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EDITORIAL COMMENT

The Swing of β-Blockers

Time for a System Reboot*

Borja Ibáñez, MD, PhD,[a,b,c] Sergio Raposeiras-Roubin, MD, PhD,[d] José M. García-Ruiz, MD[a,c,e]

β-Blockers are one of the most exciting classes of drugs in the armamentarium of physicians treating cardiovascular diseases. Indeed, the development of the first β-blocker, propranolol, was so significance that it gained Sir James Black the Nobel Prize in 1988, and 2 decades later, in 2012, Robert Lefkowitz and Brian Kobilka were awarded the Nobel Prize for discoveries of β-adrenergic receptor function. Despite the immense amount of clinical evidence accumulated with these drugs, new mechanisms of action of β-blockers are still being discovered (1). Few other classes of drug have raised more controversy with the passing of time. β-Blockers passed from being considered harmful for patients with heart failure (HF) to holding the highest recommendation in this context (2), and from being universally used during acute myocardial infarction (MI) to being suspected of inducing cardiogenic shock (3) and then finally restored as a potential, strong cardioprotector when injected very early in the course of MI (4). The role of β-blockers as a maintenance therapy in MI survivors is another example of the swings of opinion in these drugs in the cardiology community. The lack of randomized clinical trials powered to identify differences in hard endpoint and the proliferation of big data analyses from not well phenotyped populations have accelerated the pace of this swing.

β-Blockers were first identified in the 1960s as antiangina drugs for patients with acute (nonreperfused) MI. In the early 1980s, the large BHAT (Beta-Blocker Heart Attack) trial (5) and the Norwegian multicenter study (6) demonstrated a survival benefit associated with β-blocker treatment after acute (nonreperfused) MI. These and other studies set the basis for the use of these drugs as state-of-the-art therapy for MI; thereafter, the benefits of β-blockers in this clinical context appeared to be set in stone. However, since that time, the clinical scenario has changed dramatically. The widespread implementation of timely reperfusion in patients presenting with ST-segment elevation myocardial infarction (STEMI) is one of the great success stories in the history of medicine, not only because of the reduction in in-hospital mortality from 25% to 5% in 3 decades (7) but also because of the significantly better myocardial healing and remodeling in reperfused infarctions (8), resulting in a post-MI myocardium less vulnerable to arrhythmia and HF. Timely percutaneous coronary intervention of the culprit artery has also been shown to be beneficial in patients presenting with non-ST-segment elevation myocardial infarction (NSTEMI). In addition, pharmacological therapy has also been significantly improved since the 1990s, and today, MI patients receive several maintenance therapies with proven benefits (e.g., antithrombotic agents, statins, and/or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [ACEI/ARBs]). Given the fact that these approaches were not standard at the time of the "old" β-blocker trials, it is difficult to evaluate the true clinical benefit of β-blockers today.

The only large trials testing the clinical benefits of β-blockers in reperfused MI patients were the CAPRICORN (Carvedilol Post-Infarct Survival Control in LV Dysfunction) trial (9) and COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) (3). More precisely, in those trials, "only" approximately one-half of the patients underwent reperfusion.

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From the [a]Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain; [b]IIS-Fundacion Jiménez Díaz University Hospital, Madrid, Spain; [c]CIBER de enfermedades cardiovasculares, Madrid, Spain; [d]Hospitalario Universitario Alvaro Cunqueiro, Vigo, Spain; and the [e]Hospital Universitario Central de Asturias, Oviedo, Spain. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The CAPRICORN trial randomized patients with post-MI left ventricular ejection fraction (LVEF) of ≤40% to carvedilol or placebo (first dose given 3 to 21 days post MI). β-Blocker therapy was associated with significantly reduced all-cause mortality over 2.5 years of follow-up. Conversely, COMMIT recruited MI patients without LVEF restrictions, who were randomized to metoprolol therapy (very early intravenous followed by oral administration) or placebo. Over a short follow-up (4 weeks), metoprolol was not associated with increased survival. Thus, the only clinical trial-based evidence of a benefit of β-blockers in reperfused MI patients comes from the CAPRICORN trial, and thus strictly applies only to patients with LVEF of ≤40%. Both the American College of Cardiology (ACC) (10,11) and the European Society of Cardiology (ESC) (12,13) clinical practice guidelines for the treatment of MI patients strongly recommend (class IA) β-blockers for post-STEMI and for post-NSTEMI patients with LVEF of ≤40%. Notably, despite the lack of evidence of a benefit in reperfused patients without LV depression, both of the guidelines propose the use of β-blockers after STEMI: recommendation of Class I Level of Evidence: B from the ACC (10) and Class IIa Level of Evidence: B from the ESC (12). For NSTEMI without LVEF depression, use of β-blocker is an ACC Class IIa Level of Evidence: C therapy recommendation (11) but does not exist for ESC (13). As a consequence of these recommendations, the penetration of β-blocker prescription in post-MI patients without LV systolic dysfunction (LVSD) is very high worldwide today, reaching >80% of patients (14). Several observational studies and registries have tried to evaluate the clinical benefit of β-blockers in this population, with disparate results. The common outcome of most of these studies is a higher unadjusted mortality rate in patients not receiving β-blockers. This is due to a worse clinical profile among these patients, who tended to be older and sicker, probably accounting for the nonprescription of β-blockers. Complex statistical analyses (e.g., propensity scores) are needed to evaluate the association of β-blockers with clinical events independently of patient risk profile. The high rate of β-blocker prescription in post-MI patients and the differing risk profiles of patients who receive β-blockers versus those who do not make it difficult to interpret these studies. Not surprisingly, some studies have shown a mortality benefit of β-blockers after adjustment (15,16), whereas other studies have not shown any effect (17,18).

The paper by Dondo et al. (19) in this issue of the *Journal* tried to shed light on this matter by presenting an overwhelmingly large database of ~180,000 MI patients (51% STEMI) purportedly "not having HF or LVSD." Overt strengths of this study are its size (the largest study on this topic) and the unbiased source of the data (patients are included in the UK MINAP (Myocardial Ischaemic National Audit Project), which included hospitals all across England and Wales. Patients were treated according to current standards, with >50% undergoing coronary revascularization, >90% receiving dual antiplatelet therapy and statins, and >80% receiving ACEI/ARBs and enrolled in a cardiac rehabilitation program. Similar to previous retrospective/observational studies, in this study (19), β-blockers were prescribed to 95% of discharged patients, and patients not prescribed β-blockers were older and had a worse cardiovascular risk profile. Also like previous reports, the unadjusted 1-year mortality was significantly lower in patients taking β-blockers (4.9% vs. 11.2%, respectively). However, in a subsequent propensity score analysis including 24 variables, the authors found no mortality benefit in patients discharged taking β-blockers compared with those discharged without this prescription.

SEE PAGE 2710

These data should be interpreted with great caution due to the general limitations inherent in these kind of analyses (described above) and also in light of some particular features of this study. One obvious limitation is that, despite the authors' claim that the study population included post-MI patients "without HF or LVSD," the cutoff LVEF threshold used to define systolic dysfunction was 30%. The study thus includes patients with a post-MI LVEF of between 30% and 40%, for whom the clinical benefit of β-blockers is clearly established (9). In the MINAP, LVEF was recorded as poor (LVEF <30%), intermediate (31% to 49%) or good (≥50%) (20). Given the very large data set, the authors missed a great opportunity to present only patients with preserved LVEF (≥50%) or even to differentiate between patients with intermediate and good LVEF; it is not known what proportion of patients in each group (β-blockers yes or no) had LVEF of 31% to 49% versus those who had LVEF ≥50%. Notably, LVEF category, one of the variables most associated with overall mortality (outcome), as well as β-blocker prescription (treatment selection), was not included in the propensity score analysis. Another important limitation of this registry is that it recorded only the prescription of β-blockers at discharge (a variable that was missing in 17% of the total cohort), and it is not known how many patients adhered to this medication during the year after MI.

This study presents a very sophisticated statistical methodology, but there are limitations inherent to

these approaches that should be understood. Due to the observational nature of this study and given the fact that the indication for β-blocker is based on clinical guidelines, the risk of bias is very high. In particular, the existence of a "confounding by indication" is present when the prescription of the therapy is not random and is instead based on patients' clinical characteristics, especially when these characteristics are associated with the clinical outcome. Some randomness is needed to ensure that individuals with identical characteristics can be observed in both states, something that did not occur in this study. In an attempt to control these factors and to reduce these biases, the authors performed 2 types of analysis: propensity scoring and instrumental variable analysis. Propensity scoring is a method to alleviate the potential for "confounding by indication," and in this study represents the individual's probability of being treated with β-blockers given the complete set of available information about that individual. An assumption of propensity score analysis is that a fair comparison of outcomes can be made between participants with similar propensity scores who either were or were not prescribed β-blockers at discharge. To be able to compare individuals with similar propensity scores, the authors trimmed the sample to include only patients with a score between 0.1 and 0.9, thus guaranteeing the common support principle. Unfortunately, by doing this, 90% of the population was eliminated from the analysis. It is thus very unclear whether the estimated effect observed in propensity score-matched sample is representative of the entire cohort. This is of particular concern because the total and matched populations differed significantly (e.g., the relative proportion of STEMI patients was 51% in the total population versus "only" 29% in the propensity score-matched sample). In a further attempt to reduce the chances of confounding by indication and potentially unmeasured residual confounders, the authors performed an instrumental variable analysis. This method is based on identifying a variable that influences β-blocker prescription but is independent of confounders and has no direct effect on the outcome, except through its effect on treatment (β-blocker prescription). As the instrumental variable, the authors used "hospital rates of prescription of guideline-indicated treatments." Unfortunately, this instrumental variable is associated with clinical outcome independent of β-blocker prescription (e.g., dual-antiplatelet therapy reduces mortality independently of β-blocker prescription). The deviations of the authors' chosen instrumental variable make it difficult to draw certain conclusions.

In fact, it has been recently reported that conclusions obtained from data coming from observational studies using clinically available data tend to disagree with subsequent randomized clinical trials (21). Thus, even in the absence of randomized controlled trials, results from these kinds of studies should be seen with extreme caution, as they may not necessarily provide reliable answers on how to best treat patients (21). Thus, as the authors acknowledge, the present study should be viewed as hypothesis generating and should not change clinical practice. However, this important report highlights the need to reboot the system: the role of β-blockers in post-MI patients without LVSD (LVEF >40%) needs to be evaluated from scratch.

ADDRESS FOR CORRESPONDENCE: Dr. Borja Ibáñez, Translational Laboratory for Cardiovascular Imaging and Therapy, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Department of Cardiology, Instituto de Investigación Sanitaria, Fundación Jiménez Díaz, Melchor Fernández Almagro, 3, 28029 Madrid, Spain. E-mail: bibanez@cnic.es.

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