EDITORIAL COMMENT

How much is enough?
Quanto será suficiente?

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The guidelines for treatment after myocardial infarction (MI) with or without ST-segment elevation (STEMI or NSTEMI) recommend the use of beta-blockers for all patients without contraindication because, based on large observational studies and randomized clinical trials, they increase survival rates.

These guidelines recommend high doses of beta-blockers, but this recommendation is not followed in clinical practice, in which about 25% of the recommended dose is prescribed. Although widely used, these lower doses have not been tested in controlled and randomized trials. The question thus arises as to whether smaller doses of beta-blockers achieve the same benefit in reducing mortality, since the increases in survival in the trials were proportional to the decreases in heart rate obtained with incremental doses.

Studies designed to answer the question of the correct beta-blocker dose have provided important information for the follow-up of MI. The Outcomes of Beta-Blocker Therapy After Myocardial Infarction (OBTAiN) registry, of 6682 patients in centers in the USA and Canada from 2007 to 2009 with a mean follow-up of 2.1 years, used multivariate and propensity score analysis to assess the results. No improvement was observed in the survival of patients treated with the higher doses of multiple beta-blockers proposed in the randomized trials.

Similarly, a recently published multicenter registry with 5287 patients discharged on beta-blockers after an acute coronary syndrome (ACS) between 1994 and 2013 showed no difference between the two doses analyzed, ≤25% or ≥50% of an equivalent daily dose of 200 mg of metoprolol. The authors analyzed the rates of major adverse cardiac events (MACE), all-cause death, MI, and stroke or equivalent at six months and 24 months of follow-up using multivariate and propensity score analysis. They observed that patients on lower doses had higher rates of myocardial revascularization, an effect that was also seen in the OBTAiN subgroup analysis. The authors further divided the population into two periods, 1993-2003 and 2004-2013, but there was no statistical difference between them.

In this issue of the Journal, Raposeiras-Roubin et al. revisit this question, retrospectively analyzing 2092 ACS patients discharged from a single center, the Álvaro Cunqueiro University Hospital of Vigo, between June 2013 and January 2016, and followed for a mean of 18.6±9.7 months. The patients were prescribed various beta-blockers with a predominance of bisoprolol. No prognostic benefit was noted in terms of mortality for high-dose vs. low-dose beta-blockers.

A meta-analysis published in 2014 encompassing sixty clinical trials with 102,003 patients compared the effect of beta-blockers at target doses on mortality after MI in the
pre- vs. post-reperfusion era, and showed no benefit due
to beta-blockers in the post-reperfusion era. Nevertheless,
beta-blockers showed benefits for recurrent MI and angina
in the reperfusion era, at the expense of increases in heart
failure, cardiogenic shock, and drug discontinuation, but
appeared to be short term (30 days after discharge).

In the above registries, which reflect the translation
of guidelines into clinical practice, lower doses of beta-
blockers were more frequent and equally useful in reducing
cardiac mortality and MACE. These doses were probably
selected for a variety of reasons, some objective (hemody-
namic limitations and associated respiratory conditions
such as reactive airways disease), and some subjective, such as
fatigue, depression and sexual dysfunction.

These retrospective registries used robust methods for
statistical data analysis, including propensity score analy-
sis and classical regression, to minimize confounding factors
such as hypertension, prior STEMI and multivessel coronary
artery disease, which are better controlled for in clinical tri-
als. However, they do not provide information on the control
of anginal symptoms, blood pressure, heart rate or arrhyth-
mic events, or confirm the extent of patients’ adherence to
medication. The mean follow-up of 24 months may not have
been sufficient to show significant differences, such as seen
in clinical trials.

It is possible that advanced reperfusion therapies, potent
antithrombotics, statins, angiotensin-converting enzyme
inhibitors, angiotensin receptor blockers, cardiac rehabili-
tation, and lifestyle and dietary modifications were
responsible for the results observed in the registries,
although Allen et al. did not observe differences between
two periods in the last twenty years.

Several factors are taken into account when consider-
ing the optimal dose of beta-blocker therapy: severity and
extent of coronary artery disease, presentation (NSTEMI or
STEMI) and size of MI, the reperfusion method used (throm-
bolysis or percutaneous coronary intervention), presence of
residual ischemia, additional non-culprit lesions, revascular-
ization procedures needed in the follow-up period, and
assessment of cardiac function.

On the other hand, beta-adrenergic receptor polymor-
phisms have been discovered that may be responsible for
differences in dose-dependent response and beta-blocker
metabolism, with hemodynamic effects such as changes in
blood pressure and heart rate.

Recently, a new guideline for the management of acute
MI in patients presenting with ST-segment elevation has
been published that recommends the use of a beta-blocker,
started within 24 hours of hospitalization, in patients
without contraindication that should be continued after
discharge, with class Ila recommendation and level of evi-
dence B. The contraindications are acute heart failure,
hemodynamic instability and higher degree AV block, with
the recommendation that doses of proven efficacy should be
administered.

Further research should be carried out to compare the
effects of different doses of beta-blockers and the factors
used to select them in order to improve survival and MACE
after MI. Until the results of these studies are available,
the best strategy is probably to offer patients the maximum
dose tolerated, but lower than the target doses used in
the randomized trials. Registries such as that of Raposeiras-
Roubin et al. support this therapeutic decision while we
await publication of new evidence that may change the use
of beta-blockers in the follow-up of patients with MI.

Conflicts of interest
The author has no conflicts of interest to declare.

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