EDITORIAL

Should we use β-blockers for myocardial infarction?

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Introduction Physicians have used β-blockers in the management of cardiovascular disease for many years. The indications for β-blocker use have changed over the last decade, as evidence has emerged demonstrating that their benefit, in some situations, is not as important as previously believed and substantial risks have come to light.[1,2]

The first major shift in the recommendations on β-blocker use was in the area of primary prevention in the treatment of hypertension. A Cochrane systematic review of the use of β-blockers in the treatment of hypertension failed to show benefit in preventing mortality or coronary artery disease.[3] As a result, β-blockers are no longer a part of the first-line therapy for hypertension in several expert guidelines.[4,5] Another area in which a substantial shift in the recommendations has occurred is in patients undergoing a noncardiac surgery. Perioperative β-blocker use for the prevention of postoperative cardiovascular complications has been questioned owing to the increased risk of stroke and mortality associated with β-blockade.[6,7]

Although there has been a substantial change in the recommendations for β-blockers in hypertension and perioperative risk, β-blockers are still widely used in secondary prevention and in the treatment of acute myocardial infarction (MI). In patients with ST-segment elevation MI (STEMI), the use of oral β-blockers within the first 24 hours is recommended by the American College of Cardiology Foundation / American Heart Association (ACCF/AHA) STEMI guideline and has a class I recommendation.[8] The European Society of Cardiology (ESC) Guidelines also mention that oral β-blockers should be considered during hospital stay in all patients with STEMI (class IIa).[9] Intravenous β-blockers are recommended in patients suffering an acute MI with high blood pressure and without signs of heart failure both by the ACCF/AHA (class IIa) and by the ESC guidelines (class IIa).

Both guidelines recommend continuing β-blockers after the acute event in all patients with STEMI (class I and class IIa for the ACCF/AHA and ESC, respectively). Recommendations vary, however, regarding the duration of β-blockade therapy post-MI in patients with preserved left ventricular function. The ACCF/AHA guidelines recommend that β-blockers should be continued for a minimum of 3 years[10] (class I) and could be continued chronically thereafter (class IIa). The ESC recommends long-term β-blocker treatment for patients with left ventricular dysfunction but no definite duration is mentioned for patients without heart failure.[9]

These MI guidelines are primarily based on literature that antedated the arrival of modern therapies including reperfusion therapy. The introduction of reperfusion therapy has created a major paradigm shift in the approach to treating acute coronary syndromes leading to a substantial drop in the mortality rate after MI.[11] Prior to the introduction of contemporary treatment, evidence to support the benefits of β-blockers outweighed the potential adverse effects.[12] Recently, authors have questioned whether this is true with recent advances in acute MI therapies.

The COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial)[13] was a large randomized controlled trial of 45,852 patients presenting with acute MI, published in 2005. In the COMMIT, early β-blocker therapy was associated with a reduction in the risk of myocardial reinfarction (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.72–0.92; $P = 0.001$) and ventricular fibrillation (OR, 0.83; 95% CI, 0.75–0.93; $P = 0.001$) but at the expense of an increased risk of cardiogenic shock (OR, 1.30; 95% CI, 1.19–1.41; $P < 0.0001$). The data demonstrated that, for every 1000 patients treated, β-blocker therapy prevented 5 patients from suffering myocardial reinfarctions and 5 from suffering ventricular fibrillations; however, β-blockade caused 11 patients to develop cardiogenic shock. Despite earlier trials

suggesting a mortality benefit, this large trial demonstrated that β-blockade had no impact on 30-day mortality. Despite these data, β-blockers retained a high-class recommendation in major expert guidelines, and registry data suggested that the publication of the COMMIT results did not result in a significant change in β-blocker practice patterns in acute MI.[14]

To help inform the impact of contemporary treatment on the efficacy of β-blocker in acute MI, Bangalore et al.[15] undertook a systematic review and meta-analysis. Randomized controlled trials comparing β-blockers with controls in patients with MI were included in the systematic review. Trials of β-blockade in post-MI left ventricular dysfunction were excluded. In order to classify trials according to the treatment era, the authors defined reperfusion era trials as trials with more than 50% of the patients receiving reperfusion with either a thrombolytic agent, coronary revascularization, or aspirin and statin therapy. Sixty trials that included a total of 102,003 patients were included in the systematic review.

The majority of the trials were in the prereperfusion era, while 12 trials were considered in the reperfusion era. When considering the risk of bias in the included trials, the prereperfusion era trials had a higher proportion of high-risk for bias trials when compared with the reperfusion era (75% and 50%, respectively). The results of the meta-analysis showed substantial differences of effects between the pre- and postreperfusion era trials. In the acute MI trials, for the primary outcome of all-cause mortality, a significant interaction ($P_{\text{interaction}} = 0.02$) was noted with reperfusion status such that β-blockers were associated with a significant reduction in mortality in the prereperfusion era (incident ratio rate [IRR], 0.86; 95% CI, 0.79–0.94) but were not associated with a benefit in the reperfusion era (IRR, 0.98; 95% CI, 0.92–1.05).

Prereperfusion era In the prereperfusion era, the benefit of β-blockers was seen both in acute MI and post-MI. A reduction in cardiovascular mortality (IRR, 0.87; 95% CI, 0.78–0.98), MI (IRR, 0.78; 95% CI, 0.62–0.97), and angina (IRR, 0.88; 95% CI, 0.82–0.95) was associated with oral β-blocker treatment in the prereperfusion era where no difference was seen in sudden death, heart failure, cardiogenic shock, or stroke. Early intravenous β-blocker trials (ie, randomization within 48 hours of symptom onset) showed similar results with a reduction in cardiovascular mortality (IRR, 0.88; 95% CI, 0.78–0.99), sudden death (IRR, 0.59; 95% CI, 0.38–0.91), MI (IRR, 0.78; 95% CI, 0.62–0.98), and angina pectoris (IRR, 0.88; 95% CI, 0.82–0.95), with no difference in heart failure and cardiogenic shock.

Reperfusion era Although β-blocker use was associated with a reduction in MI (IRR, 0.72; 95% CI, 0.62–0.83) and angina (IRR, 0.80; 95% CI, 0.65–0.98), they were also associated with an increase in heart failure (IRR, 1.10; 95% CI, 1.05–1.16) and cardiogenic shock (IRR, 1.29; 95% CI, 1.18–1.41). No difference was seen in cardiovascular mortality, sudden death, and stroke. The same results were seen with early intravenous β-blocker therapy. The results for β-blocker in post-MI patients (ie, randomized >48 hours of symptoms) were also very similar with no benefit seen on mortality and MI and with an increase in heart failure and drug discontinuation.

Therefore, the results of the meta-analysis suggest that the reduction in mortality with β-blocker therapy in the prereperfusion era is no longer present in the reperfusion era. Furthermore, the beneficial effects on other outcomes such as MI and angina are still present but they are counterbalanced by an increase in cardiogenic shock and heart failure. These findings are not only true in the early treatment of MI but also after the first 48 hours after MI.

These results raise important questions regarding the reasons for the lack of previously seen benefit and the potential harm associated with β-blocker therapy after MI. Importantly, the meta-analysis conclusions remained unchanged when the largest trial, COMMIT, was removed suggesting that the effect was not solely driven by that trial. Consistent with the main findings, a meta-regression analysis showed that as the percentage of reperfusion therapy increased, the beneficial effect of a β-blocker decreased. The authors of the review also perform further analysis (ie, trial sequential analysis) to ensure that the number of patients allowed sufficient power to draw their conclusions.[15] The reperfusion strata had a sample size of 48,806 patients and 99% power to detect a difference between intervention and control.

One explanation for these findings may be that reperfusion therapy became widely used at the same time as new contemporary therapy including antiplatelet drugs, statins, and angiotensin-converting enzyme inhibitors (ACEIs). In the COMMIT, all patients received aspirin, 50% received clopidogrel, 54% received a fibrinolytic, and 68% received an ACEI. This is in contrast with earlier trials in the prereperfusion era such as the First International Study of Infarct Survival (ISIS-1)[12] where only 5% of the patients received antiplatelet therapy at discharge. In ISIS-1, atenolol was associated with a mortality benefit, whereas in the COMMIT, metoprolol had no impact on 30-day mortality. This suggests that the advances in medical management and reperfusion therapy have changed not only the patient's outcome but also the benefit associated with β-blocker use.

The meta-analysis results raise the question of why would a β-blocker no longer be associated with marked benefit? The answer might relate to the mechanism by which β-blockers reduced mortality in the preperfusion era. Animal studies have suggested that the use of an intravenous β-blocker after myocardial ischemic injury reduce infarct size.[16] Extensive myocardial scarring,

particularly in scar border zones, are associated with disruption in electrical conduction, providing regions at higher risk of reentrant fatal ventricular arrhythmias. Another potential explanation for the early beneficial effect of β-blockers may be associated with their impact on sympathetic activity. Electrophysiological studies have shown an increase in cardiac sympathetic nerve activity associated with coronary occlusion.[17] Both of these mechanisms could promote arrhythmogenesis. Therefore, the sympatholytic effect of β-blockers would be beneficial in reducing ventricular fibrillation; however, the negative chronotropic and inotropic effects can reduce cardiac output, which could lead to heart failure and cardiogenic shock.

In the prereperfusion era, sudden death and ventricular arrhythmia were the leading cause of death in the first 24 to 48 hours after MI. The introduction and widespread use of aggressive medical and early reperfusion therapy would contribute to a reduction in myocardial scarring in patients with acute MI and contribute to a decline in mortality seen in the past decades.[11] Another possibility could be that contemporary therapy (ie, aspirin and statin) which also have been shown to reduce the infarct size in combination with reperfusion therapy might significantly alter the substrate on which β-blockers were effective. In other words, one could hypothesize that β-blockers were acting more as a safe-guard against fatal complications (ie, ventricular arrhythmia and sudden death); however, contemporary therapy changed the underlying substrate, thus preventing a larger number of these fatal complications. In this modern setting, the risk–benefit balance may no longer favor β-blockers.

Clinical implications The results of the meta-analysis by Bangalore et al.[15] strengthen the concerns raised by the COMMIT regarding the systematic use of β-blockers in patients presenting with acute MI. For patients with extensive MI at higher risk of sudden death and ventricular arrhythmia, it may be worthwhile to consider β-blocker therapy. This is especially true since a significant portion of these patients will have impaired left ventricular function and β-blockers have been shown to be beneficial in heart failure trials.[18,19] There is also a general consensus that the early use of β-blockers should be avoided in patients who present with signs of acute heart failure as this might lead to worsened hypotension and cardiogenic shock. When comparing patients treated with or without fibrinolytic therapy, there was no mortality benefit associated with a β-blocker in the COMMIT.[13] This may reflect the effectiveness of contemporary medical therapy that may negate the potential benefit of β-blockers.

Based on these data, we believe it is reasonable to conclude that in the absence of the benefit on mortality as previously seen in the prereperfusion era, the potential benefit on recurrent MI and angina should be weighed against the potential risk of cardiogenic shock and heart failure. One should exercise caution and use clinical judgment to determine if a patient might benefit from β-blocker therapy in the light of these results.

Drug compliance should also be taken into account. Dyspnea, fatigue, and dizziness are common side effects of β-blockers[20] that can be distressing to patients recovering from an acute MI which may be in part explaining the increase in drug discontinuation associated with β-blocker therapy seen in the following year after MI.[13] Certainly that with the current evidence available, major expert guidelines should consider changing the level of recommendation to one that would better reflect the current balance of risk–benefit of β-blocker therapy in the treatment of patients with MI.

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