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Authors
Waters, David D
Bangalore, Sripal

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The Evolution of Myocardial Infarction: When the Truths We Hold To Be Self-Evident No Longer Have Evidence

David D. Waters, MD,a and Sripal Bangalore, MD, MHAb

a Division of Cardiology, University of California, San Francisco at Zuckerberg San Francisco General Hospital, San Francisco, CA
b Division of Cardiology, New York University School of Medicine, New York, NY

See article by Bastiany et al., pages 1229–1236 of this issue.

How Myocardial Infarction Used to Be

Myocardial infarction (MI) used to be a deadly and nearly untreatable disease. Half a century ago before the advent of reperfusion therapy, half of patients with MI had heart failure as a complication,1 ventricular fibrillation was so common that prophylactic intravenous lidocaine was widely advocated,2 and nearly one-quarter experienced pericardial friction rub.3 When was the last time you heard a friction rub caused by MI? In-hospital mortality exceeded 25%.4,5

Most MIs then left a large transmural zone of dead myocardium distal to a total occlusion in a major coronary artery. Functionally, this zone was akinetic or dyskinetic and electrophysiologically, it was the source of life-threatening ventricular arrhythmias. Left ventricular (LV) thrombi frequently formed on these akinetic segments, particularly if the location was anterior, and ventricular or septal rupture was a feared early complication.

Since then, treatment has advanced by large and small increments, based on the results of well-designed clinical trials. Improvements in care include the adoption of drugs that improve outcomes—such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, statin drugs, and antiplatelet agents—and the rejection of drugs that are harmful, specifically some antiarrhythmic drugs. Reperfusion therapy was a particularly giant step forward. An open infarct related artery limits myocardial damage and associated complications and improves long-term outcome.

Prophylactic Anticoagulation to Prevent Mural Thrombus and Embolization

But do the results of all the important clinical trials and expert opinions that predate the reperfusion era still apply to the contemporary patient with MI? In this issue of the Canadian Journal of Cardiology, the study by Bastiany et al.6 addresses this question for a specific subpopulation: patients with anterior ST-elevation MI (STEMI) with apical systolic dysfunction6: Should they receive prophylactic anticoagulation to prevent the development of LV thrombus and systemic embolization? Both the American College of Cardiology/American Heart Association and the European Society of Cardiology guidelines give a weak class IIb (level of evidence C) recommendation for anticoagulation in such patients.7,8

As summarized by Bastiany et al.,6 the studies that address this issue are few and inconclusive. In the pre-thrombolytic era when LV thrombus was a common consequence of large anterior STEMI, 2 of 6 small studies (including small randomized trials) showed a benefit of anticoagulation. In the modern era, among patients undergoing primary percutaneous intervention and receiving dual-antiplatelet therapy (DAPT), anticoagulation with a vitamin K antagonist appears to be more harmful than beneficial, although the evidence is weak. Anticoagulation does appear to reduce the risk of systemic embolization among patients with a documented thrombus, but such patients are far less common than they used to be. The combination of a changing underlying substrate of MI because of reperfusion and changing medical therapy, particularly DAPT, likely explain the differences between studies in the pre-reperfusion and modern eras.

The realization that the characteristics of most MIs have changed along with concomitant therapy from the era when many post-MI trials were executed, should lead us to reconsider whether or not the results of these trials still apply. More recent clinical trials have shown that in patients taking oral anticoagulants plus DAPT, the risk of bleeding at 1 year is as high as 44%.9 The lower prevalence of LV thrombus combined with this increased bleeding risk has shifted the balance against triple therapy so that it now causes more harm (bleeding) than benefit (prevention of emboli).

The benefit-to-risk ratio of therapies depends on the underlying risk of the cohort. Therapies that proved
beneficial decades ago may prove to be less effective or even harmful in contemporary practice as other treatment improves and risk decreases. Such shifts force us to continue to evaluate the value of our therapies, as illustrated in the following section.

**β-Blockers After Myocardial Infarction**

Should we continue to treat all patients after MI with β-blockers? Clinical trials done before the advent of reperfusion therapy clearly demonstrate that β-blockers reduced mortality, reinfarction, and angina in MI survivors. It was recognized even in that era that the benefits of β-blockers were largely restricted to sicker patients. In a post hoc analysis of the Beta Blocker Heart Attack Trial (BHAT), patients who had experienced either electrical or mechanical complications, or both, with their MI had large reductions in mortality during the 25-month follow-up period, whereas 95% of patients without these complications had only a small reduction in mortality (adjusted hazard ratio, 0.96).

In a meta-analysis reported by 1 of us, 60 randomized trials of β-blockers with 102,003 patients who had experienced MI were included. Trials were categorized into the reperfusion era (defined as > 50% of patients undergoing coronary reperfusion or receiving aspirin and a statin drug) or pre-reperfusion era trials. In trials of acute MI, a significant interaction ($P = 0.02$) was noted such that β-blockers reduced mortality in the pre-reperfusion era (incident rate ratio [IRR] 0.86; 95% confidence interval [CI], 0.79-0.94) but not in the reperfusion era (IRR, 0.98; 95% CI, 0.92-1.05), as illustrated in Figure 1.

In the pre-reperfusion era, β-blockers reduced 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), with no difference for other outcomes. In the reperfusion era, β-blockers also reduced MI (IRR, 0.72; 95% CI, 0.62-0.83) and angina (IRR, 0.80; 95% CI, 0.65-0.98) but at the expense of an increase in heart failure (IRR, 1.10; 95% CI, 1.05-1.16), cardiogenic shock (IRR, 1.29; 95% CI, 1.18-1.41), and drug discontinuation (IRR, 1.64; 95% CI, 1.55-1.73), with no benefit for other outcomes. Benefits for recurrent MI and angina in the reperfusion era appeared to be limited to the first 30 days.

One explanation for the failure of β-blockers to reduce mortality in the reperfusion era is that the substrate has changed—most patients with MI no longer are left with an occluded artery and a large infarct area that facilitates electrical and mechanical complications. Mortality after MI in the era before reperfusion was driven mainly by sudden cardiac death, a complication that β-blockers prevent. With sudden cardiac death being less of a problem, β-blockers are less of a solution.

Another possibility is that β-blockers provide no added reduction in mortality in addition to other guideline-mandated treatments—specifically, aspirin and other antiplatelet therapy, ACE inhibitors, and statin drugs. In the First International Study of Infarct Survival trial (ISIS-1), only 5% of patients received an antiplatelet agent at discharge, and no one was treated with reperfusion, yet atenolol significantly reduced vascular death when compared with controls. Conversely, in the Clopidogrel and Metoprolol in

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<td>Reperfusion Era</td>
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**Figure 1.** Differential effect of β-blockers on mortality in patients who have experienced myocardial infarction in the pre-reperfusion and reperfusion eras. BB, β-blockers; IRR, incident rate ratio. Data from Bangalore et al. [12]

**Myocardial Infarction Trial (COMMIT), all patients received aspirin, 50% received DAPT, two-thirds got an ACE inhibitor, and 54% received fibrinolytic agents.** Metoprolol was not superior to placebo for both of the coprimary end points: 30-day mortality and 30-day death/MI or cardiac arrest, despite almost 3 times the sample size and greater statistical power than ISIS-1.

**Adverse Metabolic Effects of β-Blockers**

β-Blockers increase the incidence of new-onset diabetes (NOD) to a greater degree than statins do. In a meta-analysis of 12 studies involving 94,492 patients, β-blocker use was associated with a 22% increase in NOD (relative risk, 1.22; 95% CI, 1.12-1.33) compared with nondiuretic antihypertensive agents. The risk of NOD increased exponentially with duration of treatment. This is different from the pattern with thiazide diuretics, in which NOD occurs mainly in the first year, or with statin drugs, in which the increased risk of NOD appears to be constant over time.

β-Blockers increase the risk of NOD both by inhibiting insulin secretion and by inducing insulin resistance. The risk of NOD with β-blockers is mitigated by the concomitant use of an ACE inhibitor. In patients with established diabetes, older β-blockers worsen glucose control, but newer β1-selective blockers appear to have little or no effect, at least in short-term studies.

In the pre-reperfusion era, when recurrent events after MI could be attributed to large myocardial scars, continued smoking, and untreated cholesterol levels, the long-term metabolic consequences of β-blockers were less worrisome. Also, fewer patients survived long-term. Contemporary patients who have experienced MI are more likely to have pre-diabetes and obesity and are less likely to smoke and have untreated lipid levels. Under these conditions, and with improved long-term survival, the metabolic consequences of β-blockers are more troublesome.

**When Should We Prescribe β-Blockers After MI?**

Many patients with MI today still resemble patients with MI from the pre-reperfusion era, with an occluded culprit coronary artery and large infarct zone. They should be treated with a β-blocker with the expectation that they will benefit similarly to patients who have experienced MI in the older β-blocker post-MI trials. Patients with heart failure experience fewer hospitalizations and better survival with a β-blocker. These agents also still have a role, although diminished, in the
treatment of angina and are appropriate for patients with this condition after MI.

Most MIs now occur in low- and middle-income countries, where the incidence is rising. Patients in these countries are less likely to receive timely reperfusion therapy compared with patients in high-income countries and are more likely to leave the hospital with the substrate in which \( \beta \)-blockers are helpful. This segment of the worldwide MI population is likely to grow as unchecked risk factors proliferate in low- and middle-income countries.

With these important exceptions, the evidence does not appear to support the use of \( \beta \)-blockers in modern patients who have experienced MI—those who have had their culprit artery stented and have only minor residual myocardial damage. DAPT, ACE inhibitors, and statin drugs are indicated, based on the results of clinical trials that enrolled patients such as these. Consideration could be given to offering a \( \beta \)-blocker for 1 month to reduce repeated infarction and angina, but the trade-off would be a slightly increased risk of heart failure.

Guidelines

Guidelines recommend that \( \beta \)-blockers be given routinely to patients after MI \(^{1,2,6,7,17}\) and health care organizations have adopted \( \beta \)-blocker use at discharge after an MI as a quality indicator. \(^{10}\) As guidelines have proliferated and expanded, attempts have been made to make them entirely evidence-based, with well-conducted clinical trials being the best form of evidence. \(^{18}\) Do guideline committees have the scope to conclude that perhaps as a disease has evolved, the relevant clinical trials may not be relevant any more, at least for most patients?

Some of “these truths that we hold to be self-evident” may no longer be true at all. The evidence has shifted. The cardiologist who considers ignoring a guideline might take solace from other words from Thomas Jefferson:

> I hold it, that a little rebellion, now and then, is a good thing, and as necessary in the political world as storms in the physical.

—Thomas Jefferson

Disclosures

The authors have no conflicts of interest to disclose.

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