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EDITORIAL

The Art of Prescribing β-Blockers After Myocardial Infarction

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Medicine is an example of the integration of science and art. Clinical science (mainly trials) allows to establish treatment algorithms (with categorical decisions) based on specific population sets. However, in daily practice, many times, patients have a clinical profile different from those included in trials who founded guidelines. Individualized treatment for specific patients based on the available evidence is a complex art that physicians practice every day. One clear example of the complex balance between science and art is the prescription of β-blockers for patients who experienced a myocardial infarction (MI) and do not have reduced left ventricular ejection fraction (LVEF). Most of the evidence leading to the general recommendation of prescribing β-blockers after an MI[1] was generated at a time where reperfusion or revascularization was not implemented and where coadjuvant pharmacological therapy (antithrombotic, lipid lowering, etc) was very limited.[2] Old prospective randomized trials demonstrated that long-term treatment with β-blockers after an MI improves outcome and lower mortality by about 20%. However, these trials, mostly from the 1980s, included many patients with large MIs in which left ventricular dysfunction was common and antedate modern reperfusion and medical therapy. Thanks to advances in invasive management and pharmacological therapy, prognosis of patients with MI has been significantly improved.[3] While the benefits of β-blockers in patients with reduced LVEF (≤40%) is well founded on several trials executed in the 21st century,[4] the question is whether β-blockers are still beneficial in the new scenario in the absence of heart failure or left ventricular dysfunction.

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There is scarce evidence of the value of maintenance β-blockers for patients with MI and preserved LVEF treated according to current standards, including reperfusion, complete revascularization, potent antithrombotics and aggressive lipid lowering therapies. In a meta-analysis, stratifying trials into prereperfusion and reperfusion era, β-blockers did not reduce mortality in the reperfusion era.[5] A recent study that examined the association between adherence or not to β-blocker therapy and long-term outcome in patients with MI in the SWEDEHEART registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) showed a significant benefit on survival and the risk of late-onset heart failure 4 years after the index event in patients with reduced LVEF while the association was less obvious albeit a positive trend in patients with preserved LVEF after adjusting for background factors.[6]

Despite the widespread use and well overall tolerability of β-blockers, these drugs have some side effects. The most frequent is the asthenia and erectile dysfunction. In addition, in patients with hypertension (not after MI), β-blockers do not reduce coronary events,[7] but their use is associated with an increased risk of stroke when compared with other treatments. β-blockers have also been shown to increase the risk of new-onset diabetes. When compared with nondiuretic antihypertensive drugs, β-blockers increase all-cause mortality and stroke in patients with new-onset diabetes.[8,9]

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In recent years, the only trials testing β-blockers in the MI context have been focused on the acute administration during ongoing ST-segment–elevation MI (STEMI). The METOCARD-CNIC trial (Metoprolol in Cardioprotection During an Acute Myocardial Infarction) demonstrated that the intravenous administration of metoprolol during ongoing anterior STEMI reduces the size of infarction,[10] reduces the presence of microvascular obstruction and reperfusion injury,[11] and improves long-term LVEF.[12] Metoprolol exerts its beneficial effects specially when there is a delay between STEMI diagnosis and reperfusion,[13] probably by delaying the progression of ischemic injury.[14] Of note, a recent study has demonstrated that the benefits of acute intravenous administration of metoprolol during an ongoing STEMI are not shared by other β-blockers.[15] The METOCARD-CNIC trial did not test the value of maintenance β-blockers since all patients received them from day 1 onward. Other trials performed in the era of reperfusion have focused only on the value of short-term β-blocker administration in STEMI.[4,16]

Given the lack of trials testing the value of maintenance β-blockers for post-MI patients without reduced LVEF treated according to current standards, several observational studies have tried to address this highly relevant issue. Unfortunately, results from these observational studies have yielded opposite conclusions, with some suggesting that β-blockers are associated with a clinical benefit[17–19] and others suggesting that they have no benefit.[20,21] Due to the observational nature of these studies, and given 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 factor 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 any of these studies. The only chance for solving the question of the benefits of β-blockers is the execution of adequately sized clinical trials. Currently, 4 large trials are ongoing in Europe: REBOOT-CNIC trial (Treatment With Beta-Blockers After Myocardial Infarction Without Reduced Ejection Fraction; https://www.clinicaltrials.gov; unique identifier: NCT03596385), REDUCE-SWEDEHEART (https://www.clinicaltrials.gov; unique identifier: NCT03278509), BETAMI (Betablocker Treatment After Acute Myocardial Infarction in Patients Without Reduced Left Ventricular Systolic Function; https://www.clinicaltrials.gov; unique identifier: NCT03646357), and DANBLOCK (Danish Trial of Beta Blocker Treatment After Myocardial Infarction Without Reduced Ejection Fraction; https://www.clinicaltrials.gov; unique identifier: NCT03778554). These trials are expected to end in 2024.

In the current issue of the journal, an analysis from the well regarded KAMIR-NIH registry, which included 13 104 MI patients between 2011 and 2015, presents data regarding the long-term (ie, beyond 1 year) benefits of β-blockers in post-MI patients according to 1-year LVEF.[22] From the 13 104 patients in the registry, 1659 were dead or lost in follow-up at 1 year and thus excluded from this analysis. An additional 7437 patients were excluded because data regarding β-blocker use or 1-year LVEF were not available. Thus, a total of 4008 patients comprise the study population. Eighty-six percent of the population was discharged from index event on β-blockers, and 79% were still on β-blockers at 1 year. At 1 year, 1001 patients had LVEF <50% (83% on β-blockers at discharge and 80% still on β-blockers at 1 year), and 3007 had an LVEF ≥50% (87% on β-blockers at discharge and 79% still on β-blockers at 1 year). The study shows that β-blockers at discharge improve 3-year mortality regardless of baseline LVEF. In survivors at 1 year, mortality 2 years later was improved by β-blocker therapy only when LVEF at 1 year is <50%. In patients with LVEF <50%, cumulative incidence of events at 3 years in those who were withdrawn from β-blockers anytime during the year after MI was significantly higher than those who were kept on β-blockers. These results are in line with current evidence showing that post-MI patients with low LVEF should be kept on β-blockers in the long term. Conversely, in patients with LVEF ≥50%, cumulative incidence of events at 3 years in those who were withdrawn from β-blockers anytime during the year after MI was not different from those who were kept on β-blockers. The fact that the study only included patients alive at 1 year precludes a definite answer on whether β-blockers can be safely withdrawn in patients with preserved LVEF at 1 year. In fact, we do not know if β-blockers were beneficial during the first year and not beyond 1 year or by contrast they were not beneficial at all. Another interesting finding from the study is the significant interaction between 1-year LVEF (not baseline LVEF) and benefits of β-blockers. This result should be interpreted with caution since the categorization of LVEF (<50% or ≥50%) based on echocardiography can be troublesome in values close to 50%. The variability of the technique (especially in a registry environment) can result in variable categorization of a patient. There were 743 patients with LVEF <50% at baseline and ≥50% at 1 year. The information on how many number of these subjects were on β-blockers and the outcome on these versus those not on β-blockers is unfortunately not provided.

In summary, data presented in this article are hypothesis generating but do not solve the question on when to withdraw β-blockers after an MI. In this regard, the ongoing AβYSS trial[23] (Beta Blocker Interruption After Uncomplicated Myocardial Infarction; https://www.clinicaltrials.gov; unique identifier: NCT03498066) will randomize 3700 patients who experienced an MI >6 months before to withdraw β-blockers or maintain them. Indeed, the strength of evidence in favor or against long-term

β-blocker treatment after MI with preserved LVEF remains uncertain underlining the need for robust and reliable data from the ongoing trials and beyond.

ARTICLE INFORMATION

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