β-Blockers for COPD inpatients

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For clinicians who treat patients with respiratory diseases, the use of β-blockers has, for a long time, posed a dilemma because of the potential risk of bronchospasm and neutralisation of the effectiveness of β-2 agonists. This predicament is particularly challenging for patients with chronic obstructive pulmonary disease (COPD), many of whom have substantial cardiovascular comorbidity,[1] and in whom the avoidance of β-blockers might deprive them of substantial cardiovascular benefit.

In the last few years, this restraint has been challenged, and rightfully so, in view of the general scarcity of data on this potential antagonism and, more importantly, its would-be effect on major outcomes. While caution is generally the sensible approach in drug safety, this is less the case here, as one would be withholding a treatment that has been demonstrated to be effective for cardiovascular disease. Several observational studies have examined the potential risks and benefits of β-blocker use in COPD. Most studies, to date, have looked at β-blocker use during the usual course of COPD without specifically examining their risk or benefit at the time of an acute exacerbation of COPD (AECOPD).[2–5]

Stefan *et al*[6] address the question of the effects of β-blockers during a serious exacerbation requiring hospitalisation. The authors specifically evaluated whether β-blockers given early to patients hospitalised for AECOPD, and who also have ischaemic heart disease or heart failure, increase the risk of mortality. They used the US Premier hospitalisation database to identify a large cohort of over 35 000 patients hospitalised for COPD, and who received prednisone and inhaled β-2 agonists. The paper reports that the 29% of patients who received β-blockers during the first 2 days of the hospital stay did not have an increased risk of in-hospital mortality, readmission within 30 days, or mechanical ventilation, compared with COPD patients who did not receive β-blockers.

This study has several noteworthy features. First, it is one of the first to look at the effects of β-blockers during a serious exacerbation requiring hospitalisation. This is a particularly crucial time, as COPD exacerbations are associated with high mortality in the first 1–2 weeks,[7] likely more so if the patients also have cardiovascular comorbidity. This study suggests that β-blockers are safe during this particularly high-risk period. Second, the authors avoided the vexing problem of immortal time bias that has plagued recent observational studies of β-blockers in COPD, suggesting erroneously spectacular benefits of these drugs.[8] This bias was present in the study by Dransfield who suggested that β-blocker use during a COPD hospitalisation was associated with an impressive 61% reduction in mortality (and an astonishing 92% reduction associated with short-acting β-agonist use).[9 10] The bias was also present in the study by Short *et al*, that reported a 22% reduction in all-cause mortality associated with β-blocker use, as noted in the related correspondence.[5] In the present study, the authors were

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careful to avoid this bias by measuring exposure during the first 2 days of hospitalisation, and only counting the outcome of death from the third day onwards. Third, the authors made careful use of propensity scores to control for potential confounding bias in comparing users and non-users of β-blockers. Table 1 of their paper demonstrates the excellent balance on the covariates between the β-blocker users and non-users, attained after matching on the propensity scores.

Yet, some methodological uncertainties that could impact on the accuracy of the findings remain, and could be addressed by future studies. First, the technique of data analysis for the outcome of in-hospital mortality and mechanical ventilation does not account for the length of stay. Indeed, logistic regression considers the outcome only as the occurrence or non-occurrence of death, but does not consider the time to death which appears to be longer for the non-users of β-blockers, as seen from the interquartile ranges of length of stay. In this case, rates per person-day or, better still, Kaplan–Meier curves and proportional hazards models would be more accurate and more informative.

Second, a major potential confounder in this study is the use of β-blockers prior to admission for AECOPD. Patients already using β-blockers at the time of admission are likely different from the ones who were not on these drugs at that time. Thus, the use or non-use of β-blockers during the first two days of hospitalisation may be a marker of specific health status that would dictate continuation or discontinuation of these drugs early in the hospitalisation. Unfortunately, this is a limitation of the Premier database used for this study, which is strictly a hospitalisation database, and does not include any data on medical services or medications dispensed prior to admission to hospital.

Third, some of the exclusions may have introduced selection bias. The 1977 readmissions within 30 days of the previous discharge are in fact outcome events in the study, and would generally not be excluded in a cohort study. More importantly, however, the 17 968 who did not receive inhaled β_2 agonists on the first 2 days of hospitalisation may not receive these because they were already on β-blockers, were intended to receive β-blockers, or received other formulations of β_2 agonists, thus potentially introducing confounding by contraindication. This large, important, subgroup could have been investigated. Last, for those with more than one admission during the study period, the authors randomly selected one of these admissions to include in the study population. This is unusual, as the common practice in cohort formation is to chronologically select the first eligible admission occurring during the period of study.

Finally, a major potential issue of contention with the study design is the appropriateness of the β-blocker exposure measure. Patients exposed to β-blockers were defined as receiving β-blockers during the first or second day of the hospital stay. The biological plausibility that short-term exposure of a single day or two of β-blockers can actually impact on lung function and mortality is uncertain. A meta-analysis of randomised trials found no effect of cardioselective β-blockers on lung function of patients with COPD in trials of duration ranging from a single-dose study to studies of 12 weeks duration.[11] If the concern is that β-blockers will cause fatal bronchospasm, future studies should investigate the effects as a function of duration of exposure, since bronchospasm may be more likely to occur once concomitant therapy changes over the course of a hospitalisation, for instance, after a reduction in the dose of bronchodilators.

In all, this study provides some evidence that β-blockers, particularly the cardioselective ones, given in-hospital to patients with COPD and cardiovascular disease during a severe COPD exacerbation, do not increase the risk of in-hospital mortality and other outcomes. More research is needed in this area, particularly to improve the management of COPD patients admitted for a severe COPD exacerbation, at a time during which they are at major risk of death, likely compounded by concurrent ischaemic heart disease and heart failure. Note should be made that the results presented should not be generalised to patients with asthma, especially those with severe disease, in whom the potential for severe bronchospasm may be such that use of β-blockers, even if cardioselective, may present more of a risk. Although, here again, the use of cardioselective β-blockers in subjects with mild to moderate and stable asthma appears to be safe.[12] A consensus table, including respirologists, cardiologists and methodologists, might provide some clarity based on the available evidence to better guide clinicians on managing patients hospitalised with concomitant cardiac and airway disease.

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