

## Cardiology 2018 : Early Intravenous Beta-blockers for Acute Myocardial Infarction - Shu Hong Guo- Zhuzhou Central Hospital

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### Review

Beta-blockers are heralded as a major advance in the treatment of patients with myocardial infarction (MI). Patients without contraindications are recommended to receive intravenous administration of beta-blockers at the time of presentation for relief of ischemic pain; for the control of hypertension, sinus tachycardia and sustained ventricular tachycardia; and for the primary prevention of sudden cardiac death (Class I, Level of Evidence B). Recent data have called into question the role of beta-blockers in MI. Recommendations on the intravenous administration of beta-blockers by current guidelines are more prudent in these cases (Class IIa, Level of Evidence B). The use of early  $\beta$ -blocker therapy for patients with AMI in China is suboptimal, with underuse in patients who could benefit and substantial use among those who might be harmed. The present article is a review on the efficacy and safeties of the early administration of intravenous beta-blockers examined in trials conducted in the pre-reperfusion era and reperfusion era, and provide an evaluation procedure to guide clinicians applying IV beta-blockers to clinical practice

### Cardiogenic Shock

Information on cardiogenic shock was not collected systematically in most of the trials in the pre-reperfusion era, which included a small number of fairly low-risk patients. In the MIAMI trial, intravenous metoprolol did not increase cardiogenic shock (3.0% vs. 3.2%,  $P>0.20$ ) as compared to placebo. No information on cardiogenic shock were recorded in the ISIS-1 trial, which only revealed that atenolol use increased the extent of inotropic drug use (5.0% vs 3.4%,  $p$ ) allocated to metoprolol group, especially on days 0 and 19. In a Swedish nationwide observational study, the use of intravenous beta-blockers in STEMI patients without cardiogenic shock and cardiac arrest at presentation treated with primary PCI was associated

with higher short-term mortality, lower LVEF at discharge, as well as a higher risk of in-hospital cardiogenic shock. While recent meta-analysis concluded that early use of intravenous beta-blockers in STEMI patients presenting in Killip Class 1 or 2 was not associated with increase in the risk of cardiogenic shock in the current reperfusion era.

Which Type of Patients Might Really Overall early intravenous beta-blockers followed by high-dose oral therapy reduced recurrent ischaemia and ventricular arrhythmia at the expense of increased cardiogenic shock and the extent of inotropic drug use. As such, it has great significance for reliable identification of subgroups of patients among whom treatment is really advantageous. Of the total vascular deaths within 14 days in the ISIS-1 trial, 43.6% occurred in the first two days. Most of the improvement in vascular mortality was seen during days 0 and 1, inferring that early intravenous beta-blockers therapy might mainly benefit higher mortality risk patients. In the MIAMI study, a retrospective subgroup analysis indicated that all the observed reduction in mortality was among the intravenous metoprolol treated patients defined as being at higher mortality risk. A completely opposite conclusion drawn from the TIMI II-B trial indicated that immediate metoprolol therapy was beneficial only in patients in the low risk subgroup but did harm to patients in the not-low-risk subgroup. An explanation for this controversy is that the pre- and in-hospital management has changed a lot since the pre-reperfusion era. Patients received timely revascularization and optimal drug therapy nowadays, which reduces the likelihood of extensive scar formation, a vital substrate for re-entrant circuits and fatal ventricular arrhythmias, which might neutralize the good impact of beta-blockers. In COMMIT trial, there was a tendency towards net benefit in those at lower risk of developing

cardiogenic shock. Patients presenting lower systolic blood pressure ( $\leq 120$  mmHg), higher heart rate ( $\geq 90$  bpm), worse Killip class ( $\geq$  III); and patients receiving no fibrinolytic agent and/or having long delay time to reperfusion were at high risk of developing cardiogenic shock, especially in the elderly  $\geq 70$  years old.

**How to Identify Eligible Patients?** In the pre-reperfusion era, Hands et al. reported that cardiogenic shock developed in 7.1% of 845 patients admitted with AMI. In half of these patients, cardiogenic shock developed at least 24 h after hospital admission. Independent predictors of the occurrence of cardiogenic shock were age ( $>65$  years), LVEF on hospital admission (large infarct as estimated from serial enzyme determinations, history of diabetes mellitus and prior MI. Patients with three, four, or five of these risk factors had a 17.9%, 33.7%, or 54.4% probability, respectively, of developing cardiogenic shock after hospital admission. In this study, parameters from the physical examination were not included in the analysis. In the reperfusion era, a scoring system algorithm was developed to predict the occurrence of cardiogenic shock among 41,021 patients with AMI receiving thrombolytic therapy in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-I (GUSTO-I) trial and validated in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-III) cohort. In this algorithm, age, heart rate, systolic blood pressure, diastolic blood pressure, weight, MI location, Killip Class and miscellaneous risk factors such as female, hypertension and prior MI were all predictors for the development of cardiogenic shock after thrombolytic therapy. Among these predictors, age, systolic blood pressure, heart rate and Killip class were the four major predictive variables which accounted for greater than 85% of the predictive information. In the GUSTO-I trial, the median time from enrollment to cardiogenic shock was 11.6 h, 39.6% cardiogenic shock occurring within 6 hours, and 63.2% within 24 h [17]. Physical examination such as altered sensorium, oliguria and cold clammy skin were also of great significance in recognizing cardiogenic shock. Rahimi et al. reported that 2.6% of 588 patients admitted with NonST-Elevation Myocardial Infarction (NSTEMI) developed

ventricular arrhythmias. In addition, more than two-thirds of arrhythmias occurred within the first 12 h after onset of symptoms. Moreover, the only factor associated with the occurrence of malignant ventricular arrhythmia was higher white blood cell count on admission. A similar study of 510 patients who underwent PCI for STEMI indicated that 60% of sustained ventricular arrhythmia occurred during the first 24 h, and 92% during the first 48 h. Independent predictors of sustained ventricular arrhythmia included higher white blood cell count, lower hematocrit and lack of beta-blocker medication. Overall, the occurrence of ventricular arrhythmias after AMI was not easy to predict. An electrocardiographic monitoring period of 48 h may be helpful in timely detection of ventricular arrhythmia based on the arrhythmia onset time window. Electrocardiogram information such as fragmented QRS wave, QT interval prolongation, QT dispersion, T-wave alternans (TWA) and late potentials (LP), reduced heart rate variability (HRV) and R-on-T phenomenon were demonstrated some value for predicting ventricular arrhythmia in patients with AMI. Also of great assistance in predicting ventricular arrhythmia were predictors such as left ventricular ejection fraction and leukocytosis. There was however, no such scoring system algorithm as predicting cardiogenic shock.

Taking the efficacy and the safety into account, it may be reasonable to intravenously administer beta-blockers in those patients at low risk of developing cardiogenic shock for its beneficial effect on reducing life-threatening arrhythmia and relieving recurrent ischemia. For patients at higher risk of developing cardiogenic shock, early intravenous beta-blockers may be potentially harmful. In such a case early emergency revascularization of occluded coronaries should be the primary treatment of choice

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