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EDITORIAL

Beta-blocker Therapy in Acute Coronary Syndromes: a Time-Trend Interpretation of Evolving Clinical Benefits

Editorial to: "The Use of Oral Beta-Blockers and Clinical Outcomes in Patients with Non-ST-Segment Elevation Acute Coronary Syndromes: a Long-Term Follow-up Study" by J.C. Nicolau et al.

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Following the introduction of beta-blocker therapy for acute myocardial infarction (AMI) in the 1960s, multiple studies attested to their benefit for preventing recurrent myocardial ischemia, reinfarction, and sudden death [1–3]. This benefit came to be especially recognized in the presence of heart failure during AMI [4]. Subsequently, the benefit of BB therapy in chronic heart failure with reduced ejection fraction (EF) evolved in several RCTs in the 1980s and 1990s establishing it as a mainstay of therapy for congestive heart failure [5].

During this 40-year period, other secondary preventive agents concurrently emerged as affecting outcomes in AMI (i.e., statins, ACE inhibitors, AII-receptor blockers [ARB], and platelet inhibitors), thereby adding a confounding interpretation to the relative benefits of the individual components of secondary preventive therapy. With the onset of the new century in 2000, the era of reperfusion therapy for AMI with thrombolysis and percutaneous catheter interventions (PCI) was firmly established and altered the balance of ischemic injury sustained in AMI or unstable angina which became referred to as acute coronary syndromes (ACS). These evolutionary therapeutic changes resulting in benefits to improve clinical outcomes more recently have given rise to the emergence of doubt regarding the importance of the ongoing benefit of beta-blocker therapy in ACS [6–8]. These doubts are completely understandable when one considers the emerging history of multiple therapies for acute MI and the specific population treated.

In part, these doubts exist predominantly within those medical communities which have access and resources to apply the most current medical therapies acutely to ACS and provide ongoing secondary prevention. That many parts of the world do not have timely thrombolytic therapy or PCI to limit myocardial necrosis and scar, and subsequently, the post-MI sequelae of serious malignant ventricular arrhythmias or a reduced EF may argue for a different viewpoint.

Thus, there exist currently two pivotal turning points of confounding factors in interpreting the benefits of beta-blocker therapy resulting from the time-trends of medical therapy for ACS: (1) the relative contributions of additional pharmaceutical therapies added over the years which now are often employed in ACS (i.e., statins, ACE inhibitors, ARB, and anti-platelet therapy) with their long-term secondary preventive benefit and utilization and (2) the avoidance of major myocardial necrosis and scar resulting from reperfusion therapy of thrombolysis and revascularization procedures (PCI or CABG) in ACS. Even without the nuances of variation imposed by consideration of the specific beta-blocker utilized, rate of administration, dosage employed, continued utilization, and length of follow-up to determine benefit, it becomes apparent that some authors in a modern developed population may conclude that ACS patients without a low EF or heart failure may not warrant beta-blocker therapy. This controversy of interpretation of the benefits of beta-blocker therapy motivated Nicolau et al. to report from a retrospective databank a 17-year experience from the country of Brazil on the benefits of beta-blocker therapy in non-STE acute coronary syndromes in the current issue of *Cardiovascular Drugs and Therapy* [9]. Notwithstanding the limitations (dutifully noted by the authors) of the retrospective data, a combination of statistical models and multivariate adjusted data sought to establish the ongoing benefits of beta-blocker therapy in the non-STE acute coronary syndromes [9].

Using models of a propensity score adjusted analysis and multivariate analyses with stepwise logistic regression, they

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retrospectively analyzed the short-term in-hospital mortality and the long-term follow-up of patients receiving oral beta-blockers within the initial 24 h of hospitalization versus those who did not receive beta-blocker therapy. In 2921 patients with non-STE acute coronary syndromes (defined as 1873 MI patients and 1048 unstable angina patients), the propensity score analysis of 2082 beta-blocker-treated patients and 838 non-beta-blocker patients resulted in a propensity matched (1:1) subgroup of 689 patients in each group. Those utilizing beta-blocker therapy showed a lower rate of in-hospital mortality (OR 0.52; 95% CI 0.33 to 0.74, $p < 0.002$) and a greater long-term mean survival time (11.9 years vs 9.9 years, $p < 0.001$). Moreover, their data showed that in those patients with an echocardiographic left ventricular EF > 55%, no statistical evidence of benefit of avoiding in-hospital mortality could be demonstrated [9]. This lends credence to the theory that beta-blockers exert their major benefits against the sequelae of major myocardial injury and necrosis which is identified most commonly by measurement of the left ventricular EF.

The authors called attention to the surprise finding that there was a significant decrease in cardiogenic shock for either the entire population of acute coronary syndromes or the matched propensity score populations. This was quite understandable in that these data were obtained where the clinical practice dictated that the majority (~ 94%) of patients received or were taking oral beta-blockers on admission, and dosages were titrated carefully with 79% of patients being discharged on such therapy [9]. Thus, this population avoided the error of starting IV beta-blocker and/or high-dosage oral beta-blocker without careful and time-delayed titration which led to adverse outcomes as experienced in the COMMIT Trial [10].

What are we to learn from such data, and how is it to shape our clinical judgment going forward? One perspective is to understand that the value of a therapy in a specific clinical disease such as acute coronary syndromes must consider the emerging confounding factors introduced by advancing medical therapies which occur over time in a specific population. Nicolau et al. have sought to achieve this by employing propensity matched models of the factors available in the databank. These included age, heart rate, EF, history of previous cardiovascular diseases, in-hospital therapies of PCI and CABG (noticeable absence of thrombolytic therapy), and ACE inhibitor or AII-receptor blockers. Despite the positive aspects of modern statistical methods, the nuances of real-world medicine with its variability of the specific pharmaceutical agent used, dosages employed, rate of administration, continued utilization, and duration of therapy are often not available in such databanks. The absence of knowledge of statins and platelet inhibitors could be cited as outstanding confounding factors not adjusted within the data. Nevertheless, the robustness of benefit of beta-blocker therapy in ACS was demonstrated in the entire population, as well as the matched population models. The authors' findings agreed with and support the emerging controversy created by time-trend medical advances, that in those patients with a normal left ventricular EF > 55%, statistical evidence of outcome benefit long-term could not be demonstrated in this non-STE ACS population [6–8].

However, atherosclerosis leading to ACS is a multifactorial pathophysiological process affecting the coronary arteries that is usually a progressive disease not easily targeted to a specific subgroup [11]. When ACS occurs in a population without medical access to the most modern preventive strategies or timely access to acute interventions with the occurrence of ACS, appreciable myocardial injury and necrosis can be sustained. Therefore, experienced physicians will individually evaluate the access to care and resources of each ACS patient within the context of their existing individual cardiovascular risks before limiting or abandoning beta-blocker therapy in such patients. Beta-blocker's adjunctive benefit in the therapy of hypertension and cardiac arrhythmias (particularly atrial fibrillation and ventricular arrhythmias) makes it a valuable therapeutic agent to be kept in mind during the natural history of ACS survivors. While there may be some current interest to utilize a precision-medicine approach to beta-blocker discontinuation in ACS patients with preserved EFs, caution should be exercised in this regard [11]. Seemingly after 60 years of utilization, given societies lack of medical resources globally and the general cost-effectiveness of beta-blockers, beta-blocker therapy should continue to have a major role in ACS survivors for many decades to come.

References

1. Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. Lancet 1986;2:57–66.
2. The Beta-Blocker Pooling Project (BBPP) subgroup findings from randomized trials in post infarction patients. The Beta-Blocker Pooling Project Research Group. Eur Heart J 1988;9:8–16.
3. Goldman L, Sia ST, Cook EF, Rutherford JD, Weinstein MC. Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction. N Engl J Med. 1988;319:152–7.
4. Goldstein S. Propranolol therapy in patients with acute myocardial infarction: the Beta-Blocker Heart Attack Trial. Circulation. 1983;67:153–7.
5. Avezum A, Tsuyki RT, Pogue J, Yusuf S. Beta-blocker therapy for congestive heart failure: a systematic overview and critical appraisal of the published trials. Can J Cardiol. 1998;8:1045–53.
6. Huang BT Huang BT, Huang FY, Zuo ZL, Liao YB, Heng Y, Wang PJ, et al. Meta-analysis of relation between oral β-blocker therapy and outcomes in patients with acute myocardial infarction who underwent percutaneous coronary intervention. Am J Cardiol. 2015;115:1529–38.
7. Puymirat E, Riant E, Aissoui N, Soria A, Ducrocq G, Coste P, et al. β blockers and mortality after myocardial infarction in patients without heart failure: multicenter prospective cohort study. BMJ. 2016;354:i4801.
8. Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H, et al. β-Blockers and mortality after acute myocardial infarction in

patients without heart failure or ventricular dysfunction. J Am Coll Cardiol. 2017;69:2710–20.
9. Nicolau JC, Furtado RH, Baracioli LM, et al. The use of oral beta-blocker and clinical outcomes in patients with non-ST-segment elevation acute coronary syndromes: a long-term follow-up study. Cardiovasc Drugs Ther 2018;32:this issue.
10. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Lancet. 2005;366:1622–32.
11. Psaty BM, Dekkers OM, Cooper RS. Comparison of 2 treatment models: precision medicine and preventive medicine. JAMA. 2018;320:751–2.