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Reevaluation of cardiac risk scores and multiple biomarkers for the prediction of first major cardiovascular events and death in the drug-eluting stent era

Toshihito Onda [a,1], Kenji Inoue [b,*,1], Satoru Suwa [c,1], Yuji Nishizaki [a,1], Takatoshi Kasai [a,1], Yuki Kimura [b,1], Kentaro Fukuda [b,1], Iwao Okai [b,1], Yasumasa Fujiwara [b,1], Jo Matsuoka [d,1], Masataka Sumiyoshi [b,1], Hiroyuki Daida [a,1]

[a] Department of Cardiology, Juntendo University School of Medicine, Tokyo, Japan
[b] Department of Cardiology, Juntendo University Nerima Hospital, Tokyo, Japan
[c] Department of Cardiology, Juntendo University Shizuoka Hospital, Shizuoka, Japan
[d] Juntendo Clinical Research Support Center, Tokyo, Japan

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ABSTRACT

Background: Risk scores and cardiac biomarker tests allow clinicians to accurately diagnose acute coronary syndrome (ACS) and perform early risk stratification. However, few investigations have evaluated the use of these risk scores and biomarkers for predicting risk of cardiovascular events in drug-eluting stent (DES) era.
Methods: This prospective cohort study included 861 patients with ACS. Three risk scores—Global Registry of Acute Coronary Events (GRACEs), Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin, and Thrombolysis In Myocardial Infarction—and levels of four biomarkers—N-terminal pro-B-type natriuretic peptide (NT pro-BNP), high-sensitivity troponin T, heart-fatty acid binding protein, and high-sensitivity C-reactive protein—were recorded on admission. Major adverse cardiac events (MACE) (death, cardiovascular events) were evaluated at 30-day and 1-year follow-up.
Results: At 30-day follow-up, there were 23 (3.1%) deaths from cardiovascular events and 4 (0.5%) cerebral accidents. NT pro-BNP levels and GRACE score were strong MACE predictors, with adjusted odds ratios (ORs) (95% CI) of 2.90 (1.63–5.20) and 1.01 (1.00–1.02), respectively, in logistic model. The C-statistic of NT pro-BNP (0.77; 95% CI, 0.67–0.86) was similar to that of GRACE score (0.76; 95% CI, 0.66–0.87); however, the combined C-statistic was higher (0.81), yielding a net reclassification improvement of 13% ($p < 0.01$). At 1-year follow-up, there were 51 (6.8%) deaths and 10 (1.3%) cerebral accidents.
Conclusion: In the DES era, GRACE score and biomarkers can still predict major cardiac events in patients with ACS for both acute and long-term prognoses.

1. Introduction

Acute coronary syndrome (ACS) encompasses a wide range of clinical conditions that are due to decreased blood flow in the coronary arteries [1]. The treatment options available to the individual patient with ACS depend on the clinical presentation of the disease and the estimated treatment benefit. Since treatment benefits are usually proportional to the risk of an adverse outcome, the selection of an appropriate treatment option should take account of the estimated baseline risk [2,3].

Many recently developed biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT pro-BNP), high-sensitivity C-reactive protein (hsCRP), heart-type fatty-acid-binding protein (H-FABP), and troponin T, have played an important role in both risk stratification and the choice of treatment strategies for patients with ACS [4–6]. The treatment of ACS has seen rapid progress since drug-eluting stent (DES) came into use, and the prognosis has greatly improved [1,7]. However, early risk stratification is still considered important for the optimal management of ACS, which represents a heterogeneous condition with a variable short-term and long-term prognosis. Although several risk scores—such as the Global Registry of Acute Coronary Events (GRACEs), Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor

* Corresponding author at: Department of Cardiology, Juntendo University Nerima Hospital, 3-1-10, Takanodai, Nerimaku, Tokyo 177-0033, Japan.
E-mail address: inouelsbm@gmail.com (K. Inoue).
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Suppression Using Integrilin (PURSUIT), and Thrombolysis In Myocardial Infarction (TIMI)—are used in the evaluation of ACS, all these scores were established before the DES era [2–4,8–10]. On the other hand, biomarkers are pivotal tools in the diagnosis of ACS or heart failure, because they are easy to measure, can be quantified, and have high reproducibility [7,11]. Several reports also suggest that these biomarkers are useful for predicting the prognosis of patients with ACS [12–14].

The lack of published data comparing risk scores with biomarkers in the DES era prompted us to conduct this study. The main objectives were to reevaluate the established risk scores in the DES era, to compare them with selected biomarkers, and to evaluate whether biomarkers have additional value in terms of their 1-month and 1-year prognostic accuracy.

2. Methods

2.1. Study design

This was a prospective, multicenter, observational study that included patients with ACS who were admitted to university hospitals in Japan between 2009 and 2014. The patients were followed up after 30 days and 1 year.

2.2. Patients

A total of 861 Japanese patients with ACS were initially screened for this study, of whom 111 were excluded because they had serum creatinine levels greater than 2.0 mg/dL (n = 48), had been diagnosed with and treated for a malignant disease (n = 1), or were followed at other clinics or hospitals (n = 62) (Fig. 1). Thus, a total of 750 patients were included in the analysis (Fig. 1). Informed consent was obtained from all patients. The study was approved by the ethics committee of Juntendo University Shizuoka Hospital and Juntendo University Nerima Hospital, and was conducted in accordance with the Helsinki Declaration of 1971, as revised in 1982.

2.3. Clinical assessment

All patients included in this study underwent an initial clinical assessment that included physical examination, clinical history, recording of smoking status (current, former smoker, and non-smoker), 12-lead electrocardiogram (ECG), pulse oximetry, blood pressure, heart rate, standard blood measurements, and chest radiography. Three validated risk scores, TIMI, PURSUIT, and GRACE, were also calculated at the same time. TIMI was calculated from age, risk factors for coronary artery disease, use of aspirin in the last 7 days, prior coronary stenosis (more than 50%), more than 1 episode of rest angina within 24 h, ST-segment deviation, and elevation of cardiac biomarkers [8]. PURSUIT was calculated from age and enrolment diagnosis (unstable angina or myocardial injury), sex, the worst angina pectoris score in the previous 6 weeks (using the Canadian Cardiovascular Society grading), signs of heart failure, and ST-segment depression [9]. Finally, GRACE

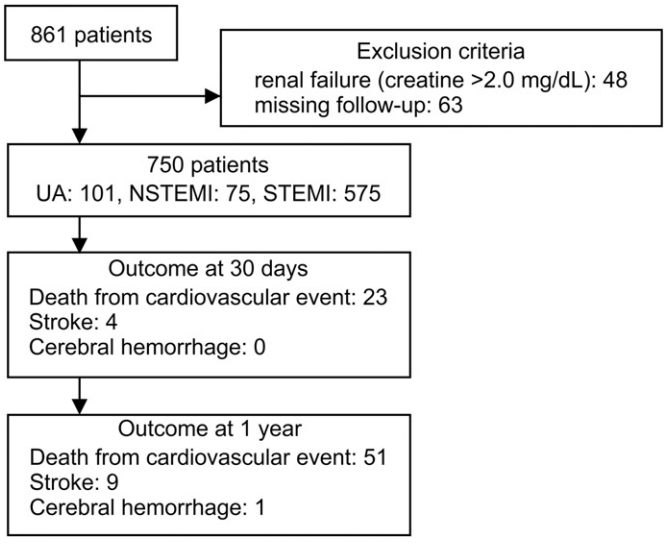

Fig. 1. Flowchart of patient enrollment in to the study. UA, unstable angina pectoris; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction.

Table 1
Baseline patient characteristics.

Patients, n	750
Age, years	66 ± 12
Female, n (%)	179 (24)
Unstable angina, n (%)	101 (13)
NSTEMI, n (%)	74 (10)
STEMI, n (%)	575 (77)
Family history, n (%)	159 (21)
Smoking, n (%)	500 (67)
Current, n (%)	305 (41)
Former, n (%)	195 (26)
Hypertension, n (%)	530 (71)
Diabetes, n (%)	278 (37)
Dyslipidemia, n (%)	494 (66)
Heart rate, beats/min	79.4 ± 20.6
Systolic blood pressure, mm Hg	138.4 ± 30.6
Two or more anginal events in the past 24 h, n (%)	220 (29)
Use of aspirin in the preceding 7 days, n (%)	97 (13)
Heart failure, n (%)	66 (9)
Cardiac arrest at admission, n (%)	32 (4)
Canadian cardiovascular society grading (class), n (%)	
I	11 (1)
II	50 (7)
III	123 (16)
IV	566 (75)
Killip class, n (%)	
I	677 (90)
II	6 (1)
III	20 (3)
IV	47 (6)
Time from symptom onset to hospital arrival, h [Quartiles]	3.3 [1.8–7.0]

STEMI, ST-elevation myocardial infarction; NSTEMI, non-STEMI.

Table 2
Risk scores and laboratory data on admission.

Risk score	Median	(Quartiles)	[Min, max]
TIMI	3	(2–4)	[0, 7]
PURSUIT	15	(14–16)	[1, 21]
GRACE	137	(115–160.75)	[44, 354]
Biomarkers		Mean	±SD
Creatinine (mg/dL)		0.8	±0.29
eGFR (mL/min/1.73 m^2)		59	±26.3
LDL cholesterol (mg/dL)		125	±38.9
HDL cholesterol (mg/dL)		48	±15.1
Total cholesterol (mg/dL)		198	±46.0
Total triglycerides (mg/dL)		122	±116
Glycated hemoglobin (%)		6.3	±1.3
Creatine kinase (IU/L)		541	±1157
Creatine kinase MB (IU/L)		62	±126
White-cell count (/mm^3)		10400	±3700
N-terminal pro-B-type natriuretic peptide (pg/mL)		967	±2335
Heart-type fatty-acid-binding protein (ng/mL)		106	±219
High-sensitivity cardiac troponin T (ng/mL)		0.85	±2.2
High-sensitivity C-reactive protein (mg/dL)		4.64	±18.0

TIMI, Thrombolysis In Myocardial Infarction; PURSUIT, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin; GRACEs, Global Registry of Acute Coronary Events; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein.