The Relationships of Left Ventricular Ejection Fraction, End-Systolic Volume Index and Infarct Size to Six-Month Mortality After Hospital Discharge Following Myocardial Infarction Treated by Thrombolysis

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OBJECTIVES We sought to relate left ventricular ejection fraction (EF), end-systolic volume index (ESVI) and infarct size (IS), as measured in a single randomized trial, to six-month mortality after myocardial infarction (MI) treated with thrombolysis.

BACKGROUND These three prognostic indicators have never been compared in the same study group. Radionuclide angiographic and single-photon emission computed tomographic sestamibi measurements of IS were performed in 1,194 and 1,181 patients, respectively, of the 2,948 patients enrolled in the Collaborative Organization for RheothRx Evaluation (CORE) trial. Ejection fraction, ESVI and IS, as measured by central laboratories in these radionuclide substudies, were tested for their association with six-month mortality.

METHODS

RESULTS Ejection fraction (n = 1,137; p < 0.0001), ESVI (n = 945; p = 0.055) and IS (n = 1,164; p = 0.03) were all associated with six-month mortality. Each of these measurements was significantly correlated with the other two, regardless of MI location. In an "overlap" group of 753 patients (25.5% of the population; 13 deaths) in whom all three measurements were available, EF (p = 0.001) was a stronger predictor than ESVI (p = 0.005) or IS (p = 0.01). Neither of the other two measurements added independent prognostic information. The highest risk subgroup (EF < 30%) had an 11% six-month mortality, but comprised only 95 patients (8.3%).

CONCLUSIONS Ejection fraction, ESVI and IS measurements performed one to two weeks after MI can each predict six-month mortality. Ejection fraction was superior to the other two measurements. However, this study had limited power to detect independent significance of ESVI or IS. (J Am Coll Cardiol 2002;39:30–6) © 2002 by the American College of Cardiology

The probability of death after myocardial infarction (MI) is substantially determined by the resulting cumulative left ventricular (LV) structural and functional derangement (1). Ejection fraction (EF) measured at the time of hospital discharge after MI has long been recognized as a strong predictor of subsequent short- and long-term mortality (2,3). In the thrombolytic era, post-MI survival has improved (4–7), but EF remains a strong prognosticator (8).

Both end-systolic volume index (ESVI) and infarct size (IS) are alternatives to EF. Using contrast ventriculography, White et al. (9) demonstrated that ESVI, measured one to two months after MI, was superior to EF for the prediction of long-term survival. Direct measurement of IS using technetium-99m (99mTc) sestamibi single-photon emission computed tomography (SPECT) correlates closely with the amount of fibrosis in human hearts (10), predicts subsequent mortality (11) and is less affected by LV loading.

The purpose of this study was to relate EF, ESVI and IS measurements obtained between days 6 and 16 after MI treated by thrombolysis to mortality at six months. The Collaborative Organization for RheothRx Evaluation (CORE) was a prospective, randomized, double-blinded, placebo-controlled trial of a novel therapy (Poloxamer 188) adjunctive to thrombolysis (12). In CORE, Poloxamer 188 had no impact on six-month mortality in 2,948 patients or on IS, EF or ESVI (each measured in substudies of ~1,000 patients by radionuclide techniques). This large clinical trial with a neutral treatment effect is an excellent setting in which to evaluate and compare these three noninvasive radionuclide measurements.

METHODS

Study protocol. Subsets of clinical centers participating in CORE also participated in one or two radionuclide substudies: 1) radionuclide angiography for measurement of EF and absolute, count-based LV volumes; and 2) rest 99mTc-sestamibi SPECT imaging for measurement of IS.
Patient inclusion criteria for CORE (12) included symptoms consistent with acute MI and ≥1 mm of ST segment elevation in at least two contiguous leads or left bundle branch block. Exclusion criteria were age <21 years, onset of symptoms >12 h before randomization, emergency revascularization, serum creatinine >220 μmol/l, pregnancy or child-bearing potential, previous exposure to RheothRx or child-bearing potential, previous exposure to RheothRx and treatment with an investigational drug or device within the previous seven days. Both radionuclide substudies were conducted between days 6 and 16 (inclusive) after MI.

**Radionuclide angiography.** If preceded by 99mTc-sestamibi SPECT, radionuclide angiography was conducted at least 48 h later. Red blood cells were labeled in vitro using ~30 mCi of 99mTc sodium pertechnetate, according to a method either locally established or prescribed per the protocol, providing high (>90%) labeling efficiency.

We have previously described and validated the count-based method for absolute LV volume measurement (13), using a skin marker for “tissue depth” and a venous blood sample. The unprocessed images were sent to a central laboratory at the Toronto Hospital for analysis.

Ejection fraction was determined using a highly reproducible, semi-automated, second-derivative LV edge-detection and count-determination method, as previously reported from our laboratory (14). The ESVI was calculated as: LV end-diastolic volume × (1 − ejection fraction)/body surface area.

**Technetium-99m sestamibi SPECT.** Each site was first required to qualify for this substudy by the acquisition of a cardiac phantom study to ensure the accuracy of a designated SPECT imaging system for IS (15). If preceded by radionuclide angiography, 99mTc-sestamibi SPECT was conducted at least 24 h later.

The procedures for image acquisition, processing and interpretation have been reported previously (16). To summarize, patients received 20 to 30 mCi of 99mTc-sestamibi at rest, and SPECT was performed 1 h later using a rotating gamma camera with a low-energy, all-purpose collimator. Raw projection images were forwarded to the IS central laboratory at the Mayo Clinic. Processing and reconstruction of SPECT images were performed using backprojection and a Ramp-Hanning filter. Infarct size was calculated as the summed proportion of points <60% of peak counts, expressed as a percentage of the LV. This technique has been extensively validated (17).

**Clinical follow-up.** All surviving patients were contacted for clinical follow-up periodically and at six months. Serious adverse events, including death, were reported by investigators within 24 h to monitors under contract to the study sponsor. These events were adjudicated blindly by an independent Central Validation Committee.

**Statistical methods.** The relationship of six-month mortality to the radionuclide outcome measurements, analyzed as continuous variables, was examined using logistic regression analysis, where the dependent variable was survival or death at six months. Stepwise logistic regression analysis was performed to evaluate the additional explanatory power of multiple outcome measurements.

The association between pairs of radionuclide measurements was assessed by linear regression analysis, with and without adjustment for the co-variates of previous MI and MI location. The EF results were stratified for display in five ranges (categories), which had been selected a priori, in accordance with those used in the Thrombolysis in Myocardial Infarction trial (TIMI-2) (8). Similarly, four ranges (categories) of ESVI were determined a priori, using values derived from those reported by White et al. (9).

Four categories of IS were likewise established a priori, but de novo. A previous investigation demonstrated a low mortality for IS <12% of the LV—the first breakpoint (11). Similarly, maintenance of normal EF was known to be associated with IS <20%, which was the second breakpoint (18). The third breakpoint for the largest infarcts, >35% of the LV, was based on clinical experience.

**RESULTS**

**Study patients.** Of 2,948 patients enrolled in CORE, 1,194 (40.5%) underwent radionuclide angiography. Of these 1,194 patients, 1,137 (95.2%) had technically satisfactory studies for determination of EF, and 945 (79.1%) had technically satisfactory studies for determination of ESVI. Similarly, 1,181 patients (39.6%) of the patients enrolled in CORE underwent 99mTc-sestamibi SPECT; of these, 1,164 (98.6%) had technically satisfactory studies for determination of IS. All three radionuclide outcome measurements were obtained in an “overlap” group of 753 patients (25.5% of the study population). Six-month follow-up was obtained in 2,841 (96.4%) of the patients enrolled, and 725 patients (96.3%) in the “overlap” group.

Patients in the radionuclide angiographic substudy with technically satisfactory studies (n = 1,137) were compared with all other patients (n = 1,577) who were alive on day 16 and thus “eligible” for the radionuclide substudies (Table 1). Of these 1,577 patients, a subset of 281 was enrolled at sites participating in the radionuclide angiographic substudy (Table 1, last column). Six-month mortality was significantly lower in the radionuclide angiographic substudy.
group, suggesting that “sicker” patients were excluded from the substudy.

Relationships among radionuclide measurements. The three radionuclide measurements were significantly associated with each other. The strongest correlation was between ESVI and EF ($r = -0.78$, $p < 0.0001$) (Fig. 1). This correlation was predictable, as EF is employed in the calculation of ESVI. However, IS was significantly correlated with both EF ($r = -0.67$, $p < 0.0001$) (Fig. 2) and ESVI ($r = 0.57$, $p < 0.0001$), although it is determined from a different radionuclide measurement. Infarct location was entered as a co-variate in each of these analyses and was not significant.

Univariate relationship of radionuclide measurements to six-month mortality. There was a strong inverse relationship between six-month mortality and EF (chi-square value $= 44.3$, $p < 0.0001$) (Fig. 3). The highest risk subgroup was composed of 95 patients with EF $\geq 30\%$; there were 10 deaths in this subgroup (11% mortality rate). In contrast, there were only four deaths in the 603 patients with EF $\geq 50\%$ (0.7% mortality rate). Ejection fraction was an important predictor of mortality, independent of the worst Killip class. Figure 4 shows a direct relationship between mortality and ESVI (chi-square value $= 7.62$, $p = 0.055$). The highest risk subgroup (ESVI $> 70$ ml/m$^2$) included 74 patients and three deaths (4.1% mortality rate). Figure 5 illustrates a direct relationship between six-month mortality and IS (chi-square value $= 9.05$, $p = 0.03$). The highest risk subgroup (IS $> 35\%$) included 266 patients and 12 deaths (4.5% mortality rate). Infarct size was an important predictor of mortality in both anterior and non-anterior infarcts.

Multivariate logistic regression. Although the previous analyses included all patients with available measurements for each of the three individual measurements, the relationship between six-month mortality and EF, ESVI and IS measurements was examined in a separate analysis limited to only the 753 patients (the “overlap” group) who had all three of these measurements obtained (Table 2). Each of the three measurements was highly predictive of six-month mortality. Of the three, EF was the strongest predictor. Once EF was considered, ESVI and IS were no longer significantly related to six-month mortality, indicating that they offer no additional predictive power. However, in a model containing either ESVI or IS, EF added significantly to its predictive power. Tables 3 and 4 show six-month mortality for patient subgroups defined by EF and the highest risk values of ESVI ($\geq 70$ ml/m$^2$) and IS ($> 35\%$).

Neither ESVI nor IS had any appreciable effect.

DISCUSSION

Clinical significance. There are no previously reported data to describe, quantify and compare the prognostic value

| Table 1. Clinical Characteristics of Patients Included and Not Included in RNA Substudy |
|---------------------------------|---------------------------------|---------------------------------|
| RNA Substudy (n = 1,137)         | No RNA/Alive on Day 16 (n = 1,577) | No RNA Site/Alive on Day 16 (n = 281) |
| Male (%)                        | 78.4                             | 78.5                             | 80.7                             |
| Mean age (yrs)                  | 58.7                             | 58.8                             | 59.4                             |
| Mean time to treatment (h)      | 3.5                              | 3.6                              | 3.7                              |
| Previous MI (%)                 | 16.7                             | 16.9                             | 17.4                             |
| Diabetes (%)                    | 17.2                             | 13.4                             | 16.0                             |
| Congestive heart failure (%)    | 2.1                              | 3.1                              | 4.6                              |
| Anterior MI (%)                 | 37.9                             | 42.4                             | 44.8                             |
| Six-month mortality (%)         | 1.9                              | 4.2*                             | 6.8†                             |

*p = 0.0006, †p < 0.0001 versus RNA substudy.
MI = myocardial infarction; RNA = radionuclide angiography.

![Figure 1](image-url). Left ventricular (LV) end-systolic volume index and LV ejection fraction in 909 patients with both measurements. There was a highly significant correlation ($r = -0.78$, $p < 0.0001$) between the two.
of IS, EF and ESVI—three safe, widely available and highly reproducible radionuclide measurements—in survivors of MI treated with thrombolysis. Our results demonstrate that each of these three radionuclide measurements can predict the likelihood of death in such patients, despite low overall mortality. This study also demonstrates that these radionuclide measurements are highly suitable for multicenter clinical trials, as the data reported here originated from hospitals engaged in a clinical trial undertaken in 16 countries on five continents.

The study group was generally a low-risk cohort. Low six-month mortality (<5%) after hospital discharge was observed not only within the patient subgroups defined by availability of the radionuclide measurements, but also in the larger groups that did not undergo SPECT imaging or radionuclide angiography. This low mortality reflects the selection process for thrombolytic therapy (19), the benefit of thrombolytic therapy (8,17) and the favorable effect of other contemporary MI management strategies (4–7). The highest mortality in the radionuclide subgroups was found in patients with the lowest EF (<30%). There were 10 deaths among 95 patients (11%) in this category, which comprised only 8.3% of all patients with EF measurements.

Previous studies. The six-month all-cause mortality in CORE subjects stratified according to EF categories is virtually coincident with analogous one-year cardiovascular...
mortality reported in TIMI-2 (8). The mortality of patients in whom EF was not measured was also similar (6.2% in TIMI-2, 4.1% in CORE). Within each category of EF, patients in this study and in TIMI-2 had much lower mortality than that observed in the older Multicenter Postinfarction Trial (2), again reflecting the effects of selection for thrombolytic therapy, as well as the benefits of contemporary therapy. Ejection fraction provided important prognostic information that was independent of Killip class.

There are few published reports on the prognostic value of ESVI after MI treated by thrombolysis. Our data suggest that ESVI is comparable to, but not better than, EF as a prognostic indicator. In contrast, White et al. (9) demonstrated that within categories of EF, there was significant additional prognostic information when patients were secondarily stratified according to a “large” or “small” ESVI. Unlike White et al. (9), we did not observe higher mortality in patients with the lowest EF who had greater ESVI.
The difference in our results, compared with those of White et al. (9), has many potential explanations. This study enrolled patients undergoing thrombolysis; White et al. (9) studied a broader, more general post-MI population. This study used radionuclide angiography to measure ESVI; White et al. (9) used contrast ventriculography, which is likely more accurate. This study evaluated patients on days 6 to 16 after MI; White et al. (9) evaluated patients four to eight weeks after MI. This study followed patients for six months; White et al. (9) followed them for 78 ± 32 months. This study was performed in the 1990s, when the use of angiotensin-converting enzyme inhibitors after MI was more common than in the early 1980s, when White et al. (9) enrolled their patients.

The prognostic value of IS reported here in 1,164 patients confirms the results previously reported in two small series: a single-center study of 274 patients (11) and a multicenter study of 249 patients (20). Because EF and ESVI are influenced by preload, afterload and myopathic processes, as well as the extent of MI, IS might conceivably be a superior prognostic indicator. However, our results do not support this hypothesis.

Each of the three measurements was closely correlated with one another. A close correlation between IS and both EF and ESVI has been reported previously in small, carefully controlled, single-center series (21,22). Our results confirm these findings in a much larger, less selected, multicenter cohort. The correlation between ESVI and EF is expected, as the EF, which is directly measured, is employed in the calculation of ESVI. The results of the multivariate logistic regression analysis in the “overlap” group of 753 patients are consistent with the close association of the three measurements, although EF appears superior with respect to its prognostic power.

Study limitations. These data have several limitations. As previously indicated, “sicker” patients appear to have been less likely to participate in these substudies. The ESVI measured by radionuclide angiography is likely to be less accurate than that obtained by contrast ventriculography (9) or electron beam computed tomography (21). Although this is the largest reported post-MI series of IS measurements, as well as one of the largest of EF measurements, the power of this study was still modest, owing to the limited number of events. In the 753 patients in the overlap group, there were only 13 deaths within six months. Given this modest number of events, the power to detect independent significance of two of the radionuclide measurements was very limited.

Despite these limitations, these data demonstrate that each one of these three radionuclide measurements, performed one to two weeks after MI treated with thrombolysis, can predict mortality over the next six months. They are closely associated and provide similar prognostic information, although EF is superior in this regard.

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REFERENCES


