of *Thorax* Dransfield *et al*[33] have added to the body of observational studies by demonstrating that patients with COPD who received β blockers during a hospital admission had a significant reduction in all-cause mortality (***see page 301***). Patients were selected to participate in the study if they had a primary diagnosis of COPD or a primary diagnosis of respiratory failure associated with a secondary diagnosis of COPD. The authors identified prescriptions for β blockers using the hospital billing records and identified both cardioselective and non-cardioselective agents. Of the 825 patients identified, 142 (17.2%) had received a β blocker and 43 (5.2%) died while in hospital. Patients who had received β blockers were older, had more co-morbid illnesses (especially cardiovascular disease), but were similar with regard to markers of severity of pulmonary disease. In an adjusted model, patients who received β blockers were nearly 60% less likely to die in hospital than those who did not receive β blockers (adjusted OR 0.39 (95% CI 0.14 to 0.99)). This estimate was robust to traditional methods of adjustments including the use of propensity scores. Although spirometric data were available for only one-third of the total cohort, there was no difference in the overall severity of airflow obstruction in those who did and did not receive β blockers.

These results are in general agreement with previous studies that have shown a decreased risk of mortality associated with β blocker use in patients with COPD.[29–32] These previous studies have focused on patients with COPD who were discharged after a myocardial infarction and those patients who were being treated for hypertension. The current study by Dransfield *et al* fits within the range of existing studies but adds the

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dimension that the authors examined only those deaths and prescriptions that occurred during an inpatient hospitalisation. Of the 306 patients who had an indication for β blockers based on cardiovascular disease, only 28% actually had received them while in hospital. It may appear that there is significant potential room for improvement, but this interpretation may not be entirely appropriate. Because of the observational design, the allocation of β blockers was certainly not random. Bias by indication and selection biases may have contributed significantly to the findings. Even though propensity models were explicitly developed to address some of these issues, previous reports suggest that the use of propensity scores rarely changes the overall interpretation of observational studies.[34] Furthermore, as acknowledged by the authors, the patient's ambulatory medications were not available and it is unknown what proportion of patients who did not receive β blockers were, in fact, taking them in the outpatient setting. Clinicians would probably stop β blockers based on the severity of the COPD exacerbation biasing the study towards the described findings. These biases significantly limit the degree by which the results of this study should be applied in the clinical setting.

In addition to the effects of decreased myocardial oxygen and myocardial excitability, there are additional potential biologically plausible explanations for these findings. Select patients who abruptly cease taking β blockers have been found to have rebound and are at increased risk of acute myocardial infarction.[35] In addition, β agonists have been shown to lead to clinically marginal tachyarrhythmias.[36 37] This effect may be exacerbated in the setting of a COPD exacerbation. Furthermore, inhaled β agonists have also been associated with an increased risk of myocardial ischaemia among patients with COPD.[38 39] Beta blockers reduce the incidence of malignant arrhythmias and have been shown to modify the increased risk of myocardial infarction associated with β agonist use.[38] Finally, the majority of β blockers in clinical use for cardiovascular disease have greater binding affinity for the β_1 adrenoceptor which is the predominant β receptor found in myocardial tissue. Used at usual doses, these medications have fewer effects on airway smooth muscle.[40–42] In fact, one study suggested that, after taking β blockers for a relatively short duration, there was no effect on overall FEV_1 but there was greater bronchodilator responsiveness.[43] Taken together, there is substantial biological plausibility that β blockers may reduce myocardial events and mortality in patients with COPD.

The current evidence from observational studies and randomised evidence examining intermediate outcome measures suggest that β blockers, on average, appear to be safe. There is clear evidence that β blockers save lives among patients who do not have COPD, and that this simple and potentially life-saving intervention is prescribed less frequently among patients with COPD.[44] There is now reasonably strong evidence that β blockers may have a similar benefit in patients with COPD. Unfortunately, studies in other clinical situations using intermediate outcomes and observational designs have led to treatment decisions that probably contributed to avoidable deaths.[45–48] Given the overall burden associated with COPD and coexisting cardiovascular disease, the question of the effectiveness of β blockers on mortality needs to be definitively addressed.

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Overdiagnosis in lung cancer: different perspectives, definitions, implications

Peter B Bach

Does lung cancer screening lead to overdiagnosis? Most lung cancer prevention experts think it does, but there is a contingent who believe that it does not. This latter group holds fast to a notion that essentially all histological foci of lung cancer pose an imminent threat to health, irrespective of how they are discovered. Enter Dr Reich's interesting and thoughtful article,[1] which provides a cohesive overview of the epidemiological data that would be explained by "overdiagnosis", and therefore the case for its existence ***(see page 377)***. Reich also considers the totality of studies that are oft cited as evidence that "overdiagnosis" does not exist. For these articles, he summarises their findings too, and raises his concerns about them. It is an important contribution, that clearly presents Reich's view that overdiagnosis is a serious concern in lung cancer screening. Because it also incorporates opposing evidence, it is a worthy reference for anyone interested in understanding this confusing issue.

My interpretation of the data is much like Reich's—I have little doubt that lung cancer screening, particularly with CT, uncovers vast numbers of lesions with relatively little malignant potential. I also harbour little doubt that surgical treatment of individuals who are overdiagnosed is potentially very harmful to them, given that surgery confers risks both short and long term. However, as a clinician, I find this epidemiologic concept hard to operationalise because current knowledge does not allow me to distinguish between those histological foci that pose a reduced threat compared with those that pose a very real and imminent threat. Therefore, faced with a positive biopsy at this point, it is essentially an instinctual response to recommend immediate and definitive treatment.

Perhaps this tension between epidemiological data and clinical instinct is what leads to different interpretations of the available data. This would make sense, as my experience is that clinicians and epidemiologists think about the world differently. An alternative is that the tension actually reflects differences in the definition of "overdiagnosis"—so, what appears to be a disagreement is actually a failure of terminology. Irrespective of the reason, whether or not there is a large reservoir of small growths that have limited malignant potential is an important question that affects our ability to interpret single arm studies of screening with survival as an outcome and our ability to manage lesions uncovered by CT screening.

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DIFFERENT WEIGHTS APPLIED TO THE SAME DATA

Contrasting views of falsifying observations

Treating victim after victim of lung cancer makes it nearly impossible for clinicians to believe that a cluster of lung cancer cells could be harmless. But, it is equally hard for epidemiologists to ignore the findings in virtually every study of lung cancer screening with either chest *x* ray or CT—namely, that screening uncovers more lung cancers than would otherwise appear sporadically or could conceivably cause illness. Which set of observations you take more seriously depends on your perspective. Clinicians, by the nature of what we do, must view the world in a binary way, because the rubber hits the road each time we make a treatment decision. We must decide to give antibiotics or not to the patient with a pulmonary infiltrate. We do not have the option of reducing the dose of antibiotic so that it reflects a blended probability that pneumonia is present or not. If the patient improves, this makes us more confident that we had the right diagnosis—only if the patient fails to improve do we switch diagnoses. Epidemiologists (many, like Reich, are also clinicians) have as their focus the underlying but unobservable distributions that cause events to happen at a certain frequency. They know that some people with infiltrates have pneumonia and some do not. The rubber hits the road for them when they compare the total number of pneumonias occurring in a population to what their theory predicted. If those numbers are roughly the same, they stick with their theory. When the two do not add up, they switch theories.

This difference between clinical and epidemiologic insights might explain disagreements regarding "overdiagnosis"