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EDITORIAL

Beta-blockers and COPD: how can harmony be restored in a marriage in crisis?

Roberto Ferrari [1,2]*, Rita Pavasini[1], and Gianluca Campo[1,2]

[1]Centro Cardiologico Universitario di Ferrara, University of Ferrara, Italy; and [2]Maria Cecilia Hospital, GVM Care & Research, Cotignola (RA), Italy

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This editorial refers to 'Association of beta-blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis'†, by Y. Yang *et al.*, on page 4415.

Since their discovery in the 1960s, scientists are still talking about beta-blockers for better and for worse. These medicines were developed for the treatment of angina.[1] The underlying mechanism is a reduction of oxygen consumption due to negative inotropism and chronotropism. Soon, hypertension became another indication. The underlying mechanism is less straightforward, but negative inotropism, resulting in reduced cardiac output, is thought to be important. Thus, negative inotropism and reduced cardiac output were the 'dogma' at that time, and heart failure (HF) was an absolute contraindication. When working as a PhD student on beta- and calcium blockers in London, I remember my mentor saying: 'If you prescribe a beta-blocker for HF, you can be taken to court!' Time goes by, and today I say to my students: 'If you do not prescribe a beta-blocker for HF you can be taken to court!'. The underlying mechanism for this contraintuitive indication is a sort of 'positive instead of negative inotropic effect on the failing ventricle', mainly due to a reduction of heart rate but also other more sophisticated mechanisms, such as a reduction of apoptosis, and of toxicity of noradrenaline and cytokine, etc.[2] Today, beta-blockers are a landmark treatment for HF with reduced ejection fraction (HFrEF); however, convincing the cardiological community to use these drugs in HF was not an easy task, despite the overwhelming evidence. In Italy, for instance, we had to conduct a national cardiology programme called the 'BRING-UP' to use beta-blockers instead of calcium blockers in HFrEF.[3]

But, today, can we say that cardiologists are prescribing beta-blockers as they should? The answer is no!

There are still 'unjustified' limitations to their prescription, one being chronic obstructive pulmonary disease (COPD).[4] The arguments behind these practices are: concerns for a potential reduction in basal lung function, lowest efficacy of emergency rescue of a beta-agonist, and difficulty in distinguishing COPD from asthma.

The *European Heart Journal* should be complimented for publishing the study of Yang *et al.*,[5] which is a systematic review and meta-analysis of 670 594 subjects with COPD and cardiovascular disease (CVD) receiving beta-blockers. Data from 22 studies (335 419 patients) confirm that beta-blocker treatment reduces all-cause mortality [hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.59–0.83, $P < 0.0001$]. This is independent of beta-blocker selectivity or their up-titration, emphasizing the importance of 'target effect (heart rate reduction) vs. target dose'. However, more importantly, our Chinese colleagues found out that beta-blockers are associated with a significant reduction in the number of acute exacerbations of COPD (17 studies, 183 685 patients, HR 0.77, 95% CI 0.67–0.89, $P = 0.0003$), thus confirming the belief of pneumologists that beta-blockers are useful for COPD.[5] The impact of this finding is important for the entire spectrum of CVD and not only for HF. Previous studies linked the occurrence of acute exacerbation of COPD to all-cause and cardiovascular mortality in patients with myocardial infarction (MI) and COPD. Hospital readmission is linked to a four-, two-, and six-fold increased risk of death, MI, and HF, respectively.[6] Thus, beta-blocker treatment for CVD patients with concomitant COPD is strongly advocated and supported by the meta-analysis of Yang *et al.* which, in turn, is not without limitations. To start with, it is a meta-analysis and not a trial, with all the intrinsic limitations. The definition of CVD is wide, ranging from arterial hypertension to HF, through effort angina and MI. Data on cardiovascular mortality are missing, preventing discrimination as to whether benefits are driven by reduction of cardiac complications (ventricular arrhythmias, MI, HF progression, etc.) or

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* Corresponding author. Chair of Cardiology, Azienda Ospedaliero-Universitaria di Ferrara, Ospedale di Cona, Via Aldo Moro 8, 44124 (Cona) Ferrara, Italy. Tel: +39 0532 239882. Email: fri@unife.it

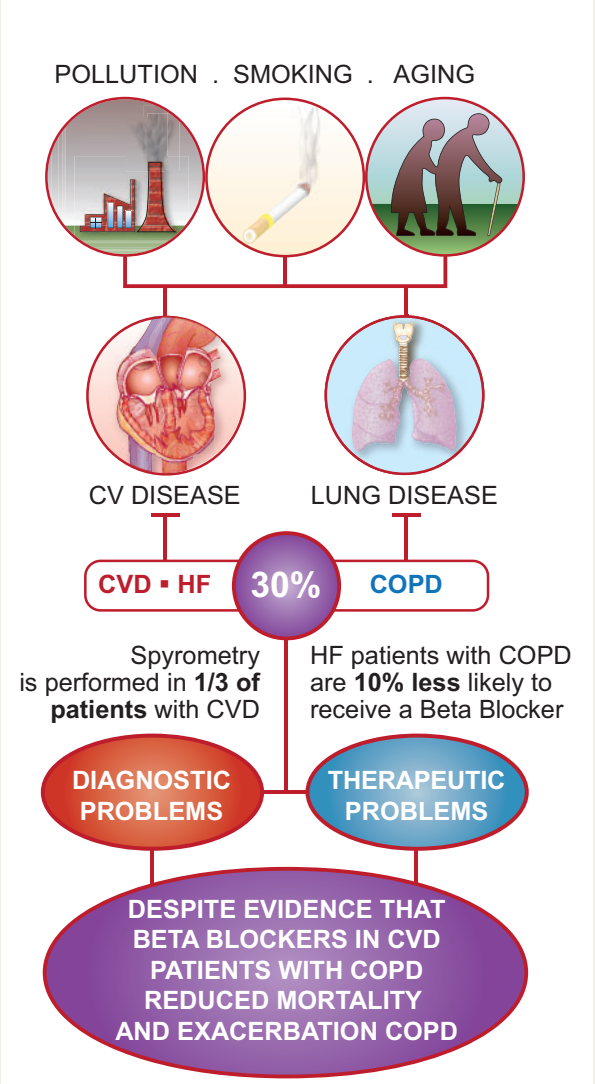

Figure 1 CVD and COPD share the same risk factors and occur in 30% of cases. Unfortunately, there are diagnostic and therapeutic problems related to the underdiagnosis of COPD and the underuse of beta-blockers.

by improvement of COPD. The analysis includes a few randomized clinical trials (n = 12) and many observational cohort studies, often retrospective (n = 37). But . . . as someone once said, 'nobody is perfect!'.

The value of the work of Yang *et al.* relies on three points. The first, and obvious one, is of not depriving our patients with COPD of the evidence-based benefits of beta-blockers. The second is to bring COPD, which is often undiagnosed, to the attention of cardiologists.[7] As shown in *Figure 1*, CVD and COPD share the same risk factors (ageing, tobacco smoking, and pollution). Thus, it is not surprising that a third of patients with CVD may have or develop COPD and are at a higher risk of further complications and death.[8] Cardiologists should be aware of COPD prevalence in their patients, of its negative prognostic impact, and of the importance of performing systematic spirometry in CVD patients with multiple risk factors. Perhaps we should conduct a further nationwide programme to convince cardiologists to liaise more with pneumologists to diagnose COPD. The last and most important aspect that shines through in several parts of the article of Yang *et al.* is the strong, passionate, and honest appeal to doctors to avoid unjustified bias in the use of a class of drugs that has and still can save several lives.

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References

1. Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, Manolis AJ, Marzilli M, Rosano GMC, Lopez-Sendon JL. A 'diamond' approach to personalized treatment of angina. *Nat Rev Cardiol* 2018;**15**:120–132
2. Ferrari R, Fox, K. Heart rate reduction in coronary artery disease and heart failure *Nat Rev Cardiol* 2016;**13**:493–501.
3. Maggioni AP, Sinagra G, Opasich C, Geraci E, Gorini M, Gronda E, Lucci D, Tognoni G, Balli E, Tavazzi L; Beta blockers in patients with congestive heart failure: guided use in clinical practice Investigators. Treatment of chronic heart failure with b adrenergic blockade beyond controlled clinical trials: the BRING-UP experience. *Heart* 2003;**89**:299–305.
4. Canepa M, Straburzynska-Migaj E, Drozdz J, Fernandez-Vivancos C, Pinilla JMG, Nyolczas N, Temporelli PL, Mebazaa A, Lainscak M, Laroche C, Maggioni AP, Piepoli MF, Coats AJS, Ferrari R, Tavazzi L; ESC-HFA Heart Failure Long-Term Registry Investigators. Characteristics, treatments and 1-year prognosis of hospitalized and ambulatory heart failure patients with chronic obstructive pulmonary disease in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur J Heart Fail* 2018;**20**:100–110.
5. Yang Y, Xiang Z, Yang J, Wang W, Xu Z, Xiang R. Association of beta-blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis. *Eur Heart J* 2020;**41**:4415–4422.
6. Campo G, Guastaroba P, Marzocchi A, Santarelli A, Varani E, Vignali L, Sangiorgio P, Tondi S, Serenelli C, De Palma R, Saia F. Impact of COPD on long-term outcome after ST-segment elevation myocardial infarction receiving primary percutaneous coronary intervention. *Chest* 2013;**144**:750–757.
7. Almagro P, Lapuente A, Pareja J, Yun S, Garcia ME, Padilla F, Heredia JL, De la Sierra A, Soriano JB. Underdiagnosis and prognosis of chronic obstructive pulmonary disease after percutaneous coronary intervention: a prospective study. *Int J Chron Obstruct Pulmon Dis* 2015;**10**:1353–1361.
8. Campo G, Pavasini R, Malagù M, Mascetti S, Biscaglia S, Ceconi C, Papi A, Contoli M. Chronic obstructive pulmonary disease and ischemic heart disease comorbidity: overview of mechanisms and clinical management. *Cardiovasc Drugs Ther* 2015; **29**:147–157.