

Future Directions in the Treatment of Acute Myocardial Infarction

Where does the future of heart attack treatment lie? One of the trail blazers in evidenced-based cardiology, Dr. Frans Van de Werf of the University Hospital Gasthuisberg in Leuven, Belgium, led a distinguished panel of experts to discuss the future of acute myocardial infarction treatment. Although much progress has been made in reducing early mortality from heart attacks (from 13% 30-day mortality in 1986 to 4% today), much work remains to be done. One sobering statistic is the out-of-hospital death rate. "It is important to know that out-of-hospital death rates remain high and have not changed significantly between 1990 and 2001", noted Dr. Van de Werf. He predicts that reperfusion and tissue regeneration will be at the core of future research.

Timing is Everything

Minimizing delays in heart attack treatment leads to less damage to heart tissue. Current AHA/ACC guidelines recommend that patients receive fibrinolytic therapy within 30 minutes of arriving at the hospital or percutaneous coronary intervention (PCI) within 90 minutes of arriving at the hospital. In reality, less than 50% of patients are treated within these guidelines.

Alice K. Jacobs, MD, of Boston Medical Center discussed the challenges faced in getting heart attack patients the appropriate interventions in time. In a meta-analysis of 23 trials of acute ST-elevation myocardial infarction treatment, Keely et al reported that PCI was superior to fibrinolysis in short-term clinical outcomes of death, non-fatal reinfarction, and stroke ($p < 0.0001$; Keeley et al. *Lancet* 2003; 361:13-20). This finding was still true even if patients were transferred to receive PCI. Recent re-analysis of door-to-needle and door-to-balloon time effect on mortality in the NRM1 registry, reported by Pinto and colleagues, would argue that with increased delays superiority of PCI to fibrinolysis greatly depends on patient characteristics such as age and location of MI (Pinto et al. *Circulation* 2006; 114:2019-25).

It does become imperative that patients receive timely PCI, even if a transfer to another facility is required. However, timely reperfusion is limited by several factors:

- Patients often do not recognize symptoms and call for medical assistance.
- Patient transportation can take a long time, especially in rural areas. Emergency medical service (EMS) personnel may also be required to take all patients to the nearest hospital, which may not have the necessary expertise.
- Once a patient arrives at the hospital, additional time may be lost as the medical team determines the treatment approach. In off-hours, additional time is needed to assemble a PCI team.

Some cities are addressing this issue by using what is called a bypass protocol. In this situation, emergency service vehicles have the capability to do ECGs on board. If needed, they bypass the closest hospital and instead take the patient to the nearest PCI center. For example, in the Boston Massachusetts EMA bypass protocol, technicians have 12-lead ECG capability in the field. If a patient having a heart attack has >2 mm ST elevation in 2 continuous leads, the EMS personnel take the patient to the nearest PCI facility. The plan is constructed such that the receiving hospital is never on diversion, which further shortens treatment time.

Of course there are many hurdles in implementing such a protocol:

- Many patients do not use EMS (<50% in the United States)
- The majority of EMS vehicles currently in service do not have ECG capability
- Geographic locations of hospitals may make transfers difficult and time consuming
- Many major hospital emergency rooms are so busy that they are on diversion
- Institutions may not want patients transferred as it could lower their reimbursements

The American Heart Association is becoming an advocate to facilitate gap reduction between the guidelines and the current state of treatment. It is hoped that these efforts will result in more patients receiving timely reperfusion therapy.

Stem Cells Show Promise in Cardiac Repair

Stem cells, one of the most promising and controversial areas of contemporary medical research, are being explored as potential therapies in cardiac repair. Andreas Zeiher, MD, of Johann Wolfgang Goethe University in Frankfurt, Germany gave an overview of the results

from the REPAIR-AMI trial. This was a multi-center, randomized, placebo-controlled trial comparing progenitor cells derived from bone marrow (BMC) to placebo. Patients with acute ST-elevation myocardial infarction (STEMI) that had obtained successful reperfusion underwent bone marrow aspiration under local anesthesia 3-7 days post-MI. They were then randomized and received an intracoronary infusion of BMC (n=103) or placebo medium (n=101) into the artery where the infarct occurred. Left ventricular angiography was performed shortly after the infusion and again 4 months later.

After 4 months, the BMC group had significant improvement in left ventricular ejection fraction (LVEF) when compared to the placebo group (mean 5.5% improvement vs. 3.0%, respectively; p=0.01). At 12 months, the data indicated that the BMC group had a reduction in death, another heart attack, or revascularization procedures (p=0.01), the difference was predominantly driven by recurrent MI risk and non-target vessel revascularization. Dr. Zeiher speculated that the success of this investigation may have been related to infusion timing. It's possible that by delaying the infusion to a few days after reperfusion that the cells were introduced to a more hospitable environment or that the bone marrow progenitor cells were somehow different. Although the exact mechanism of action is unknown, these promising data warrant additional, larger investigations. A similar trial in acute MI conducted by Lunde et al (2006) failed to demonstrate any benefit with respect to increase in ejection fraction. This work was recently published in the *New England Journal of Medicine* (Schächinger et al. *NEJM* 2006; 355:1210-1221).

In summary, the future of acute myocardial infarction treatment lies in removing barriers to timely treatment as well as further exploration of novel ways to restore heart function.