Intravenous β-Blockers in Primary Percutaneous Coronary Intervention

New Hope for an Old Therapy

Gjin Ndrepepa, MD; Adnan Kastrati, MD

Primary percutaneous coronary intervention (PCI) is the preferred strategy of reperfusion for patients with ST-segment-elevation myocardial infarction (STEMI). With contemporary PCI techniques and adjunctive pharmacological therapy, primary PCI restores optimal epicardial flow in as many as 95% of patients with STEMI. However despite remarkable improvement in the outcomes of patients with STEMI, mortality and morbidity remain significant. To further improve the efficacy of reperfusion, considerable efforts are being made on 2 fronts: the development of systems to provide timely access to PCI for patients with STEMI to reduce time to reperfusion and the investigation of therapies to minimize reperfusion injury (ie, to render myocardial cells more resistant to the detrimental effects of the ischemia/reperfusion cycle). The restoration of blood flow to the ischemic myocardium is associated with reperfusion injury manifested as myocardial stunning, no reflow, arrhythmias, and myocardial hemorrhage. Experimental studies in animals suggest that reperfusion injury may account for up to 50% of the final infarct size. Despite decades of research, an understanding of reperfusion injury remains elusive, and remarkably little success has been achieved with translational research in cardioprotective therapeutics.

Article see p 1495

β-Blockers have long been a component of care in patients with acute myocardial infarction because of their ability to reduce myocardial oxygen consumption by reducing heart rate and myocardial contractility. Preclinical studies showed reduced infarct size in dogs, particularly when the β-blockers are administered before coronary artery ligation. Several clinical studies performed in the prereperfusion era have demonstrated beneficial effects of β-blockers in acute myocardial infarction in terms of reduction of infarct size or improved survival. Conversely, in the thrombolytic era, randomized studies involving early intravenous administration of β-blockers were largely disappointing, with no improvement in left ventricular function, infarct size, or mortality. Moreover, the large-scale Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) showed not only no favorable effect of β-blockade on death resulting from any cause or the composite of death, reinfarction, or cardiac arrest but also a significant increase in the incidence of cardiogenic shock. This further dampened enthusiasm for the early use of β-blockers in patients with acute myocardial infarction, at least in the setting of thrombolysis.

In patients with STEMI undergoing primary PCI, several observational studies or post hoc analyses showed that preemptive β-blockade was associated with significant improvement in clinical outcome, including reduced short-term mortality. However, studies that have investigated the impact of β-blockade before primary PCI on the enzymatic infarct size have produced conflicting results. A recent study that included 96 patients with STEMI who were randomized to landiolol (an ultra–short-acting, β₁-receptor–selective blocker with a half-life of 4 minutes initiated immediately after PCI and continued for 24 hours) or a control group showed that landiolol improved left ventricular function over a 6-month period but did not affect cardiovascular events either in the acute phase or during the 6-month follow-up. However to date, no randomized studies have investigated the impact of intravenous β-blockers before primary PCI on clinical outcome in patients with STEMI. Overall use of β-blockers in the acute setting in patients with STEMI may be summarized as predominantly beneficial in the prereperfusion era, controversial in the thrombotic era, and poorly investigated in the primary PCI era. Guideline-writing authorities are somewhat cautious in recommending β-blocker use, assigning a Class Ia indication for intravenous β-blockers in STEMI but only in patients who are hypertensive or show signs of ongoing ischemia.

In this issue of Circulation, the report by Ibanez and colleagues on the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) study seems to fill, at least in part, the existing gap in the clinical investigation of intravenous β-blockade administered before primary PCI in patients with STEMI. The METOCARD-CNIC trial was a randomized, multicenter, assessor-blinded study that investigated whether early prereperfusion intravenous β-blocker therapy (up to three 5-mg intravenous boluses of metoprolol tartrate 2 minutes apart) reduces infarct size in 270 patients with STEMI of the anterior wall presenting within 6 hours from symptom onset. The primary end point was infarct size estimated by magnetic resonance imaging; other efficacy end points included extent of myocardial salvage and peak area under the curve of creatine...
kinase release (72 hours). Patients with Killip class III or greater, lower blood pressure (<120 mmHg), atrioventricular conduction block (prolonged PR interval >240 milliseconds or second- or third-degree atrioventricular block), persistent bradycardia (<60 bpm), or active treatment with β-blocking agents were excluded. The safety end point was a composite of death, malignant ventricular arrhythmias, advanced atrioventricular block, cardiogenic shock, and reinfarction within the first 24 hours after STEMI.

In brief, infarct size calculated either in grams of infarcted tissue (25.6±15.3 versus 32.0±22.2 g; \( P=0.013 \)) or as a percentage of the left ventricle (21.2±11.5% versus 25.1±13.9% of the left ventricle; \( P=0.029 \)) was significantly reduced by metoprolol. Of note, 34.9% of the initial myocardial area at risk was salvaged in the metoprolol group compared with 27.7% in the control group (\( P=0.028 \)). The left ventricular ejection fraction was slightly but significantly higher in the metoprolol group. There was no difference in the safety end point between groups (\( P=0.21 \)). The authors concluded that in patients with anterior wall STEMI, intravenous metoprolol before PCI reduced infarct size and improved left ventricular function with no excess of adverse events within the first 24 hours after STEMI.

Primary PCI with routine use of modern antithrombotic drugs is a highly effective reperfusion strategy, and thus far, it has been difficult to demonstrate further significant improvement in myocardial salvage capacity with adjunctive interventions. Adjunctive treatments that showed promise in the pre–primary PCI era produced disappointing results when used in the setting of primary PCI, for example, glucose-insulin-potassium infusion and adenosine therapy. Although the reasons for the failure of such strategies to show measurable clinical benefit in the setting of primary PCI remain unknown, the powerful salvaging capacity of primary PCI overwhelms the small benefits of cardioprotective strategies, which may otherwise have shown benefit in other circumstances.

In the METOCARD-CNIC trial, β-blockade with intravenous metoprolol reduced the infarct size by ≈20%. In this regard, a pharmacoprotective strategy able to reduce infarct size by 20% when used in conjunction with primary PCI nurtures great hope in clinical benefit. Moreover, an infarct reduction effect by β-blockade at the time of reperfusion is theoretically plausible. The heightened sympathetic tone and the surge in the circulating catecholamine levels in patients with STEMI—resulting in tachycardia, elevated blood pressure, and increased myocardial oxygen demand—may exacerbate myocardial damage. β-Blockers reduce myocardial oxygen demand, inhibit platelet aggregation and thromboxane synthesis, cause blood flow redistribution to ischemic subendocardial regions, and preserve mitochondrial structure. The net effect is to slow necrosis progression at the peri-infarct border. Moreover, β-blockers may have a direct protective effect against reperfusion injury, scavenging free radicals by binding to hydrophobic sites in the cellular membranes and exerting an antioxidant effect.

The METOCARD-CNIC trial is the first randomized study to test the efficacy of intravenous β-blockade before primary PCI; therefore, its results are important and stimulating. In addition, magnetic resonance imaging provides a reliable assessment of infarct size. However, although the trial is methodologically sound and well conducted, some concerns remain. The lack of placebo control is one of them, although it should be acknowledged that complete protection against ascertainment bias would in any case be difficult because of the measurable effect of β-blockade on heart rate and blood pressure. Moreover, consistent with recommendations to avoid the use of β-blockers in patients with STEMI and hemodynamic instability, patients with a Killip class III or greater were excluded. Consequently, patients with large infarctions who potentially are mostly in need of protection at the time of reperfusion were excluded. In a similar vein, the exclusion of patients with inferior infarction means that the true impact of β-blockade on bradyarrhythmias remains unexplored. In addition, there was a trend toward a larger initial area at risk in patients in the control group. This may have overestimated the difference in infarct size reduction in favor of metoprolol. Finally, the apparently discrepant results in patients with pre-PCI Thrombolysis in Myocardial Infarction grade 0 to 1 flow (significant reduction of infarct size by metoprolol) and in those with grade 2 to 3 flow (infarct size not reduced by metoprolol) are not readily explainable. On one hand, in the absence of blood flow, the cardioprotective agent may not reach the infarcted territory to exert its beneficial effects. On the other hand, spontaneous reperfusion (in patients with Thrombolysis in Myocardial Infarction grade 2–3 flow) may have promoted myocardial salvage in advance with fewer ischemic cells left to be salvaged compared with patients in whom coronary occlusion persists until the time of reperfusion by PCI. A more complete analysis including initial areas at risk in both subgroups might be helpful.

Overall, on the basis of studies that have investigated the association between infarct size reduction and mortality, the benefit achieved in the METOCARD-CNIC trial is expected to be clinically relevant. However, although infarct size is an important predictor of outcome, it is still a surrogate and cannot substitute for hard clinical end points such as mortality. Thus, although important and encouraging, the results of the METOCARD-CNIC trial are probably not strong enough to warrant a change in the clinical practice of the use of β-blockade in patients with STEMI. Instead, these data provide a solid basis for further investigation of intravenous β-blockers and should stimulate the performance of dedicated randomized trials powered for hard clinical end points so that we may more fully know the role of an old therapy in the contemporary era of reperfusion with primary PCI.

Disclosures

None.

References


---

**Key Words:** Editiorials ■ adrenergic beta-antagonists ■ magnetic resonance imaging ■ myocardial infarction
Intravenous β-Blockers in Primary Percutaneous Coronary Intervention: New Hope for an Old Therapy
Gjin Ndrepepa and Adnan Kastrati

Circulation. 2013;128:1487-1489; originally published online September 3, 2013; doi: 10.1161/CIRCULATIONAHA.113.005500

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/14/1487

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/