

Inexpensive drug costing less than three dollars may minimize damage from heart attack

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This shows METOCARD-CNIC Trial study investigators with Valentin Fuster, M.D., Ph.D., Director of Mount Sinai Heart at the Mount Sinai Medical Center and General Director of CNIC in Spain. Credit: CNIC

Early treatment of heart attack patients with an inexpensive beta-blocker drug called metoprolol, while in transit to the hospital, can significantly reduce damage to the heart during a myocardial infarction, according to clinical trial study results published Oct. 1 in the journal *Circulation*. The study was a collaboration between Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) in Spain and Icahn School of Medicine at Mount Sinai in New York.

The study, involving emergency ambulances and seven hospitals across Spain, shows this simple, low-cost intervention strategy with metoprolol could be easily extended throughout the world, to provide significant clinical benefit and could change current treatment practice for heart attack

patients. Currently, patients receive no medication before undergoing routine angioplasty, the standard treatment for removing a heart blockage that causes a heart attack and damages heart tissue.

Borja Ibáñez, MD, PhD, head of the Experimental Cardiology Group at CNIC and clinical cardiologist at the Hospital Clínico San Carlos in Spain, is the joint lead investigator of this novel study with Valentín Fuster, MD, PhD, General Director of CNIC, who also serves as Director of Mount Sinai Heart and Physician-in-Chief at The Mount Sinai Medical Center. Also, Dr. Fuster will begin his term in 2014 as the next Editor-in-Chief of the *Journal of the American College of Cardiology* (JACC).

Metoprolol, a drug of the beta-blocker family, has been available for more than 30 years to treat arterial hypertension and other cardiovascular conditions. In this new study, the team of researchers were able to examine the potential usefulness of metoprolol after a heart attack. The clinical trial named METOCARD-CNIC is the first to test metoprolol therapy, at a cost less than three dollars (or less than two euros), in heart attack patients undergoing standard angioplasty treatment procedures.

According to researchers, the potential savings from this medical therapy intervention may go far beyond the low cost of metoprolol itself, since patients experiencing less-extensively damaged heart muscle are less likely to need more costly treatments such as an implantable defibrillator or to require costly hospitalization for treatment of heart failure. Dr. Ibáñez explains, "the savings in healthcare costs will run into millions; a per-patient outlay of less than two euros (or less than three dollars) will over the years save thousands." Currently, researchers are now carrying out a cost-effectiveness analysis to give a firm estimate of the

expected savings.

An acute myocardial infarction, or heart attack, is caused by a sudden obstruction of one of the coronary arteries. A blockage requires immediate medical attention and the response time is critical. With every minute that the artery is blocked, the cells of the heart die becoming necrotic, in exponentially growing numbers. According to researchers, the best strategy for limiting the size of an infarct is to carry out the angioplasty procedure as soon as possible. A delay in reopening the coronary artery could mean a larger region of damaged or necrotic tissue. When necrosis is extensive, the heart loses a large part of its pumping strength, which does not recover.

In addition to the high risk of death during the infarction, survivors are likely to suffer from heart failure and severe arrhythmias, and often may die in the months or years following the attack. "The larger the infarct (death of cardiac muscle), the greater the probability that survivors will suffer these complications in the future," says co-lead investigator Dr. Fuster, who also serves as Director of the Zena and Michael A. Wiener Cardiovascular Institute and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health at The Mount Sinai Medical Center.

Therefore, Dr. Fuster stresses reducing the amount of tissue that is damaged or dies during an infarction is of the utmost importance. Over the last several decades investigators have searched unsuccessfully for a complementary therapy that would further reduce the extent of heart damage.

A total of 270 patients with infarction were recruited since 2010 in four of Spain's regions including: Madrid, Galicia, León, and Cantabria. In the randomized study, patients were assigned to receive either intravenous metoprolol or a placebo treatment at the moment of diagnosis of a myocardial infarction during ambulance transit to the catheterization laboratory. Hospitals in Spain participating in the METOCARD-CNIC trial included: Hospital Clínico San Carlos, Hospital de La Princesa, Hospital 12 de Octubre, Hospital Puerta de Hierro, and Hospital Quirón (Madrid), Hospital Meixoeiro (Galicia), Hospital de León

(León), and Hospital Marqués de Valdecilla (Cantabria).

The efficacy of the medical intervention was evaluated by magnetic resonance imaging (MRI) a week after the infarction. MRI measured the mass of damaged heart tissue in all patients. The results showed patients who received metoprolol had much smaller infarcts than those who received the control treatment, and that this smaller infarct size was linked to greater heart contractility.

"MRI is a unique tool for studying heart tissue that enables us to explore in exquisite detail heart function, necrosis, the state of the microcirculation, and many other parameters that are critical in determining the post-infarction status of the myocardium," says Dr. Fuster.

The MRI scans were analyzed at the central CNIC laboratory by cardiologists blinded to the treatment. The CNIC team of cardiologists are experts in this analysis, and most of them received their training from Dr. Fuster at The Mount Sinai Medical Center in New York through a bilateral training agreement with the CNIC.

Initial research investigations about the potential benefits of metoprolol were first launched at The Mount Sinai Medical Center in 2006 while Dr. Ibáñez was working there with Dr. Fuster and Mount Sinai's Juan Badimon, PhD, Director of the Atherothrombosis Research Unit at its Cardiovascular Institute. Their preclinical research findings about metoprolol in animal models, analyzed using MRI and published in the journal *Circulation* in 2007, showed early administration of metoprolol during heart attack increased myocardial salvage and led to the translational medicine potential for human clinical trial.

The research team is currently investigating the molecular mechanism underlying the therapeutic action of metoprolol. Antonio Fernández-Ortiz, MD, PhD, co-investigator on the METOCARD-CNIC study and leader of this sub-study, explains that "this project analyzes the effect of metoprolol on the interaction of blood platelets with inflammatory cells, which might explain the benefit of early treatment with this drug as soon as possible after

diagnosis of a heart attack."

Researchers are planning to extend the clinical trial to a much larger number of patients in a multinational study, to demonstrate not only a reduced infarct size, but also a reduced mortality in patients who receive early metoprolol during transit to hospital. The CNIC research team, colleagues in the emergency services, and hospitals are already working on the logistics of a new international clinical trial.

In an editorial accompanying the published article in *Circulation*, experts from the Technische Universität and the Munich Heart Alliance, Gjin Ndrepepa and Adnan Kastrati, affirmed that, if confirmed by a subsequent analysis of large numbers of patients, the results of METOCARD-CNIC trial are likely to lead to a change in clinical practice: "In this regard, a pharmaco-protective strategy able to reduce infarct size by 20 percent when used in conjunction with primary PCI nurtures great hope in clinical benefit."

In addition, Dr. Ibáñez adds: "the professionals of the emergency ambulance services were the driving force of this study. Their hard work is a professional and human example to us all; we are deeply humbled by the readiness of so many professionals to commit themselves 24 hours a day, 365 days a year to an altruistic project."

Provided by The Mount Sinai Hospital

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