Relationship between Therapeutic Effects on Infarct Size in Acute Myocardial Infarction and Therapeutic Effects on One-Year Outcomes: A Patient-Level Analysis of Randomized Clinical Trials

Harry P. Selker, James E. Udelson, Robin Ruthazer, Ralph B. D’Agostino, Melissa Nicholas, Ori Ben-Yehuda, Ingo Elliott, Christopher B. Granger, Paul Jenkins, Akiko Maehara, Manesh R. Patel, E. Magnus Ohman, Holger Thiele, Gregg W. Stone

From the Institute for Clinical Research and Health Policy Studies and the Division of Cardiology, Tufts Medical Center, Boston, MA; (1) Boston University (2), University Heart Center Lübeck, and the German Center for Cardiovascular Research (DZHK), Lübeck, Germany (4) Duke University Medical Center, Durham, NC; (5) Columbia University Medical Center, New York Presbyterian Hospital and the Cardiovascular Research Foundation, New York, NY (3)

ABSTRACT

Background: Studies of acute myocardial infarction (AMI) have shown that measured infarct size is related to long-term outcomes such as mortality or heart failure. However, not yet shown is whether therapeutic effect on infarct size will be reflected in effects of therapy on longer-term outcomes. We used patient-level data from trials of treatments for AMI to assess the relationship between short-term therapies, infarct size, and treatment effects seen on longer-term outcomes. We hypothesized that a therapy-induced change in infarct size would be related in direction and magnitude to the one-year-outcome effects of that therapy.

Methods: Data obtained from 10 randomized clinical trials that tested various therapies for ST-elevation myocardial infarction (STEMI). Infarct size was assessed by septal magnetic resonance imaging in 3 trials, and by cardiac magnetic resonance imaging in 7 trials, with techniques analyzed in core labs, and was expressed as a percent of left ventricular mass. Data obtained from each trial included patients’ clinical features and a variable representing the treatment effect on infarct size. The treatment effect on infarct size was analyzed for 7 therapies using CRISP, AIDA-INFUSE, CRISP-AMIHOT2, CRISP, APEX, INFUSE-35, and MIAMIOT2 trials. The results were further analyzed in 3 trials, which used their data in 3 trials, and in 3 trials it was assessed by using the Cox proportional hazards model.

Results: The differences in infarct size between the treatment and control groups in each of the 10 trials ranged from 16-35% of the LV, and from 12-40% among treatment groups. There was a significant relation between the difference in infarct size and treatment effect on one year heart failure hospitalization with HR 0.34 (95% CI 0.20 to 0.59, p=0.001). There was a significant relationship between treatment effect on infarct size and treatment effect on one-year mortality (HR 0.01, 95% CI 0.00 to 1.12). The relationship to heart failure hospitalization was stable in sensitivity analyses adjusting for time from MI to infarct size assessment and for considering heart failure as the main outcome and death as a competing risk.

Conclusion: This patient-level analysis of randomized placebo-controlled trials of multiple therapeutic strategies for STEMI suggests that a treatment-induced reduction in infarct size is related in direction and magnitude to a treatment effect on heart failure hospitalization. This study provides further validation of the consideration of increasing infarct size in future clinical trials as an outcome into novel trial analytic approaches to assess new medications.

METHODS: Trial and Patient Inclusion

We combined patient-level data from 10 randomized trials that tested various treatments for STEMI. Data were pooled from a common data management center at the Cardiovascular Research Foundation. This was an independent academic project conceptualized and executed by the authors, study sponsors were not involved in any aspect of this study.

Table 1: Trials Included in the Analysis

Table 2: Baseline characteristics for Dataset 1 and Dataset 2

Table 3: HF and Mortality Outcomes for Patients in Dataset 1 and Dataset 2

Table 4: Mean Infarct Size for Control, Treatment, and Control minus Treatment

Table 5: Adjusted Hazard Ratio for Infarct Size based on C-T Treatment Effect on Outcomes

Table 6: Sensitivity Analyses

Limitations

• Representativeness of these trials which were available to the investigative team

• Only involved STEMI, not all ACS

• Created a new variable to represent group-level effect on infarct size for individual patients, to allow assessment of influence of infarct size on individual outcomes, with adjustment for co-variates

Conclusion

This analysis, using patient-level data from 10 randomized controlled trials of treatment interventions for STEMI, suggests that therapeutic effect on infarct size, measured by invasive imaging, is related in direction and magnitude to the longer-term (one-year) therapeutic effect on hospitalization for HF and all-cause mortality. For many of the reported adverse outcomes measured in the Cox models, a priori, the following factors were chosen as covariates: age, sex, prior MI, coronary disease type (LMVD vs. not), and the days between randomization and infarct size assessment.