The Association Between the Risk Scores for Cardiovascular Disease and Long-Term Mortality Following an Acute Coronary Event

Avishay Elis MD[1,6], David Pereg MD[3,6], Zaza Iakobishvili MD[2,6], Dikla Geva PhD[4] and Ilan Goldenberg MD[5,6]

[1]Departments of Internal Medicine "C" and [2]Cardiology, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
[3]Department of Cardiology, Meir Medical Center, Kfar Saba, Israel
[4]IACT-Israeli Association for Cardiovascular Trials, Leviev Heart Center and [5]Department of Cardiology, Sheba Medical Center, Tel Hashomer, Israel
[6]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** A patient`s individual chance of being diagnosed with cardiovascular disease can be determined by risk scores.
Objectives: To determine the risk score profiles of patients presenting with a first acute coronary event according to pre-admission risk factors and to evaluate its association with long-term mortality.
Methods: The research was based on a retrospective study of a cohort from the 2010 and 2013 Acute Coronary Syndrome Israeli Surveys (ACSIS). Inclusion criteria included first event and no history of coronary heart disease or cardiovascular disease risk equivalent. The Framingham Risk Score, the European Systematic COronary Risk Evaluation (SCORE), and the American College of Cardiology/American Heart Association (ACC/AHA) risk calculator were computed for each patient. The risk profile of each patients was determined by the three scores. The prognostic value of each score for 5 year survival was evaluated.
Results: The study population comprised 1338 patients enrolled in the prospective ACSIS survey. The ACC/AHA score was the most accurate in identifying patients as high risk based on pre-admission risk factors (73% of the subjects). The Framingham algorithm identified 53%, whereas SCORE recognized only 4%. After multivariate adjustment for clinical factors at presentation, we found that no scores were independently associated with 5 year mortality following the first acute coronary event.
Conclusions: Patients with first acute coronary event had a higher pre-admission risk scores according to the ACC/AHA risk algorithm. No risk scores were independently associated with 5 year survival after an event.

IMAJ 2018; 20: 419–422

KEY WORDS: acute coronary syndrome, Acute Coronary Syndrome Israeli Surveys (ACSIS), American College of Cardiology/American Heart Association (ACC/AHA) risk calculator, Framingham Risk Score (FRS), Systematic COronary Risk Evaluation (SCORE)

An individual's risk for developing cardiovascular disease can be determined by various risk scores. These scores are calculated by algorithms that are based on the person's gender, age, blood pressure, smoking habits, and cholesterol levels (total and high-density lipoproteins).

The various scores differ by the risk factors they include, the risk assigned to each factor, and the definition of high-risk state. The Framingham Risk Score (FRS) [1] is an algorithm that estimates the 10 year risk of an individual to develop cardiovascular disease. It is based on data from the Framingham cohort of middle-aged subjects from the United States [2]. The European Systematic COronary Risk Evaluation (SCORE) estimates the 10 year risk for fatal cardiovascular disease for low- and high-risk regions [3,4]. Recently, the American College of Cardiology/American Heart Association (ACC/AHA) developed an algorithm that assesses the 10 year risk for heart disease or stroke [5,6]. A high-risk state is defined as > 20% risk based on the FRS, > 10% risk based on the SCORE, and > 7.5% risk according the ACC/AHA algorithm [1-5].

The retrospective cardiovascular disease risk determination of patients presenting with a first acute coronary syndrome (ACS) based on their pre-admission risk profile has not been reported. In addition, to the best of our knowledge, the usefulness of the scores for long-term risk stratification following ACS has not been assessed.

The aims of this study were to explore the retrospective risk profile of patients hospitalized with their first ACS based on their pre-admission risk profile and to evaluate the long-term prognostic value of the risk scores following a first ACS event.

PATIENTS AND METHODS

STUDY POPULATION

The study group was based on cohorts from the 2010 and 2013 Acute Coronary Syndrome Israeli Surveys (ACSIS). The ACSIS registry is a biannual prospective, observational, national survey of all patients with ACS who were hospitalized in any of the

25 coronary care units and cardiology wards in Israel during a 2 month period. During each survey, patient data are collected by comprehensive pre-specified case report forms. Patient management is at the discretion of the attending physicians. Admission and discharge diagnoses are recorded as determined by the attending physicians. The diagnoses are based on clinical, electrocardiographic, and biochemical (elevated troponin and/or creatine kinase [CK]-MB levels) criteria. Data were collected by dedicated study physicians and checked for consistency and completeness. Available data included demographic information, historical and clinical data including in-hospital medical management, and performed procedures. Five year mortality was ascertained by the Israeli National Population Registry.

Study protocol was approved by the review boards at the participating institutes and conducted in compliance with the Declaration of Helsinki [7].

Inclusion criteria for the present study included first ACS event, no history of coronary heart disease or cardiovascular disease risk equivalent (diabetes mellitus, peripheral vascular disease), or no history of stroke. Among 3665 ACSIS patients who were included in the 2010 and 2013 survey, 1338 (36.5%) met the inclusion criteria to be included as part of the study population.

STUDY DESIGN

Three scores (FRS [1], SCORE [2], and the ACC/AHA risk assessment [3]) were computed for each patient and calculated according to risk levels (low/intermediate and high) based on their pre-admission clinical characteristics and baseline lipid profile. High-risk state was defined as > 20% risk by the FRS, > 10% risk by the SCORE, and > 7.5% according to the ACC/AHA risk assessment [1-5].

The characteristics of low/intermediate (int.) vs. high-risk patients were calculated for each score followed by a comparison of the rate of patients with high risk levels for each score. The prognostic value of each score for a 5 year survival rate after the index event was evaluated.

STATISTICAL METHODS

A box plot was used to exhibit the risk distribution (median and inter quartile distance) along with the mean (indicated by an X). The characteristics of low/int. vs. high risk were calculated using *t*-test for continuous variables and chi-square for categorical variables. Kaplan–Meier survival curves were plotted to assess the prognostic value of each score on 5 year survival rates. The log-rank test was used to compare the survival distributions of low- and high-risk groups. Finally, a Cox proportional-hazard model was used to compare each score to the 5 year mortality hazard after controlling for the event severity as classified by the Killip score, and by adding one by one (≥ 50% vs. < 50%) to model the ejection fraction and ST elevation myocardial infarction (STEMI) vs. non-STEMI. The hazard ratio and 95% confidence interval are presented in Table 1. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). $P < 0.05$ was regarded as statistically significant with no correction for multiple comparisons. Computation of the tree scores followed the algorithms as described in the supplementary material.

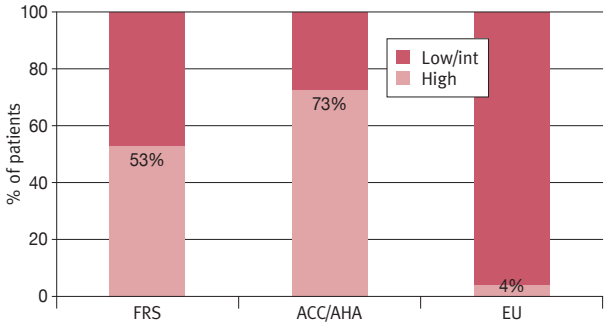
RESULTS

The distribution of risk levels (high vs. low/int.) among the 1338 study patients by the studied scores is provided in Figure1. The ACC/AHA algorithm performed the best at identifying high-risk ACS patients based on their pre-admission characteristics (73% of the subjects). The FRS identified 53%; whereas, SCORE identified only 4% of these subjects as at high risk. Similar findings are shown by the box plot shown in Figure 2A. The advantage of the ACC/AHA algorithm was consistent regardless of age [Figure 2B].

Only 3% of the patients were considered high risk by all three scores, while a high-risk state by both the ACC/AHA and the FRS scores was found in 43%.

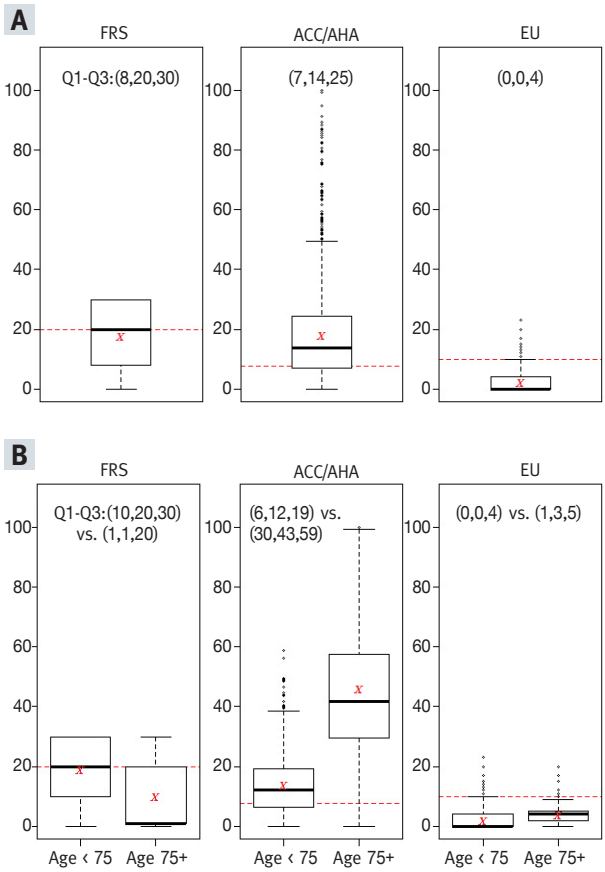
Major differences among the three score included the fact that high-risk patients were significantly older when using ACC/AHA and SCORE criteria (63 ± 12 vs. 49 ± 8 and 70 ± 7 vs. 59 ± 12, $P < 0.001$, respectively) but not the FRC (60 ± 9 vs. 59 ± 15, $P = 0.431$). Males constituted a significantly higher proportion of the high-risk group using SCORE (96% vs. 79%, $P = 0.003$). Smokers constituted a significantly higher proportion of the high vs. lower/int. risk groups using the FRC and ACC/AHA criteria (59% vs. 38% and 53% vs. 40%, $P < 0.001$, respectively), but not the SCORE (53% vs. 49%, $P = 0.701$). The rate of treatment with statins was very high (around 90%) in all risk scores, without any clinically significant difference between risk levels. However, the rate of aspirin treatment was low (around 20%), but significantly higher in the high-risk patients according the ACC/AHA and SCORE criteria. The risk groups did not differ in electrocardiography (ECG) changes on admission, whereas

Figure 1. Distribution of risk according to the scores (n=1338)



FRS = Framingham Risk Score, ACC/AHA = American College of Cardiology/American Heart Association score, EU = European Systematic COronary Risk Evaluation (SCORE)

Figure 2. [A] Boxplots according to the three scores (above the red-dot line indicates high risk) **[B]** Distribution of high risk according to age (above/below 75 years)



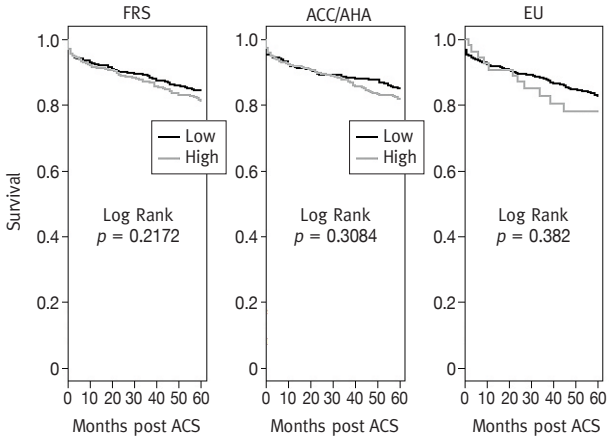
FRS = Framingham Risk Score, ACC/AHA = American College of Cardiology/American Heart Association score, EU = European Systematic COronary Risk Evaluation (SCORE)

the risk level by SCORE was significantly related to the admission Killip class (data not shown).

LONG-TERM MORTALITY FOLLOWING ACS BY RISK SCORE

Kaplan–Meier survival analysis showed that at the 5 year follow-up patients who were categorized as high risk in each of the three scores experienced higher mortality rates during long-term follow-up. However, the differences in outcomes between high- and lower-risk patients by each of the three scores did not reach statistical significance [Figure 3]. Consistent with the univariate Kaplan–Meier findings, multivariable Cox proportional-hazard model regression showed that the high score resulted in a non-significant 5 year hazard ratio for all three different scores. This finding was true in a model with Killip score > 1 class as presented in Table 1 and for other models not presented here, which included ejection fraction (EF) ≥ 50% and ST elevation myocardial infarction (STEMI) vs. Non-STEMI.

Figure 3. Kaplan–Meier analysis for 5 year survival according risk the three algorithms



FRS = Framingham Risk Score, ACC/AHA = American College of Cardiology/American Heart Association score, EU = European Systematic COronary Risk Evaluation (SCORE), ACS = acute coronary syndrome

Table 1. COX model: 5 year mortality hazard ratio (95% confidence interval)

	FRS	ACC/AHA	EU
Score High vs. low/int	1.23 (0.927–1.64)	1.15 (0.836–1.590)	1.29 (0.701–2.370)
Killips score › 1	1.850* (1.270–2.710)	1.790* (1.230–2.620)	1.800* (1.240–2.630)

FRS = Framingham Risk Score, ACC/AHA = American College of Cardiology/American Heart Association score, EU = European Systematic COronary Risk Evaluation (SCORE), low/int.= low/intermediate

*P ‹ 0.001

DISCUSSION

Our findings provide several important clinical implications regarding the utility of the commonly used cardiovascular disease risk scores for risk stratification among ACS patients.

We have shown that:

- Using baseline risk factors, the ACC/AHA algorithm and the FRS identified most of the high-risk patients who presented with a first ACS, whereas the SCORE was less predictive of a first ACS
- None of the cardiovascular disease risk scores seem to predict independently subsequent long-term mortality following a first ACS event.

In contrast, simple clinical markers of the index ACS admission, such as Killip Class on presentation, appear to be more closely associated with long-term outcome in this population.

The scores are based on a prospective population risk assessment for an individual, although we used them retrospec-

tively in pre-specified group of patients who presented ACS. Although the algorithms determined high- and low/int.-risk patients, most patients, irrespective of risk level, were treated by statins but not aspirin at presentation.

The differences between the scores in determining high-risk patients are based on their nature. The ACC/AHA algorithm and the FRS predicted the risk of morbidity, heart disease, and stroke or cardiovascular disease; whereas, the SCORE predicted mortality. Furthermore, the definitions of high risk differ in the scores (> 7.5% risk at the ACC/AHA algorithm, > 20% at the FRC and > 10% at SCORE) [1-5].

The scores could not be used to predict ECG changes at admission, while only the risk by the SCORE had an association with the administration Killip score.

We analyzed the long-term, 5 year, survival after the index ACS event because the scores are based on predicting long term, 10 year outcomes. The scores did not predict the 5 year survival after ACS. The same result was found for FRS considering secondary events after percutaneous transluminal coronary angioplasty [8]. However, high risk by the FRS among hospitalized ischemic stroke patients was reported to be independently associated with poor prognosis, namely death or disability at discharge as well as lower likelihood of being discharged directly home. The effect was found after adjustment for cofounders [9].

The evaluation of scores that are used in one disease to predict the outcome of another illness was previously reported for the CHA_2DS_2-VASc score, used for systemic embolization risk in atrial fibrillation. This score was found to be a useful predictor for subsequent adverse events in ACS patients [10], and to be useful in determining stratify acute myocardial infarction patients according to long-term prognosis, irrespective of the presence of atrial fibrillation [11]. Recently, Pereg et al. reported that higher CHA_2DS_2-VASc scores were associated with a significant increase in 1 year mortality, even following a multivariate analysis [12].

The main limitations of this study is that it evaluated algorithms for prospective general use retrospectively in a pre-specified group and evaluated all cause mortality instead of cardiovascular disease mortality.

CONCLUSIONS

Patients with a first ACS had higher pre-admission risk scores according the ACC/AHA risk algorithm. Nevertheless, no cardiovascular disease risk scores were independently associated with 5 year mortality after the first ACS event.

Correspondence
Dr. A. Elis
Dept. of Medicine C, Rabin Medical Center (Beilinson Campus), Petah Tikva 4941492, Israel
Phone: (972-3) 937-6301
Fax: (972-3) 922-1605
email: avishayel@clalit.org.il

References

1. The Framingham Risk Score. Available from: http://www.nhlbi.nih.gov/health-pro/guidelines/current/cholesterol-guidelines/quick-desk-reference-html/10-year-risk-framingham-table.
2. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; 117: 743–53.
3. The European Systematic COronary Risk Evaluation (SCORE). Available from: https://www.escardio.org/static_file/Escardio/Subspecialty/EACPR/Documents/score-charts.pdf.
4. Conroy RM, Pyörälä K, Fitzgerald AP, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003; 24: 987-1003.
5. The American Heart Association/American College of Cardiology algorithm. Available from: http://ncook.bwh.harvard.edu/sas-macros.html.
6. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2935-59.
7. Behar S, Battler A, Porath A, et al. Israel Heart and Internal Medicine Societies: a prospective national survey of management and clinical outcome of acute myocardial infarction in Israel, 2000. *IMAJ* 2003; 5: 249-54.
8. Sara JD, Lennon RJ, Gulati R, et al. Utility of the Framingham Risk Score in predicting secondary events in patients following percutaneous coronary intervention: a time-trend analysis. *Am Heart J* 2016; 172: 115-28.
9. Ovbiagele B, Liebeskind DS, Kim D, et al. Prognostic value of Framingham Cardiovascular Risk Score in hospitalized stroke patients. *J Stroke Cerebrovasc Dis* 2011; 20: 222-6.
10. Chua SK, Lo HM, Chiu CZ, et al. Use of $CHADS_2$ and CHA_2DS_2-VASc scores to predict subsequent myocardial infarction, stroke, and death in patients with acute coronary syndrome: data from Taiwan acute coronary syndrome full spectrum registry. *PLoS One* 2014; 9: e111167.
11. Kim KH, Kim W, Hwang SH, et al. The CHA_2DS_2VASc score can be used to stratify the prognosis of acute myocardial infarction patients irrespective of presence of atrial fibrillation. *J Cardiol* 2015; 65: 121-7.
12. Rozenbaum Z, Elis A, Shuvy M, et al. CHA_2DS_2-VASc score and clinical outcomes of patients with acute coronary syndrome. *Eur J Intern Med* 2016; 36: 57-61.

"We need to internalize this idea of excellence. Not many folks spend a lot of time trying to be excellent"

Barack Obama, (born 1961), American politician who served as the 44th President of the United States from 2009 to 2017

"The problem is not that there are problems. The problem is expecting otherwise and thinking that having problems is a problem"

Theodore Isaac Rubin, (born 1923), an American psychiatrist and author