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EDITORIALS

β blockers for adults with chronic obstructive pulmonary disease

Don't withhold treatment after a myocardial infarction

Frans H Rutten *general practitioner*, Rolf H H Groenwold *clinical epidemiologist*

Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, 3508 AB Utrecht, Netherlands

In a large observational study (doi:10.1136/bmj.f6650), Quint and colleagues show that β blockers started before or during hospital admission after myocardial infarction are associated with substantial survival benefits for adults with chronic obstructive pulmonary disease (COPD). They found an adjusted hazard ratio of 0.59 (95% confidence interval 0.44 to 0.79) in those who were already taking β blockers and 0.50 (0.36 to 0.69) in those who started taking them in hospital.[1]

Randomised controlled trials have already shown that β blockers reduce mortality after myocardial infarction in the general population,[2] and a decade ago two large observational studies suggested that this was also true for people with COPD.[3 4] Other observational studies have even suggested that β blockers may be beneficial for a wider population of patients with COPD.[4 5] A recent meta-analysis of nine cohort studies that comprised nearly 100 000 patients with COPD showed a consistent pattern, with a pooled relative risk of mortality of 0.69 (0.62 to 0.78) with β blockade.[6] In one study, β blockade was associated with a reduction in exacerbations.[5] Cardioselective β blockers seemed more effective than non-selective agents.[5]

Quint and colleagues' study is a welcome addition to the existing literature. The design is more robust than previous observational studies and corrects more comprehensively for the many differences in baseline prognosis between treated and untreated groups. The fact that patients prescribed a β blocker during hospital admission for myocardial infarction were younger, fitter before their infarction, less intensively treated with bronchodilators, and had fewer exacerbations than adults not prescribed a β blocker could not explain the observed effect. Furthermore, adjustment for confounding by severity of pulmonary obstruction (using the global initiative for chronic obstructive lung disease stage) in the subsample of 600 (56.4%) patients in whom these data were available did not materially change the effect estimate. Confounding by indication looks unlikely.[1]

Researchers can only adjust for known confounding factors that are recorded in datasets. Unobserved confounding is still possible. However, sensitivity analysis suggests that any unobserved confounder would have to be present in 25% of β blocker users and 75% of non-users, be independent of all observed confounders, and would need to increase mortality fivefold to nullify the apparent benefits of β blockers in this study.[7] The combination of these scenarios is extremely unlikely, although the true effects of β blockers may still be overestimated.

If β blockers do reduce mortality in patients with COPD who have had a myocardial infarction, what are the likely mechanisms? These drugs could reduce deaths through their well known beneficial effects on cardiovascular disease,[2] which is common in these patients.[5] COPD is characterised by poorly reversible airflow limitation, together with frequent exacerbations and pulmonary infection, but it is also associated with an abnormal pulmonary and systemic inflammatory response to tobacco smoking. This abnormal response contributes to all stages of atherosclerosis, from endothelial dysfunction and plaque formation to plaque rupture and thrombosis.[8]

Another mechanism by which β blockers could act is by controlling the excessive adrenergic drive and heart rate in these patients.[5] Both the parasympathetic system and the (ortho)sympathetic system are activated in COPD.[9] Sympathetic overactivity results in increased heart rates, vasoconstriction, and direct cardiotoxicity.[9] People with COPD have higher heart rates than those of the same age in the general population,[10] and this acts synergistically with systemic inflammation to increase mortality. β blockers also reduce the risk of sudden death by slowing the progression of coronary artery disease and helping to prevent malignant arrhythmias. Finally, β blockers can modulate the immune response and may improve clearance of bacteria from the circulation.[11] A small randomised trial already suggests that β blockade prolongs survival in patients with sepsis,[11] and an observational study hints at benefits in patients experiencing episodes of acute bronchitis.[12]

Comorbid COPD and asthma are the most common reasons cited for withholding β blockers in patients admitted with myocardial infarction. Quint and colleagues found that only 38.6% of people with COPD received a β blocker during their admission.[1] The fear of bronchospasm comes from case reports

F.H.Rutten@umcutrecht.nl

of patients with asthma who received high doses of β blockers, and short term falls in pulmonary function that are confined to patients with COPD who have reversible airway obstruction. We already know that β blockade should be started at a low dose and gradually titrated upwards ("start low, go slow"). A practice study showed that 88% of patients with COPD can tolerate β blockers when prescribed in a structured way for comorbid heart failure without adverse pulmonary effects.[13] Importantly, cardioselective β blockers are 20 times more effective at blocking β_1 receptors (mainly present in the heart) than blocking β_2 receptors (mainly in the lungs), and they have negligible effects on the lung when given in therapeutic doses. Moreover, β blockers can be used in combination with inhaled β mimetics.[3]

After more than 50 years of use, the effects of β blockers are still not fully understood. We urgently need a randomised trial to confirm the benefits and risks of these agents for people with COPD, but in the meantime there is enough evidence to support prescribing them to patients with COPD who have had a myocardial infarction.

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