SCIENTIFIC LETTER

Prognostic implications of increased cardiac biomarkers and ST segment depression in non-ST elevation acute coronary syndromes: lessons from the acute coronary syndrome Israeli survey (ACSIS) 2002

I Ben-Dor, D Hasdai, S Behar, D Zahger, J Leor, H Hammerman, A Sandach, H Hod, S Gottlieb, on behalf of the Working Group on Intensive Cardiac Care, Israel Heart Society

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The prognostic value of increased concentrations of cardiac troponin (cTn(+)) in patients with acute coronary syndromes (ACS) for short and long term mortality is well established by both meta-analyses of clinical trials and cohort studies. The clinical implications, however, of acute myocardial infarction (AMI) diagnosed on the basis of cTn(+) in the absence of creatine kinase (CK) rise (CK(–)) among unselected patients with ACS is unclear. Several studies noted that cTn(+)/CK(+) patients had the worst prognosis, whereas others found that CK(+) did not confer any incremental prognostic value above cTn(+).^{1–4} In risk stratification of patients with non-ST elevation (NSTEMI) ACS another important tool is the ECG, particularly when ST segment depression is observed. Whether this information is independent of and additive to that provided by a biomarker rise is insufficiently studied. The main purpose of this study was to examine whether cTn, CK, and ST depression offer complementary prognostic information in the risk stratification of unselected patients presenting with NSTEMI-ACS in the “real world”.

METHODS

ACSIS (acute coronary syndrome Israeli survey) was a prospective observational national survey of all patients with ACS hospitalised in all 25 coronary care units and cardiology wards in all general hospitals in Israel from 1 February to 30 March 2002. For the present study we analysed all patients with an admission diagnosis of NSTEMI-ACS. All biomarkers were measured at local hospital laboratories. CK assays were considered CK(+) if they were > 2 times the upper limit of normal in conjunction with an increased CK-MB mass or CK-MB > 8%. cTn assays were considered cTn(+) when cardiac troponin I was > 1.0 µg/L, cardiac troponin T > 0.1 µg/L, or a point of care strip reader was positive. Mortality at six months was determined for all participants from hospital charts and by matching the identification number of the patients with the Israeli National Population Register.

Differences in frequencies of categorical variables were compared by χ^2 test. Students' *t* test was used for comparison of continuous variables. Two sided *p* values are reported. Multivariate logistic regression analyses were used to assess the adjusted odd ratios, with 95% confidence intervals (CIs), on six month mortality in the different subgroups and to assess the independent prognostic value of cTn(+) and ST depression. Survival curves were estimated by the method of Kaplan-Meier. The significance of the differences between the survival curves was assessed by the log rank test.

RESULTS

Of the 2049 patients enrolled in the ACSIS 2002 survey, 970 (47.3%) presented with NSTEMI-ACS and form the basis for this report. Of the 639 (66%) patients with available cTn data, 461 (72%) were cTn(+). Patients with cTn(+) were older (66 (12) v 62 (14) years) and more of them presented with ST depression and Killip $\geq$ II. Six month mortality was significantly higher in cTn(+) patients (8.9% v 2.2%, *p* = 0.003) and higher in patients with ST depression than in patients without ST depression on the admission ECG (9.7% v 4.1%, *p* = 0.07). Analysis of both cTn and ST depression status found that six month mortality was significantly higher in patients with cTn(+)/ST depression(+) than in patients with cTn(+)/ST depression(–) (11.9% v 5.3%, respectively, *p* = 0.01). Among cTn(–) patients, ST depression status did not affect mortality (2.9% v 1.8% respectively, *p* = 0.63). By multivariate logistic regression analysis adjusted for age, sex, prior AMI, prior angina, diabetes, prior revascularisation, and Killip class > I on admission, both cTn(+) and ST depression(+) were associated with six month mortality, with odds ratios of 2.82 (95% CI 1.05 to 9.80) and 1.57 (95% CI 0.81 to 3.11), respectively.

Of the 970 patients with NSTEMI-ACS on admission, both assays of cTn and CK were available for 629 (64.8%) patients. These patients were divided into three groups: CK(+) (*n* = 235 (37%)), CK(–)/cTn(+) (*n* = 239 (38%)), and CK(–)/cTn(–) (*n* = 155 (25%)). CK(–)/cTn(–) patients were younger (62 (12) years) than CK(+) patients (67 (12) years) and CK(–)/cTn(+) patients (66 (12) years, *p* < 0.001). Compared with CK(+) and CK(–)/cTn(+) patients, more CK(–)/cTn(–) patients had previous angina (45% v 48% v 58%, respectively, *p* = 0.03) and revascularisation (29% v 40% v 67%, respectively, *p* < 0.0001) but fewer presented with heart failure (28% v 20% v 8%, respectively, *p* < 0.001) and ST depression (46% v 51% v 38%, respectively, *p* = 0.01). In-hospital coronary interventions and management, as well as recommended medication at discharge, did not differ between the three groups. Left ventricular function, as determined by echocardiography, was available for 434 patients. Left ventricular dysfunction (ejection fraction < 40%) was present in 58 (33%) CK(+) patients, in 46 (25%) CK(–)/cTn(+) patients, and in 15 (18%) CK(–)/cTn(–) patients (*p* = 0.001). Seven day, 30 day, and six month mortality in the CK(+), CK(–)/cTn(+), and CK(–)/cTn(–) groups was as follows: 11.9% v 5.3% v 2.2% respectively, *p* = 0.003; 11.9% v 5.3% v 2.2% respectively, *p* = 0.003; 11.9% v 5.3% v 2.2% respectively, *p* = 0.003.

Abbreviations: ACS, acute coronary syndromes; ACSIS, acute coronary syndrome Israeli survey; AMI, acute myocardial infarction; CI, confidence interval; CK, creatine kinase; cTn, cardiac troponin; NSTEMI, non-ST elevation

Figure 1 Six month mortality by cardiac biomarkers in three groups: creatine kinase (CK) (+), CK(-)/cardiac troponin (cTn) (+) and CK(-)/cTn(-). P (log rank) = 0.006 for comparison between the three groups. P (log rank) = 0.02 for comparison between the CK(-)/cTn(+) and CK(-)/cTn(-) groups.

groups were 3.4% v 0.4% v 0.6% ($p = 0.01$); 4.7% v 1.7% v 1.3% ($p = 0.06$); and 10.7% v 7.1% v 1.9% ($p = 0.004$), respectively (fig 1). In multivariate analysis, after adjustment for age, sex, past AMI, past angina, past revascularisation, diabetes, Killip class > I, cTn, and ST depression, the adjusted odds ratios of death at six months were 3.57 (95% CI 1.13 to 15.9), 2.63 (95% CI 0.82 to 3.10), and 1.0 for CK(+), CK(-)/cTn(+), and CK(-)/cTn(-), respectively

DISCUSSION

This prospective observational nationwide community based survey of unselected patients in the real world indicates that in risk stratification of patients with NSTEMI-ACS, cTn(+) and ST depression(+) are complementary and both should be employed in addition to the routine use of CK. In combination, the markers appear to provide an integrated and improved delineation of the risk spectrum of ACS, with the lowest mortality in cTn(-)/ST depression(-) patients and the highest mortality in cTn(+)/ST depression(+) patients. However, ST depression adds significant prognostic information only for patients with cTn(+) and not for patients with cTn(-). cTn(+) patients had about three times the likelihood of six month mortality than cTn(-) patients. ST depression(+) patients had about 1.5 times the likelihood of six month mortality than ST depression(-) patients. Both tests were independently associated with prognosis and thus both

should be employed to determine prognosis. There are few contradictory data regarding the clinical implication of AMI diagnosed on the basis of cTn(+) but normal CK compared with cTn(+)/CK(+).¹⁻⁴ Our results show that the prognosis of patients with CK(+)/cTn(+) is worse than that of CK(-)/cTn(+) patients. The worse prognosis of CK(-)/cTn(+) patients than of CK(-)/cTn(-) patients further supports the routine use of cTn assays for patients with NSTEMI-ACS in addition to the use of the CK assay. The more widespread use of cTn assays for patients with NSTEMI-ACS will therefore facilitate prognostication, improve tailoring of management, and strengthen the adherence to the new definitions of AMI.

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Authors' affiliations

I Ben-Dor, D Hasdai, Department of Cardiology, Rabin Medical Center, Petach-Tikva, Israel

S Behar, J Leor, A Sandach, H Hod, S Gottlieb*, The Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, Israel

D Zahger, The Department of Cardiology, Soroka University Medical Center, Beer Sheva, Israel

H Hammerman, The Department of Cardiology, Rambam Medical Center, Haifa, Israel

*Also The Heiden Department of Cardiology, Bikur Cholim Hospital, Jerusalem, Israel

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Correspondence to: Professor Shmuel Gottlieb, Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, Israel, 52621; sgott@md.huji.ac.il

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