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Commentary

Who's Afraid of the Big Bad Wolf? Safety of Beta-Blockers in COPD

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Since their development in the 60's, β-blockers have been used to treat hypertension, chronic ischemic heart disease, and heart failure. The pharmacological benefits of beta-blockers are based on their binding to β1-receptors, thereby preventing unwanted effects of endogenous catecholamines on the heart and vasculature. However, the flip side of this is a concomitant binding to β2-adrenoceptors -which are prominent in bronchial smooth muscle cells- and therefore it is anticipated that this can favor bronchial constriction, with consequent worsening of symptoms in patients with concomitant chronic obstructive pulmonary disease (COPD). Subsequent development of newer β-blockers, with greater selectivity toward β1-receptors, has not allayed this concern, and β-blockers remain underprescribed to patients with cardiac disease and COPD, out of fear that they may aggravate respiratory symptoms [1], and outweigh cardiovascular benefits [2].

Interestingly, concerns over the risk of β-blocker use in COPD are not supported by actual data. Indeed, the safety of cardioselective β-blockers in patients with COPD, even when a bronchospastic component is present, has been shown in randomized trials [3], and in observational studies [4,5]. In a broad spectrum of COPD patients, many of whom with cardiovascular comorbidities, long-term treatment with β-blockers actually reduced the risk of COPD exacerbations, and improved survival [5]. More recently, another observational study showed similar benefits of use of β-blockers in patients with moderate to very severe COPD, in terms of significant reduction in exacerbations [6]. In addition, in a cohort of 2837 acute heart failure patients with COPD (derived from administrative health databases), β-blocker use was associated with a lower total risk of mortality. Finally, in the specific setting of high-risk survivors of myocardial infarction with COPD, β-blockers were associated with better outcome [7].

Nevertheless, in spite of this evidence, physicians still withhold, or seem reluctant to prescribe β-blockers to COPD patients, fearing of provoking bronchospasm and inducing respiratory failure [2]. Regrettably, it is quite unlikely that a large randomized trial to specifically evaluate β-blocker effect in cardiac patients with COPD will ever be performed. In the absence of such ultimate evidence, investigating observational cohorts though specific methods capable to decrease attribution bias would likely increase evidence regarding effects and safety of β-blockers in such patients.

In this respect, robust reassurance with respect to the safety of β-blockers in those patients may finally be at hand, as in this issue of EClinicalMedicine Nielsen et al. [8] provide a thorough assessment of this issue. They leveraged a huge population-based database, which had accrued data about over 1 Million patients enrolled in Denmark between 1995 and 2015, and followed up for more than 6 months. Specifically, Nielsen et al. evaluated the long-term effect of β-blockers on risk of COPD in 301,542 hypertensives who were "new users" of β-blockers, and compared them to 1,000,633 users of any other antihypertensive drugs, with no history of COPD hospital admission. Compared to patients not treated with β-blockers, β-blocker users actually had a significantly lower risk of COPD hospitalization. Of even greater relevance, all-cause mortality and COPD mortality rates were also significantly lower. Benefits of β-blockers were already detectable after 6 months of follow-up [8]. Also, authors were able to capture use of non-β1-selective blockers, and compare to the outcome in COPD patients who instead took β1-selective blockers; importantly, even non-β1-selective blockers proved safe.

Strengths of the study include the use of a nation-wide healthcare database, with nearly 100% population coverage, as well as the fact that the very large sample size allowed use of propensity scores to minimize unknown or unmeasured confounders and selection biases, inherent in a post-hoc observational study. In this respect, one limitation is the lack of information regarding smoking status, which may obviously affect COPD exacerbations. Importantly, it is now appreciated that healthcare databases are useful sources to investigate the epidemiology and to assess longitudinal outcomes of chronic disease -such as COPD- yet, to represent a reliable source, they need to be validated [9]. In this respect, accuracy of diagnosis of COPD in the Danish National Patient Registry had been previously validated, and found to yield an excellent positive predictive value of 93% [10].

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In conclusion, in the absence of prospective trials the study by Nielsen et al. comes as close as possible to reassure us not to be scared of the "wolf", as β-blockers (even older non-β1-selective ones) do prove quite safe to be chronically administered to cardiac patients with COPD. Furthermore, their data solidly reinforced previous indications that β-blocker use are actually of benefit in such patients. Cardiac patients should not be unreasonably deprived of time-honored, guideline-directed therapy with β-blockers when necessary.

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