



LETTER TO THE EDITOR

**Beta-blockers in acute coronary syndrome patients: The concept of 'gradient of benefit'**



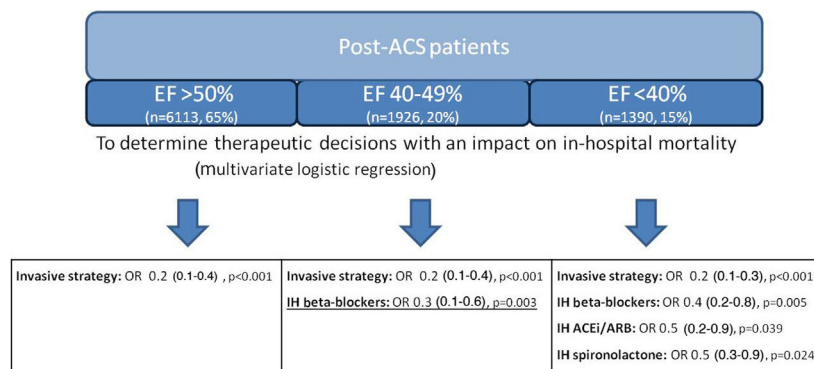
**Betabloqueadores no doente pós SCA: o conceito de gradiente de benefício**

We read with interest the article by Velásquez-Rodríguez et al. published in the April 2021 issue of the *Journal*,<sup>1</sup> which analyzes the impact of beta-blocker (BB) therapy in post-acute coronary syndrome (ACS) patients. In this important study, the population consisted of ST-elevation myocardial infarction (STEMI) patients divided into two groups according to left ventricular ejection fraction (LVEF):  $\leq 40\%$  vs.  $>40\%$ . The impact of BB therapy in the  $\leq 40\%$  population is well known, and current guideline-directed medical therapy (GDMT) includes it as the first-line treatment to reduce heart rate.<sup>2</sup> The real challenge is to understand the impact of BB therapy in currently treated post-ACS patients with LVEF  $>40\%$ , since the main studies were performed in the pre-revascularisation era and the role of BB therapy in patients treated according to contemporary practice has been questioned.<sup>3</sup> Our team has previously published a study investigating the therapeutic impact on in-hospital mortality in currently treated post-ACS patients (n=9429) stratified according to LVEF, adding a third group – patients with mid-range LVEF, between 40 and 50% (n=1926, 20%).<sup>4</sup> Regarding the group with low LVEF, our results support the conclusions achieved by Velásquez-Rodríguez et al., with BB therapy

having an impact in reducing in-hospital mortality. However, in the intermediate LVEF group, BB therapy also had an impact on in-hospital mortality. In patients with LVEF  $>50\%$  there was no benefit from BB therapy (Figure 1).<sup>4</sup> Similar findings were also seen in the Japanese CHART-2 study.<sup>5</sup>

In the study by Velásquez-Rodríguez et al., application of other forms of GDMT was lower than expected in the no-BB group (69.3% were on angiotensin-converting enzyme inhibitors). However, in our study, all GDMTs were used very frequently, and although other forms of ACS were included, coronary angiography was performed in  $>90\%$  of the overall population.<sup>6</sup> Only 6.2% of the population analyzed by Velásquez-Rodríguez et al. had atrial fibrillation, while in our study atrial fibrillation was diagnosed in less than 10% of the overall population, and thus its deleterious effects on BB efficacy may not have had a significant impact in either study.<sup>4</sup> Neither study analyzed BB dosages, but a previous study by Ibrahim et al. assessed dosing and concluded that a higher dosage was only modestly beneficial in improving prognosis.<sup>7</sup> A previous individual patient data meta-analysis by Cleland et al. including 11 trials also reinforced our conclusions, showing that BB therapy improved LVEF for patients in sinus rhythm and with LVEF  $<40\%$ , and that for patients in the 40-50% range it appeared more likely to help than to harm.<sup>8</sup>

In conclusion, it seems that as LVEF begins to fall, the margin for therapeutic benefit increases (Figure 1). The ideal cut-off for each GDMT is difficult to attain, but according to both these recent results, BB therapy may in fact start to be beneficial sooner than other GDMTs,<sup>4</sup> at least



**Figure 1** Gradient of benefit for post-acute coronary syndrome patients. ACEi: angiotensin converting enzyme inhibitors; ACS: acute coronary syndrome; ARB: angiotensin receptor blockers; EF: ejection fraction; IH: in-hospital.

<https://doi.org/10.1016/j.repc.2021.05.009>

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for patients in sinus rhythm. This is a burning question that should be answered through future randomized controlled trials such as the ongoing REBOOT trial (ClinicalTrials.gov identifier: NCT03596385).

### Conflicts of interest

The authors have no conflicts of interest to declare.

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