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REVIEW

Beta-Blockers in Post-MI Patients: Need to Re-consider?

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Abstract

International clinical practice guidelines recommend early introduction and continued treatment with beta-blockers for all patients without contraindications after STEMI. Although there seemed to be little question that patients with STEMI, regardless of revascularization strategy, derive substantial benefits from both long- and short-term beta-blockade, there has been a paucity of high quality evidence supporting this notion and the majority of data predate modern reperfusion therapy and current medical management strategies with statins and antiplatelet agents. Recently published data question this "one-size-fits-all" approach, showing that the use of beta-blockers increased the risk of heart failure and cardiogenic shock with no mortality benefit.

Key Words: acute myocardial infarction; beta-blockers; heart failure; cardiogenic shock

List of Abbreviations

AMI = acute myocardial infarction; EF = ejection fraction; ICD = implantable cardioverter defibrillator; HF = heart failure; LV = left ventric-le(-ular); MACE = major cardiovascular events; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; RAAS = renin-angiotensin aldosterone system; STEMI = ST-elevation myocardial infarction; VF = ventricular fibrillation

Introduction

Beta adrenergic receptor blockers have long been recommended for the treatment of all stages of ischemic heart disease, with the exception of Prinzmetal's vasospastic variant angina. Beta-Blockade is still regarded as standard therapy for effort angina, mixed effort and rest angina, and unstable angina. International clinical practice guidelines recommend beta-blocker therapy, both short- and long-term, to all acute coronary syndrome patients without contraindications, regardless of the revascularization strategy. However, much of the data to support their use predates reperfusion and contemporary medical therapy, while controversy also exists over the optimum timing of therapy initiation and discontinuation.

Mechanisms of beta-blockers action

Potentially beneficial effects of beta-blockers in patients with acute myocardial infarction (MI) include: ^{1,2}

- Decreased oxygen demand due to the reductions in heart rate, blood pressure, and contractility, and the consequent relief of ischemic chest pain.
- Decreased risk of ventricular fibrillation (VF), as suggested by experimental studies demonstrating an increase in the VF threshold and by clinical trials showing a relative risk reduction in sudden cardiac death.³⁻⁵
- Decreased automaticity, increased electrophysiologic threshold for activation, and slowing of conduction.
- Bradycardia, which prolongs diastole and therefore improves coronary diastolic perfusion and reduces after-depolarizations and triggered activity.
- Reduction in remodeling and improvement in left ventricular hemodynamic function, depending upon infarct size and the timing of treatment.⁶⁻⁸
- Improved left ventricular diastolic function with a less restrictive filling pattern.⁹
- Slowing of the yearly rate of progression of coronary atherosclerosis in patients with and without MI, as demonstrated by intravascular ultrasound evaluation of atheroma volume.¹⁰
- Inhibition of platelet aggregation and thromboxane synthesis.¹¹
- One or more of the above mechanisms may contribute to a reduction in reperfusion injury.

Clinical trials

Studies prior to the use of thrombolysis have demonstrated both short- and long-term benefits, and a meta-analysis of these trials showed a 25% reduction in mortality at one year.¹² Likewise, a similar analysis of the studies in patients treated with thrombolysis showed an overall 23% reduction in mortality.¹³ Early intravenous beta-blocker therapy also has been shown to improve both short-term and long-term outcome in the Thrombolysis in Myocardial Infarction II-B trial.¹⁴ In the Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, high-risk STEMI patients with reduced left ventricular (LV) function who were treated with the beta-blocker carvedilol realized a reduction in mortality of 23% over a 2.5-year period.¹⁵

The COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) examined the effect of early intravenous then oral metoprolol in 45,852 patients with STEMI (93% with ST elevation or left bundle branch block), one-half of whom received fibrinolytic therapy. Patients who were going directly for percutaneous coronary intervention (PCI) were excluded. In this trial, patients were randomly assigned to placebo or to three 5 mg intravenous boluses of metoprolol tartrate followed by oral metoprolol extended release (succinate) 200 mg/day for 30 days. The trial did find that beta-blockers resulted in

less reinfarction and ventricular fibrillation at the expense of more cardiogenic shock, which is consistent with the benefit of this therapy in hemodynamically stable patients (who are not susceptible to shock).¹⁶

The best evidence for early initiation of beta-blocker therapy in patients treated with current recommended therapies (e.g., statins, dual antiplatelet therapy) comes from the METOCARD-CNIC trial.¹⁷ In METOCARD-CNIC, 270 patients with Killip class II or less anterior STEMI were randomly assigned to receive intravenous metoprolol (up to three 5 mg boluses of metoprolol tartrate given two minutes apart) or not before reperfusion and all patients received oral metoprolol within 24 hours. The primary end point of infarct size on magnetic resonance imaging performed 5-7 days was significantly smaller in the group that was treated early (25.6 vs 32.0 g; $p = 0.012$). In addition, left ventricular ejection fraction was higher in the treated group at 5-7 days and at 6 months (adjusted treatment difference 2.67%; $p = 0.045$ and 3.49%; $p = 0.025$), and early metoprolol administration was associated with reduced incidence of severe LV systolic dysfunction, ICD indications and fewer heart failure admissions.¹⁸ There was no difference in the safety end point. Limitations of the study include lack of a placebo control and exclusion of patients with inferior MI.

The effect and optimal duration of oral beta-blocker therapy after primary PCI for patients with STEMI, has not been investigated in prospective, randomized studies and results from non-randomized studies are inconsistent.

A retrospective review of observational data from 4 of the PAMI (Primary Angioplasty in Myocardial Infarction) studies, including 2,442 patients, found lower 6-month mortality associated with oral beta-blocker therapy at discharge (2.2% vs 6.6%, $p > 0.0001$; odds ratio [OR]: 0.43, $p = 0.0016$).¹⁹ This study also showed that the associated lower mortality was confined to high-risk subgroups defined as those with an ejection fraction (EF) $<50\%$ (OR: 0.34, $p > 0.0001$) and those with multivessel coronary disease (OR: 0.26, $p < 0.001$). In a prospective observational study, OACIS (Osaka Acute Coronary Insufficiency Study), which included 5,628 patients with median follow-up of 1,430 days, the reduction in mortality associated with oral beta-blocker therapy was also seen in high-risk patients (hazard ratio [HR]: 0.60, $p = 0.005$) or those who received diuretic agents (HR: 0.60, $p = 0.016$).²⁰

For low-risk patients with a preserved EF who had STEMI treated with PCI, registry data from Japan including 12,824 patients with an EF $>40\%$ did not show a difference in 3-year mortality associated with oral beta-blocker therapy at hospital discharge.²¹ Similarly, the REACH (Reduction of Atherothrombosis for Continued Health) registry showed that the use of beta-blockers was

not associated with a lower risk of adverse events in stable patients with a previous history of MI.²² In this registry 14,000 patients with known prior MI were enrolled in 2003 and 2004 and followed prospectively for up to four years. The primary outcome was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke. Propensity score matching identified 3599 pairs of patients with and without beta blocker use. Aspirin and statin use (each) was approximately 75%. After a median follow-up of 44 months, there was a trend toward a lower incidence of the primary outcome with beta-blocker therapy (16.9 vs 18.6 percent, respectively; hazard ratio 0.90). However, little difference was seen in the event rates in the beta-blocker and no beta-blocker groups as early as two years.

On the other hand, the results from a high-quality, large registry of 8,510 patients with STEMI treated with primary PCI focusing on outcomes associated with oral beta-blocker therapy are different.²³ The beta-blocker group had a significantly lower incidence of all-cause death (beta-blocker group vs. no-beta-blocker group: 2.1% vs. 3.6%, unadjusted hazard ratio [HR]: 0.52, $p < 0.001$). The incidence of cardiac death was significantly lower in the beta-blocker group than in the no-beta-blocker group (1.1% vs. 2.4%, unadjusted HR: 0.41, $p < 0.001$), whereas both groups had comparable incidences of MI and any coronary revascularization. Although all-cause death or MI occurred less frequently in the beta-blocker group than in the no-beta-blocker group (3.1% vs 4.7%, unadjusted HR: 0.58, $p < 0.001$), there was no significant difference between the 2 groups in the rates of MACE. Interestingly, the association with better outcome of beta-blocker therapy in terms of all-cause death was consistent across various subgroups including patients with relatively low-risk profile such as left ventricular ejection fraction $>40\%$ or single-vessel disease. Limitations of this (and other related observational studies), is the selection bias for the use of beta-blockers and the fact that beta-blocker therapy was defined as having a beta-blocker prescribed at the time of discharge, with little information about whether and how beta-blockers were continued. Thus, so far, most but not all observational data have suggested a benefit, varying with risk, with oral beta-blockers post-AMI.

Recently, a large meta-analysis including 60 clinical trials with 102 003 patients, who were followed up for a mean of 10 months (range: in-hospital to 4 years) of follow-up, was published.²⁴ Patients were stratified into two distinct eras: the reperfusion era, which included 12 trials of 48 806 patients, treated in the modern era of thrombolysis and interventional procedures, and the pre-reperfusion era, which included 48 studies with 31,479 patients. In their analysis, the researchers observed a significant interaction between clinical outcomes and

reperfusion era. In the acute MI trials, a significant interaction (P interaction=0.02) was noted with reperfusion status such that beta-blockers reduced mortality in the *pre-reperfusion era* [Incident Rate Ratio (IRR)=0.86] but not in the reperfusion era (IRR=0.98). In the pre-reperfusion era, beta-blockers were associated with reductions in cardiovascular mortality (IRR=0.87), MI (IRR=0.78), and angina (IRR=0.88), with no difference for sudden death (IRR=0.77), heart failure, cardiogenic shock or stroke (IRR=2.96). In the *reperfusion era*, beta-blockers were associated with reductions in myocardial infarction (IRR=0.72) and angina (IRR=0.80) at the expense of an increase in heart failure (IRR=1.10), cardiogenic shock (IRR=1.29) and drug discontinuation (IRR=1.64), with no impact on cardiovascular mortality (IRR=1.00), sudden death (IRR=0.94) or stroke (IRR=1.09). Results in the post-MI trials were largely similar. Regarding therapy duration, in the pre-reperfusion era, beta-blockers were associated with significant benefit at 30-days (for all-cause mortality, cardiovascular mortality and angina), between 30-days to 1 year (for all-cause mortality, cardiovascular mortality, sudden death and MI) and even for events >1 year (for all-cause mortality and sudden death). However, in the reperfusion era, beta-blockers were associated with no benefit at most time-points except MI and angina at 30-days, a significant increase in heart failure, cardiogenic shock and drug discontinuation at 30-days, and an increase in heart failure and drug discontinuation between 30-days to 1 year. Researchers conclude that in patients undergoing contemporary treatment, data supports use of beta-blockers short-term (30-days) to reduce recurrent MI and angina but this has to be weighed at the expense of increase in heart failure, cardiogenic shock and drug discontinuation with no mortality benefit and so clinical guidelines recommending the use of beta-blockers in post-MI patients need to be "re-considered".

Current Guidelines

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) STEMI guideline gives a class I (Level of Evidence B) recommendation for oral beta-blockers within the first 24 hours in patients with myocardial infarction and a class IIa (Level of evidence B) indication for intravenous beta-blockers, for patients who are hypertensive or having ongoing ischemia. Patients with initial contraindications to the use of beta-blockers in the first 24 hours after STEMI should be reevaluated to determine their subsequent eligibility. Beta-blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use. The long-term duration of routine beta-blocker therapy after uncomplicated MI in

patients without HF or hypertension has not been prospectively addressed. ACCF/AHA secondary prevention guidelines recommend a 3-year treatment course in this patient subset. Possible contra-indications to beta-blocker therapy include: signs of HF, evidence of a low output state, increased risk for cardiogenic shock (patients with age >70 years, systolic BP <120 mm Hg, presenting heart rate >110 bpm, or increased time since onset of symptoms of STEMI), PR interval more than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease.^{25, 26} European Society of Cardiology (ESC) ST-elevation myocardial infarction guidelines include similar recommendations.²⁷

Discussion

Many of the key studies on which the recommendations of beta-blocker therapy are based, were performed in the era prior to routine administration of antiplatelet agents, thrombolysis or primary percutaneous coronary intervention, statins, and renin-angiotensin-aldosterone system (RAAS) blockers. There seemed to be little question that patients with STEMI, regardless of whether or not they have received thrombolysis or undergone PCI, derive substantial benefits from short- and long-term beta-blocker therapy. The practice of prescribing beta-blockers is well accepted and widespread. However, accumulating data have called into question the role of beta-blockers in myocardial infarction. The rationale for beta-blockade, especially in revascularized patients without any significant residual coronary obstructions and uncomplicated hospital course is more or less unclear. Prompt reperfusion and contemporary medical and device therapies reduce the likelihood of extensive scar formation, modify the underlying substrate in patients with a myocardial infarction and reduce the risk of arrhythmic death, possibly lowering the effect of beta-blocker therapy. Conceivably, beta-blockers, due to their negative inotropic effects may reduce myocardial contractility, which in the setting of stunned myocardium during an myocardial infarction, could lead to heart failure and cardiogenic shock.²⁴ On the other hand, data are more conclusive regarding patients who develop extensive scar (patients with delayed presentation and large myocardial infarction), have reduced LV function or multi-vessel disease and therefore are prone to develop heart failure or ventricular arrhythmias. Beta-blockers will remain highly efficacious in preventing events, as has been shown in numerous heart failure trials and in preventing ventricular arrhythmias and sudden death.^{28, 29, 30, 31} Furthermore, most of the evidence supporting the benefit of beta-blockers has been obtained primarily from randomized trials that included predominantly patients with ST-elevation MI

(STEMI). There have been no randomized trials specifically addressing the efficacy of these drugs in non-ST elevation MI (NSTEMI) or unstable angina, however, there is no observational evidence to suggest different outcomes in patients with NSTEMI. Despite the favorable findings of the earlier studies and widespread use, compelling questions remain: whether low-risk patients (with normal ejection fraction and single vessel disease who have undergone successful angioplasty) receive any benefit from either long- or short-term beta-blocker therapy, what is the role of early intravenous or oral, pre-procedural administration of beta blockers, do patients undergoing primary percutaneous intervention benefit from beta blocker therapy, when to start therapy and how long post myocardial infarction should beta-blockade be continued.

Conclusions

Beta-blockers are part of the quadruple therapy suggested by clinical practice guidelines post-MI (beta-blockers, antiplatelet agents, statins, RAAS inhibitors). Beta-blockers act primarily by reducing myocardial oxygen demand, with negative chronotropic and inotropic effects that reduce heart rate, stroke volume, and blood pressure, increase coronary diastolic blood flow and myocardial perfusion, have antiarrhythmic effects showing a relative risk reduction in sudden cardiac death, reduce infarct size and reverse adverse left ventricular remodeling. The overall evidence for the benefits of beta-blocker therapy mainly in reducing morbidity and mortality are considered to be in favour of their use in this setting. Recent data have called into question the role of beta-blockers post-acute MI, demonstrating no mortality benefit, but reduced recurrent myocardial infarction and angina in the short term, at the expense of increased risk of heart failure and cardiogenic shock. Further data from a prospectively designed, randomized trial are needed to resolve this issue.

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