Rev Port Cardiol. 2018;37(3):247–248

Revista Portuguesa de Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

How much is enough?

Quanto será suficiente?

Gláucia Maria Moraes de Oliveira

Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Available online 26 March 2018

The guidelines for treatment after myocardial infarction (MI) with or without ST-segment elevation (STEMI or NSTEMI)[1–3] 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,[4] 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[5] 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, $\leq$25% or $\geq$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.[6] 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[7] encompassing sixty clinical trials with 102 003 patients compared the effect of beta-blockers at target doses on mortality after MI in the

DOI of original article: https://doi.org/10.1016/j.repc.2017.06.022
E-mail address: glauciamoraesoliveira@gmail.com

https://doi.org/10.1016/j.repc.2018.03.002

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,[4–6] 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 (hemodynamic limitations and associated respiratory conditions such as reactive airways disease), and some subjective, such as fatigue, depression and sexual dysfunction.[5]

These retrospective registries used robust methods for statistical data analysis, including propensity score analysis and classical regression, to minimize confounding factors such as hypertension, prior STEMI and multivessel coronary artery disease, which are better controlled for in clinical trials. However, they do not provide information on the control of anginal symptoms, blood pressure, heart rate or arrhythmic 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 rehabilitation, and lifestyle and dietary modifications were responsible for the results observed in the registries, although Allen et al.[5] did not observe differences between two periods in the last twenty years.

Several factors are taken into account when considering 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 (thrombolysis or percutaneous coronary intervention), presence of residual ischemia, additional non-culprit lesions, revascularization procedures needed in the follow-up period, and assessment of cardiac function.[8]

On the other hand, beta-adrenergic receptor polymorphisms 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.[9,10]

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 IIa recommendation and level of evidence 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.[11]

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.[6] 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.

References

1. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61:e78–140.
2. Roffi M, Patrono C, Collet JP, et al., Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267–315.
3. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64:e139–228.
4. Goldberger JJ, Bonow RO, Cuffe M, et al. Effect of beta-blocker dose on survival after acute myocardial infarction. J Am Coll Cardiol. 2015;66:1431–41.
5. Allen JE, Knight S, McCubrey RO, et al. β-blocker dosage and outcomes after acute coronary syndrome. Am Heart J. 2017;184:26–36.
6. Raposeiras-Roubin S, Abu-Assi E, Caneiro-Queija B, et al. Effect of beta-blocker dose on mortality after acute coronary syndrome. Rev Port Cardiol. 2018;37:239–45.
7. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with β-blockers for myocardial infarction: a meta-analysis of randomized trials. Am J Med. 2014;127:939–53.
8. Nakatani D, Sakata Y, Suna S, et al. Impact of beta blockade therapy on long-term mortality after ST-segment elevation acute myocardial infarction in the percutaneous coronary intervention era. Am J Cardiol. 2013;111:457–64.
9. Aleong RG, Sauer WH, Robertson AD, et al. Adrenergic receptor polymorphisms and prevention of ventricular arrhythmias with bucindolol in patients with chronic heart failure. Circ Arrhythm Electrophysiol. 2013;6:137–43.
10. Cresci S, Dorn GW 2nd, Jones PG, et al. Adrenergic-pathway gene variants influence beta-blocker-related outcomes after acute coronary syndrome in a race-specific manner. J Am Coll Cardiol. 2012;60:898–907.
11. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2017:1–66.